Progress in Neuropsychopharmacology & Biological Psychiatry 98 (2020) 109801

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

# Connectivity strength of the EEG functional network in schizophrenia and bipolar disorder

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ARTICLE INFO

*Keywords:*
Connectivity strength
Functional network
Graph-theory
Schizophrenia
Bipolar disorder

ABSTRACT

The application of graph theory measures in the study of functional brain networks allows for the description of their general properties and their alterations in mental illness. Among these measures, connectivity strength (CS) estimates the degree of functional connectivity of the whole network. Previous studies in schizophrenia patients have reported higher baseline CS values and modulation deficits in EEG spectral properties during cognitive activity. The specificity of these alterations and their relationships with pharmacological treatments remain unknown. Therefore, in the present study, we assessed functional CS on EEG-based brain networks in 79 schizophrenia and 29 bipolar patients in addition to 63 healthy controls. The subjects performed a P300 task during the EEG recordings from which the pre-stimulus and the task-related modulation CS values were computed in the global and theta bands. These values were compared between the groups and between the patients who had and had not received different treatments. The global band pre-stimulus CS was significantly higher in the schizophrenia group compared with the bipolar and control groups. Theta band CS modulation was decreased in schizophrenia and bipolar patients. Treatment with antipsychotics, lithium, benzodiazepines, and anticonvulsants did not significantly alter these CS values. The first-episode and chronic schizophrenia patients did not show significant differences in CS values. Higher global band pre-stimulus CS values were associated with worse general cognition in schizophrenia patients. These data support increased connectivity in the whole-brain network that is specific to schizophrenia and suggest a general hyper-synchronized basal state that might hamper cognition in this syndrome.

## 1. Introduction

Parameters derived from graph theory have been applied to biological signals to assess brain network properties in healthy subjects and those with pathological conditions (Gomez-Pilar et al., 2017; Rubinov et al., 2009; van den Heuvel et al., 2008; van den Heuvel et al., 2010). Electroencephalography (EEG) has been widely used to this end, since its temporal resolution is adequate to evaluate the fast changes in these networks that are linked to cognitive function.

Given the likely widespread cerebral involvement in mental functions, assessing the functional connectivity of whole-brain networks and its modulation by cognition is relevant to the study of mental disorders. Thus, our group has previously calculated the small-world (SW) index from EEG recordings to assess network characteristics during cognitive activity (i.e., during a P300 task performance) and has reported that, compared with controls, a lower increase in this index occurs in schizophrenia patients in association with task performance (Gomez-Pilar et al., 2017).

In this line, other network measures can increase our understanding of functional alterations in mental disease. Among these, connectivity strength (CS), which is an extension of the density measure in binary networks, summarizes the averaged edge values of all of the nodes in the network. These edges are usually calculated from phase-locking values (PLV) that in the case of EEG indicates the degree of synchronization among sensors because a higher synchronization is associated with greater PLV among sensors.

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https://doi.org/10.1016/j.pnpbp.2019.109801
Received 3 June 2019; Received in revised form 16 September 2019; Accepted 29 October 2019
Available online 01 November 2019

CS represents a quantitative index of synchrony among neural assemblies. Since this synchronous firing of transitory neural assemblies is related to the interneuron mediated inhibitory neural activity (Buzsáki, 2006), from a theoretical perspective it could be proposed that possible CS alterations might relate to an abnormal excitatory/inhibitory balance. Because deficits in inhibitory transmission have been reported in major psychoses (Fee et al., 2017; Gonzalez-Burgos et al., 2011), CS alterations may be expected in these disorders.

Our group has previously reported higher pre-stimulus CS values in the EEG global and theta bands in schizophrenia (Gomez-Pilar et al., 2018a). Of these, the increase in the theta band was related to decreased modulation of the spectral properties during a P300 task in schizophrenia, defining modulation as the difference between the pre-stimulus and the response windows values (Gomez-Pilar et al., 2018b). The decreased task-related modulation of spectral properties is a finding that has been replicated in two different schizophrenia patient samples (Bachiller et al., 2014; Molina et al., 2018). Task-related modulation is likely to reflect a re-shaping in the functional connections between distributed neural assemblies, considering the role proposed for these assemblies in cognition (Buzsaki and Draguhn, 2004; Varela et al., 2001), and the fact that the evolving EEG record results from the coordinated action of such assemblies (Uhlhaas and Singer, 2010). Thus, the task-related modulation of network parameters may be proposed to reflect the re-shaping of the underlying neural assemblies related to the corresponding cognitive activity.

To our knowledge, the specificity of these CS alterations described in schizophrenia and the possible effects of antipsychotic treatment have not yet been assessed. To this end, in the present study we assessed the CS values that were altered in our previous reports in a partially new schizophrenia sample and in a bipolar sample using a denser EEG array (Gomez-Pilar et al., 2018b). Based on these previous reports, and in order to reduce the number of comparisons, in this study we only focused on theta and global frequency bands. Our primary hypothesis was that pre-stimulus CS would be specifically higher in the schizophrenia group, and this group would exhibit lower task-related CS modulation that would be correlated with cognitive deficits. The inclusion of bipolar subjects also allowed us to assess the effects of antipsychotic treatment through the comparison between drug-free and medicated patients. In this case, our hypothesis was that the network alteration would not depend on antipsychotic treatment.

## 2. Subjects and methods

### 2.1. Subjects

In the present study, we included 79 schizophrenia (48 males) and 29 bipolar patients (17 males) in addition to 63 healthy controls (32 males). The schizophrenia group included 31 first-episode (FE) patients. Data from 38 healthy controls and 31 schizophrenia patients (7 FE) have been included in previous reports from our group (Gomez-Pilar et al., 2018a, b). None of the bipolar subjects have been included in any previous report, although diffusion tensor imaging data from 24 of these subjects have been published elsewhere (Cea-Cañas et al., 2019). All participants provided written informed consent after receiving full oral and printed information. The local ethical committee approved this study.

The patients were diagnosed by one of the psychiatrists in the group (V. M., the treating psychiatrist of most of the cases) according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, based on full interviews and all available evidence. The healthy controls were recruited through newspaper advertisements. The socio-demographic and clinical characteristics are presented in Table 1.

The exclusion criteria for patients and controls included a history of neurological illness (including cranial trauma with loss of consciousness), past or present substance abuse (except for nicotine and caffeine), and an intelligence quotient (IQ) below 70. Additionally, controls were excluded in cases of any current psychiatric diagnosis or treatment.

All chronic schizophrenia patients were receiving stable doses of atypical antipsychotics. Of these patients, 15 were also receiving antidepressants, and 27 were receiving benzodiazepines (BZD). The FE patients were also receiving stable doses of antipsychotics. Eleven of these patients had been so doing for fewer than 15 days. Regarding the bipolar patients, 15 were receiving atypical antipsychotics, 18 were receiving lithium, 4 were receiving anticonvulsants, 7 were receiving BDZ, and 6 were receiving antidepressants.

### 2.2. Clinical and cognitive assessment

The symptoms were scored using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Depression and mania were scored using the Hamilton Depression (HAM-D) and Young Mania Rating scales (YMRS). Cognitive data from the patients and controls were collected using the Wechsler Adult Intelligence Scale (third edition; WAIS-III) and the Spanish version of the Brief Assessment in Cognition in Schizophrenia Scale (BACS) (Segarra et al., 2011).

### 2.3. EEG recording and processing

#### 2.3.1. EEG data acquisition and preprocessing

We recorded the EEG data using a 29-channel EEG system (BrainVision®, Brain Products GmbH). Electrodes were place at 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 following the international 10–10 system; the impedance was below 5 kΩ, and the sampling frequency was 500 Hz. The channels were referenced over Cz during acquisition and re-referenced offline to the averaged activity of all of the sensors (Bledowski et al., 2004; Gomez-Pilar et al., 2018c). We recorded 13 min of eyes-closed EEG activity during an auditory odd-ball 3-condition paradigm that presented 600 random stimuli in the sequence of a target (500-Hz tone, probability of 0.2), distractor (1000-Hz tone, probability of 0.2), and a standard (2000-Hz tone, probability of 0.6) tone. Each tone lasted 50 milliseconds (ms) and comprised a rise and fall time of 5 ms with an intensity of 90 dB. The inter-stimulus interval randomly jittered between 1.16 and 1.44 s. The participants were asked to press a button upon hearing targets, that were considered 'attended' when followed by a button press. Only the 'attended' target tones were considered for further analysis. Alertness differences were controlled for by comparing the accuracies of the target responses.

The following three-step artifact rejection algorithm was applied to minimize electrooculographic and electromyographic contamination (Bachiller et al., 2015): (i) an independent component analysis (ICA) was performed to discard noisy ICA components; (ii) the signals were divided after ICA reconstruction into trials of 1 s (from 300 ms prior to the stimulus onset to 700 ms after); and (iii) the trials with amplitudes that exceeded an adaptive statistical-based threshold were automatically rejected (Núñez et al., 2017). The signals were band-pass filtered between 1 and 70 Hz, and a 50-Hz notch filter was utilized to remove the power line artifact.

#### 2.3.2. EEG-based brain graphs and connectivity strength calculation

In the construction of EEG-based brain graphs, network nodes are a mathematical representation of the EEG electrodes whereas the values of the network edges are calculated from the neural coupling between each pair of electrodes (Stam and van Straaten, 2012). This coupling can be estimated with different methods. Here, we selected the phase-locking value (PLV) across successive trials (Lachaux et al., 1999), which is sensitive to low-amplitude oscillatory EEG components (Spencer et al., 2003) in addition to nonlinearities (van Diessen et al., 2015).

The PLV, in turn, can be computed using different methodologies; we used the continuous wavelet transform (CWT) to compute the phase

**Table 1**
Sociodemographic, clinical, and cognitive data of the patient and control groups. Individual cognitive scores are summarized in the general cognitive factor (see text).

| | Schizophrenia patients | Bipolar patients | Healthy controls | Statistic (*p* value) |
|---|---|---|---|---|
| M:F ratio | 48:31 | 17:12 | 32:31 | $X^2 = 2.05$ ($p = 0.358$) |
| Age (years) | 35.66 (10.57) | 46.41 (10.45) * | 38.19 (10.14) | $F = 10.66$ ($p < 0.001$) |
| Illness duration (months) | 101.69 (116.10) | 182.22 (106.04) | N/A | $t = -2.95$ ($p = 0.004$) |
| Education (years) | 14.59 (3.64) | 13.10 (4.44) | 15.75 (1.48) | $F = 1.10$ ($p = 0.341$) |
| Parental education (yrs) | 12.11 (4.40) | 9.63 (3.29) | 9.75 (2.49) | $F = 1.81$ ($p = 0.177$) |
| Positive PANSS | 11.07 (3.62) | 7.37 (0.83) | N/A | $t = 7.70$ ($p < 0.001$) |
| Negative PANSS | 16.50 (7.26) | 9.05 (2.48) | N/A | $t = 7.17$ ($p < 0.001$) |
| Young mania | 0.83 (1.91) | 1.81 (1.34) | N/A | $t = 0.47$ ($p = 0.435$) |
| Hamilton depression | 5.87 (5.09) | 4.98 (3.81) | N/A | $t = 0.10$ ($p = 0.811$) |
| Verbal memory | 34.72 (13.44) ** | 36.00 (9.25) ** | 49.12 (8.37) | $F = 27.61$($p < 0.001$) |
| Working memory | 16.41 (4.73) ** | 17.58 (4.03) ** | 21.44 (3.37) | $F = 23.84$ ($p < 0.001$) |
| Motor speed | 59.05 (19.31) ** | 66.11 (13.67) | 73.91 (16.64) | $F = 10.88$ ($p < 0.001$) |
| Verbal fluency | 17.13 (7.10) ** | 19.79 (7.87) | 24.78 (9.88) | $F = 12.25$ ($p < 0.001$) |
| Processing speed | 41.94 (14.59) ** | 41.48 (12.40) ** | 64.93 (13.74) | $F = 45.82$ ($p < 0.001$) |
| Problem solving | 16.02 (4.36) | 15.95 (3.30) | 17.11 (3.25) | $F = 1.42$ ($p = 0.245$) |
| General cognitive factor | −0.84 (0.89) ** | −0.79 (0.69) ** | 0.31 (0.62) | $F = 35.92$ ($p < 0.001$) |
| Total IQ | 92.06 (14.73) ** | 98.32 (10.23) ** | 114.02 (11.44) | $F = 44.11$ ($p < 0.001$) |
| CPZ equivalents (mg/d) | 411.21 (377.28) | 157.40 (152.90) | N/A | $t = 3.35$ ($p = 0.001$) |
| P300 amplitude (μV) | 1.04 (0.61) | 1.23 (0.63) | 1.58 (0.76) | $F = 0.68$ ($p = 0.260$) |
| P300 latency (ms) | 423.22 (95.43) | 464.69 (96.11) | 458.54 (71.40) | $F = 0.59$ ($p = 0.371$) |

Results are displayed as the mean (SD); N/A = not applicable. Statistics for the between-groups comparisons (MANOVA or Chi tests) are shown in the right column (F (p) or $X^2$(p)) comparisons between patient groups are shown as t(p).

* $p < 0.01$ in the bipolar compared with the schizophrenia and control groups.

** Significance levels for post-hoc comparisons between patient groups and controls are shown when applicable ($p < 0.01$).

information from each trial (Bob et al., 2008) considering cones of influence to remove edge effects (Torrence et al., 1998).

Applying the CWT approach for the performance of filter and phase extraction in one operation, the PLV between two signals, $x(t)$ and $y(t)$, was obtained evaluating the variability of the phase difference across successive trials (Gomez-Pilar et al., 2018b; Lachaux et al., 1999):

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

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.

We generated functional connectivity matrices using the PLV values. Due to the fact that no threshold was applied, these connectivity matrices ranged between 0 and 1; 0 was obtained when two signals had no synchronization and 1 was obtained when two signals were perfectly synchronized.

We selected two windows from the EEG signal: (i) the pre-stimulus window, which corresponded to a period of expectation before the stimulus onset from −300 ms to the stimulus onset, thereby the pre-stimulus window is located during the task performance and is completely different from the resting state; and (ii) the response window, which is related to the P3b response (150 to 450 ms after the stimulus onset). This procedure was applied both for the EEG theta band (4–8 Hz) and the global band (1–70 Hz), in which higher values of pre-stimulus CS have been reported in previous studies in schizophrenia (Gomez-Pilar et al., 2018a, b).

Thus, adjacency matrices were computed for the pre-stimulus and the response windows. From these matrices, the connectivity strength was computed as follows:

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

where $w_{ij}$ refers to PLV between nodes $i$ and $j$, and $N$ is the total number of nodes of the network (Gomez-Pilar et al., 2018b). Finally, task-related CS modulation was defined as the change of the CS values between the pre-stimulus and the response windows (i.e., CS at the response minus CS at the pre-stimulus windows, which allowed us to measure the intra-individual change of this measure secondary to the cognitive task).

### 2.4. Statistical tests

We compared the age and sex distribution between the groups using an analysis of variance (ANOVA) and chi-square ($X^2$) tests, respectively. The normality of the distribution of the CS values in each group was tested using Kolmogorov-Smirnov tests. Treatment doses and illness duration were compared between the schizophrenia and bipolar groups using *t*-tests for independent samples.

We tested the primary hypothesis (i.e., the specificity of higher pre-stimulus CS values and the decreased task-related modulation) by comparing the pre-stimulus and the task-related modulation CS values in the global and theta band between the groups using a multivariate analysis of covariance (MANCOVA) with these CS values as the dependent variables and age as a covariate. This procedure was followed by the corresponding pairwise comparisons to determine which pairs showed significantly different values if a significant effect of group was found. Effect sizes were calculated using eta squared values.

Next, several analyses were performed to assess the effects of treatment and illness duration on the CS values that were altered in the patients, and the cognitive and clinical correlates of these alterations.

To assess the possible effects of treatment, we (i) calculated the Pearson's rho correlations between the current antipsychotic doses and the altered CS values, (ii) compared these values between the bipolar patients receiving and not receiving antipsychotics (because all schizophrenia patients were receiving antipsychotics), and (iii) compared these values between the patients receiving and not receiving lithium (bipolar patients only), BZD, anticonvulsants, or antidepressants. Given the small corresponding sample sizes, comparisons (ii) and (iii) were performed using Mann-Whitney *U* tests.

To test the effects of illness duration, we planned comparisons of the altered CS values between the chronic and FE schizophrenia patients with a t-test.

Finally, to test the possible relevance of these altered CS values in the patients, we used stepwise linear regression to assess the relations between these parameters and cognitive performance and positive and negative symptoms scores. As in previous studies (Gomez-Pilar et al., 2018a), we calculated an overall score that summarized cognition by introducing the individual cognitive scores of all subjects into a

principal component analysis and saved the factor scores for further analysis.

## 3. Results

There were no significant differences in the sex distribution between the groups. The bipolar patients were significantly older than the schizophrenia patients and healthy controls. The bipolar patients had received significantly smaller doses of antipsychotics and had longer duration of illness than the schizophrenia patients (Table 1).

The pre-stimulus and task-related modulation CS values in and the global and theta bands were normally distributed in each group.

The principal component analysis of the cognitive scores yielded a single factor for which all individual scores positively loaded, and this factor explained 55.40% of the variance (eigenvalue 3.34). The factor scores were saved. Compared with the healthy controls, the factor scores were significantly smaller in both groups of patients, which implied worse general cognitive performance (Table 1).

### 3.1. Comparison of CS values

#### 3.1.1. Between-group differences

The multivariate effect of group was significant (Wilk's $\lambda = 7.44$, df = 8.318, $p < 0.001$; eta squared = 0.158). The effect of age was not significant (Wilk's $\lambda = 0.81$, df = 4.159, $p = 0.52$; eta squared = 0.02).

The between-subject effect tests revealed significant effects of group for the global band pre-stimulus CS (type III sum of squares = 0.012, F = 3.30, df = 2, $p = 0.04$; eta squared = 0.04) and theta band CS task-related modulation (type III sum of squares = 0.037, F = 27.48, df = 2, $p < 0.0001$; eta squared = 0.25; Table 2, Fig. 1).

Pair-wise comparisons revealed higher global band pre-stimulus CS values in the schizophrenia patients compared with the controls (mean difference = 0.016; 95% CI = 0.002–0.031, $p = 0.027$) and the bipolar patients (mean difference = 0.020; 95% CI = 0.000–0.040, $p = 0.049$). The global band pre-stimulus CS values were not significantly different in the bipolar patients compared with the healthy controls (mean difference = −0.004; 95% CI = −0.024-0.016, $p = .70$). There were no significant between-group differences in the pre-stimulus CS in the theta band.

Compared with the controls, the theta band task-related CS modulation was significantly smaller in the schizophrenia patients (mean difference = −0.043; 95% CI = −0.055 to −0.031, $p < 0.001$) and bipolar patients (mean difference = −0.044; 95% CI = −0.061 to −0.027, $p < 0.001$).

Although unplanned, we explored the possible relation between the pre-stimulus global band CS and the theta-band CS modulation in the patients; the difference was significant ($r = -0.24$, $n = 108$, $p = 0.01$) and indicated that larger pre-stimulus CS values were associated with smaller increases in the theta band CS with the task response.

#### 3.1.2. Regional analysis

We also performed a regional analysis of the pre-stimulus and modulation CS values for both the theta band (Fig. 2) and the global band (Fig. 3). This regional analysis showed higher significant differences when comparing controls and schizophrenia patients than when comparing controls and bipolar patients.

In the theta band, the main differences in the pre-stimulus window were located in the right parieto-occipital and fronto-temporal regions when comparing the control and the schizophrenia groups (Fig. 2, first row); in the modulation window, the main differences were located in the central and frontal regions for the comparison between controls and both patient groups (Fig. 2, second row).

In the global band, the main differences in the pre-stimulus window were located in the parietal and left frontal when comparing controls and schizophrenia patients (Fig. 3, first row); in the modulation window, the main significant differences were found in the central region for the comparison between controls and both patient groups (Fig. 3, second row).

### 3.2. Treatment and illness duration effects

The correlations of antipsychotic dose with global band pre-stimulus CS ($r = 0.058$, $n = 94$, $p = 0.58$) and theta band CS modulation ($r = -0.05$, $p = 0.53$) were not statistically significant. Likewise, these correlations were non-significant in the schizophrenia (global band pre-stimulus CS: $r = -0.004$; theta CS modulation $r = -0.046$) nor in the bipolar patients (global band pre-stimulus CS: $r = -0.025$; theta CS modulation $r = -0.008$).

The global band pre-stimulus CS did not differ between the bipolar patients receiving and not receiving antipsychotics (U = 84, z = −0.19, $p = 0.86$; Fig. 4a) or between the bipolar patients receiving and not receiving lithium (U = 73, z = −0.37, $p = 0.73$). This parameter did not differ significantly between the patients receiving BZD (U = 481, z = 0.69, $p = 0.48$), anticonvulsants (U = 99, z = 0.28, $p = 0.79$), or antidepressants (U = 201, z = 0.83, $p = 0.40$). When considering only the schizophrenia patients, there were no significant differences in global band pre-stimulus CS between subjects receiving or not BZD (U = 84, z = −0.293, p = 0.79) or antidepressants (U = 60, z = −1.08, $p = 0.29$).

Similarly, the theta band CS modulation did not differ between the bipolar patients receiving and not receiving antipsychotics (U = 70, z = −0.88, $p = 0.37$; Fig. 4 b) or between the bipolar patients receiving and not receiving lithium (U = 55, z = −1.13, $p = 0.18$). This parameter did not significantly differ between the patients receiving BZD (U = 220, z = 1.32, $p = 0.19$), anticonvulsants (U = 84, z = −0.79, $p = 0.42$), or antidepressants (U = 190, z = −1.09, $p = 0.27$). When considering only the schizophrenia patients, there were no significant differences in theta band CS modulation between subjects receiving or not BZD (U = 61, z = −1.41, $p = 0.17$) or antidepressants (U = 59, z = −1.13, p = 0.27).

The difference in the global band pre-stimulus CS between the FE (mean = 0.32, sd = 0.06) and chronic schizophrenia patients (mean = 0.31, sd = 0.03) was not statistically significant ($t = 1.04$, p = 0.29). Similarly, these differences were also non-significant for the theta band CS modulation (chronic = 0.016, sd = 0.03; FE = 0.024, sd = 0.03; $t = 1.14$, $p = .25$).

**Table 2**
Connectivity strength (CS) values in the pre-stimulus window and the modulation of the CS in the global and theta bands. Modulation indicates the difference between the response and pre-stimulus windows during a P300 task (see text).

| | Schizophrenia patients | Bipolar patients | Healthy controls |
|---|---|---|---|
| CS pre-stimulus (global band) | 0.3136 (0.0438)* | 0.2963 (0.0337) | 0.2981 (0.0425) |
| CS pre-stimulus (theta band) | 0.3600 (0.0448) | 0.3486 (0.0397) | 0.3507 (0.0364) |
| CS modulation (global band) | −0.0003 (0.0084) | −0.0030 (0.0081) | 0.0005 (0.0124) |
| CS modulation (theta band) | 0.0195 (0.0298)*** | 0.0192 (0.0236)*** | 0.0636 (0.0467) |

Significant differences.
* $p < 0.05$ in the schizophrenia compared with the bipolar and control groups.
*** $p < 0.001$ in the schizophrenia and bipolar groups compared with the control group.

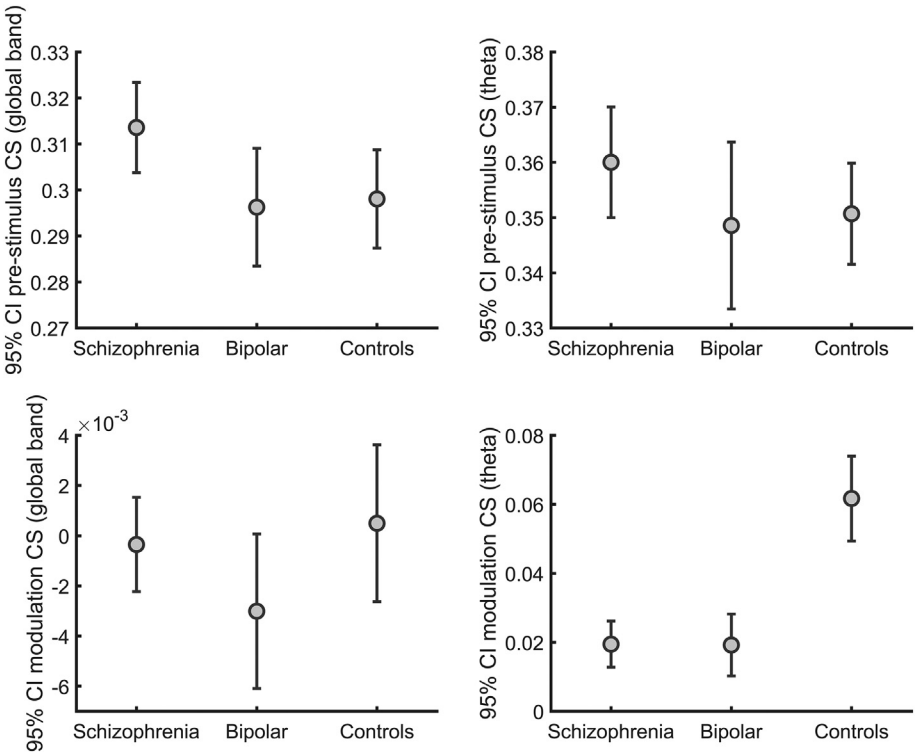


**Fig. 1.** Differences between groups in the pre-stimulus CS and its task-related modulation in the global band and theta bands.

### 3.3. Clinical and cognitive correlates

Multivariate linear regression selected the global band pre-stimulus CS as a significant predictor of general cognition in the schizophrenia patients ($R^2 = 0.137$, $F = 8.70$, $p = 0.005$). Thus, in this group, a higher global band CS in the pre-stimulus window was associated with worse cognitive performance (Fig. 5a). There were no significant predictors of general cognition in the bipolar group. For illustrative purposes, correlation coefficients were calculated between global band pre-stimulus CS and individual BACS domains in schizophrenia and bipolar patients (Table S1).

Moreover, linear regression selected the theta band CS modulation as a significant predictor of negative symptoms in the schizophrenia patients ($R^2 = 0.084$, $F = 6.23$, $p = 0.015$; Fig. 5b). Positive symptoms were not predicted in this group by the CS values. In the bipolar group, there were no significant associations of the CS values with the PANSS scores.

Illness duration and the HAM-D, and YMRS scores were uncorrelated with the global band pre-stimulus and theta band modulation CS in all cases.

## 4. Discussion

In this study, we found a higher global band pre-stimulus CS in schizophrenia patients compared with bipolar patients and healthy controls and a highly significant deficit of theta band CS modulation (i.e., a lesser increase with task performance of the CS in this band) in both the schizophrenia and bipolar patients. The larger global band pre-stimulus CS in schizophrenia was associated with worse cognitive performance, and lower theta band CS modulation was associated with negative symptoms. Antipsychotics and other treatments seemed to have no significant effect on this alteration, and age did not play a

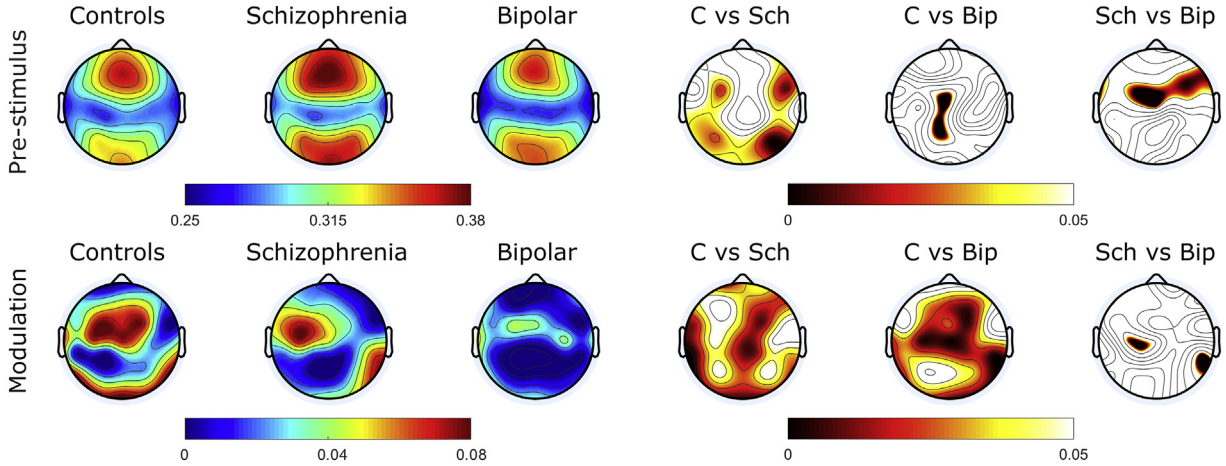


**Fig. 2.** Spatial distribution of the connectivity strength (CS) in the theta band for each electrode (i.e. node degree) for each group in the pre-stimulus and modulation windows (left), and the regional statistical differences between groups (right) (C: controls, Sch: schizophrenia patients, Bip: bipolar patients).

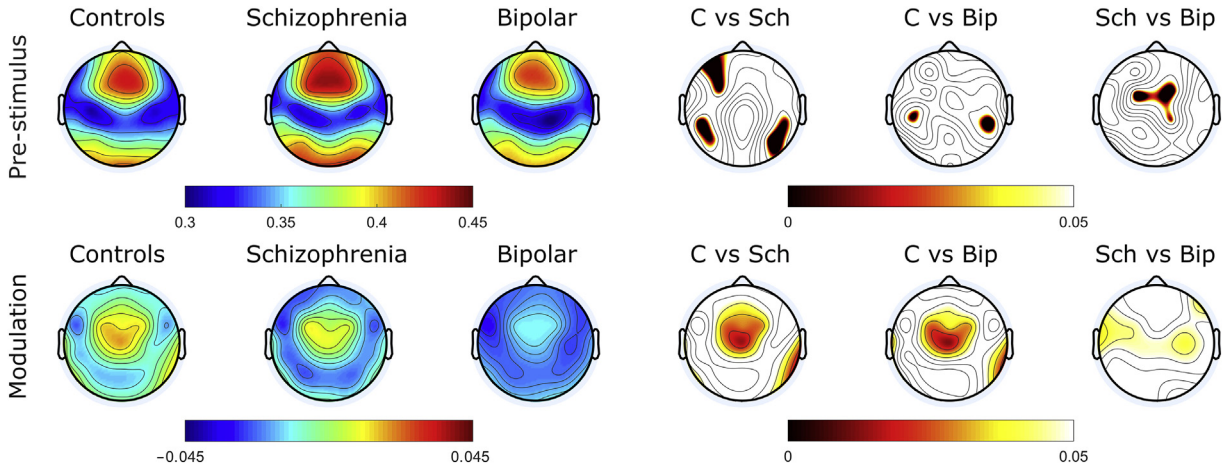


**Fig. 3.** Spatial distribution of the connectivity strength in the global band for each electrode (i.e. node degree) for each group in the pre-stimulus and modulation windows (left), and the regional statistical differences between groups (right) (C: controls, Sch: schizophrenia patients, Bip: bipolar patients).

major role in the CS differences between groups.

The abnormally high pre-stimulus CS found in this sample of schizophrenia patients is in line with previously reported findings with partially overlapping samples (Gomez-Pilar et al., 2018a, b). We were able to replicate the finding of larger global band pre-stimulus CS (Gomez-Pilar et al., 2018a) but were unable to replicate the finding in the theta band (Gomez-Pilar et al., 2018b). In addition, we have found that the higher global band pre-stimulus CS is not regional-dependent, but shows more widespread statistical significant differences when comparing the schizophrenia patients with controls. In this context, the present data suggest that a global band pre-stimulus CS increase may be specific to schizophrenia.

We calculated the CS from the phase-locking values (PLV) between sensors. Therefore, because neurons firing within a functional assembly synchronize their signal phases, the larger pre-stimulus CS in the schizophrenia patients (i.e., higher average PLV values among the sensors) suggests a hyper-synchronized state in this condition. The significant negative association between cognition and the pre-stimulus CS suggests that this potentially hyperactive basal state hampers cognitive processing. Correspondingly, the reduced increase in the theta band CS modulation implies a hypo-synchronization in this band with test performance.

The most remarkable differences between the patients and controls were those of the smaller theta band CS modulation, which were common to schizophrenia and bipolar patients and likely unrelated to pharmacological treatment. This smaller modulation may be interpreted as an overall smaller increase in theta activity in patients. This assertion agrees with previous results that have demonstrated a smaller modulation in media frequencies towards slower bands and a lower increase in the relative theta power during the same task in a different schizophrenia sample (Bachiller et al., 2014) (replicated in (Molina et al., 2018)).

We cannot discard a relation between these two alterations as suggested by their significant correlation in the patients; i.e., we cannot discount the possibility that a general hyper-synchronized brain activity during the pre-stimulus window could modify the expected response to the task in the patients. This pattern would be in line with proposals of a relevant role for the basal or resting state of the brain in the stimulus-induced patterns of cerebral activity (Northoff, 2018). Theta activity increases in normal conditions during odd-ball task performance (Başar-Eroglu and Demiralp, 2001); thus, basal hyperactivity may hamper the expected pattern of brain activation during P300 task performance. Theta oscillations play a role in the synchronization between relatively distant regions (von Stein et al., 2000), and the dominant frequency of a neuronal assembly is dependent on the number of participating neurons so that lower frequencies involve larger assembly sizes (Buzsaki and Draguhn, 2004). Moreover, slow-band oscillations may subtend cortico-cortical interactions (Devrim et al., 1999). In this context, our findings of a higher global band pre-stimulus CS and its reduced modulation in the theta band may imply a lower capacity for general signal integration in psychoses, which could be related to negative symptoms that might be influenced by the pre-stimulus state. Finally, the greater pre-stimulus CS in schizophrenia, which is coherent with a hyper-active basal state, may agree with the GABA-transmission deficit found in this disorder (Gonzalez-Burgos et al., 2011).

Our data were measures of the whole-brain network (i.e., the CS represents averaged individual nodal degrees). Nevertheless, our regional analysis supports the idea that some regions might have prominent roles in increasing the CS. For instance, the default mode network has been reported to exhibit a hyperactive basal state and a smaller task-related deactivation in schizophrenia patients compared with healthy controls (E. Pomarol-Clotet et al., 2008; Whitfield-Gabrieli et al., 2009), although similar findings have been reported in bipolar disorder (Edith Pomarol-Clotet et al., 2012). As shown in Fig. 2, the lower modulation in theta is not regional-dependent, whereas Fig. 3 shows that the lack of modulation in the global band is associated with the central and frontal brain regions, where the modulation deficit is also prominent in the theta band. This area overlaps with the default network area, thus our results would support a hyperactive state in this network that might hamper cognitive performance and task-related modulation of cerebral activity. However, care must be taken when comparing these results because our data in both the pre-stimulus and response windows were acquired during the performance of a task while the cited functional assessments of the default mode network were performed in the resting state.

In the schizophrenia group there was an increased global band pre-stimulus CS and a reduced theta band CS modulation, whereas in the bipolar group, only the latter was observed. This pattern might suggest a different substrate of this modulation deficit between these groups, which could be further investigated.

Our study has limitations, most of which are related to the lack of completely treatment-free patients and the small sample of bipolar patients. Since many patients were receiving different drugs at the same time, their potential interaction was not fully controlled. Moreover, conducting connectivity analyses on scalp signals could introduce bias in the results. Thus, we checked that connections with phase differences of 0 or 180 ( ± 1 degree) were < 1%. In addition, in order to minimize volume conduction effects, we followed a well-known strategy based on the assumption that volume conduction similarly affects the

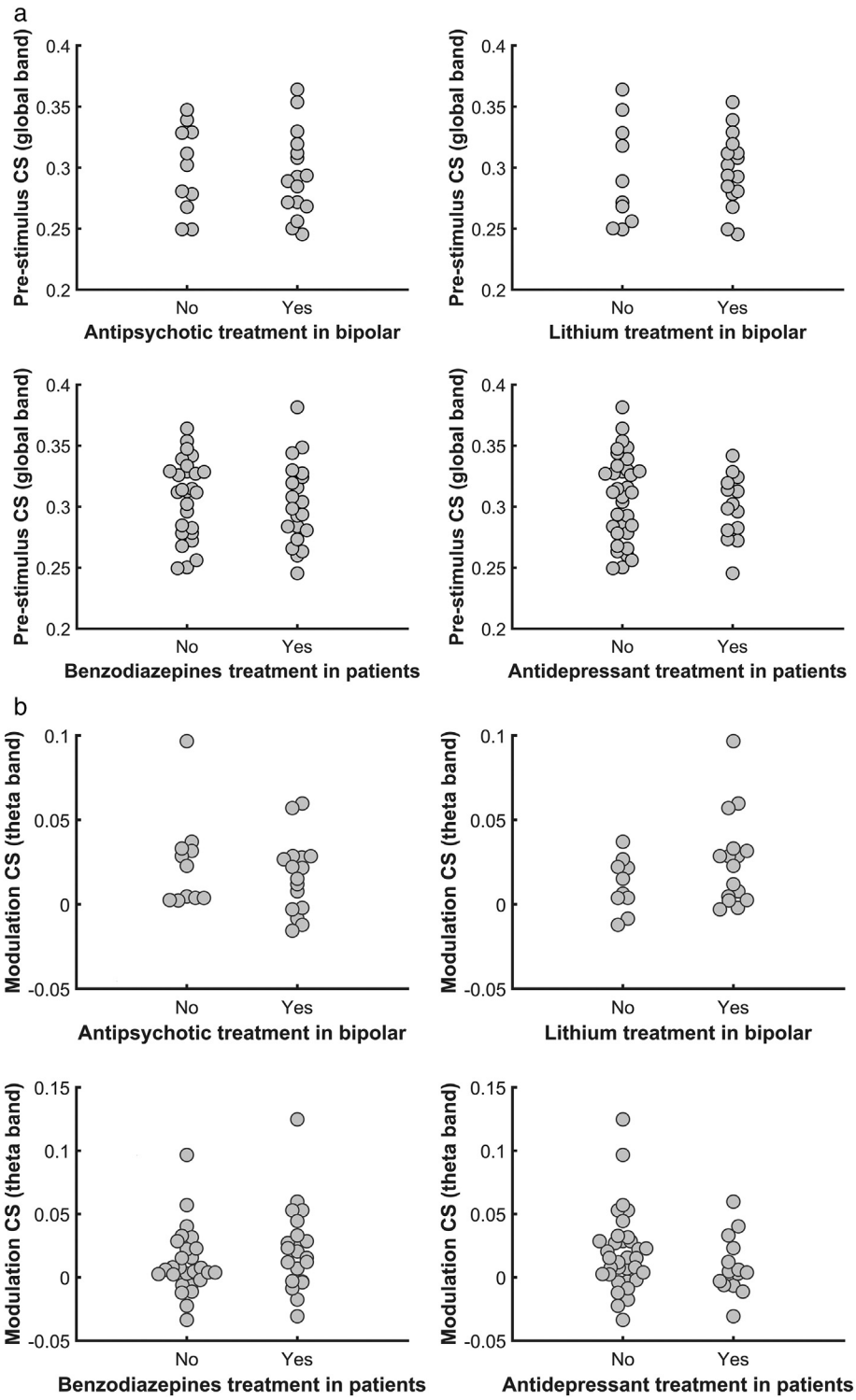


**Fig. 4.** (a) Individual distributions of the pre-stimulus CS in the global band in the bipolar patients receiving and not receiving antipsychotics and lithium (upper row) and the patients receiving or not receiving benzodiazepines and antidepressants (lower row). (b) Individual distributions of the theta band CS modulation in bipolar patients receiving or not receiving antipsychotics and lithium (upper row) and patients receiving or not receiving benzodiazepines and antidepressants (lower row).

connectivity estimates in two different experimental contrasts (Bastos and Schoffelen, 2016), so that spurious estimates can be effectively eliminated by comparing both conditions (Bastos and Schoffelen, 2016). Furthermore, source analyses would be appropriate to assess the possible roles of key regions in the overall differences. Finally, it would be of interest to assess the CS properties of the patients during the resting state (which might be different from the pre-stimulus window during task performance).

## 5. Conclusion

Connectivity strength in the functional brain network was higher in schizophrenia patients, and this difference was associated with cognitive deficits and negative symptoms. These findings may indicate a

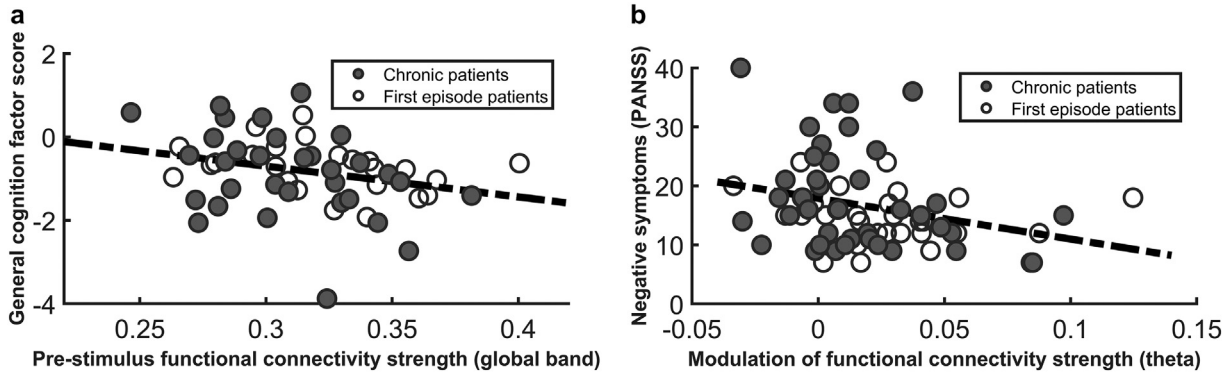


**Fig. 5.** Scatterplots representing (a) the association between the global-band pre-stimulus CS and the general cognition score in the schizophrenia patients, and (b) the association between the theta band task-related CS modulation and the PANSS negative symptom scores in the schizophrenia patients.

hyperactive synchronization among neural groups in schizophrenia that may hamper cognition.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2019.109801.

## Funding

This work has been supported by the following grants: the "Instituto de Salud Carlos III" (PI15/00299 and PI18/00178), the "Gerencia Regional de Salud de Castilla y León" (GRS 1485/A/17 and GRS 1721/A/18), and the "Consejería de Educación de la Junta de Castilla y León" (VA059U13 and VA057P17). P. Núñez was in receipt of a predoctoral scholarship 'Ayuda para contratos predoctorales para la Formación de Profesorado Universitario (FPU)' grant from the 'Ministerio de Educación, Cultura y Deporte' (FPU17/00850).

## Ethical statement for Progress in Neuro-Psychopharmacology & Biological Psychiatry

I testify on behalf of all co-authors that our article submitted to Progress in Neuro-Psychopharmacology & Biological Psychiatry:

- This material has not been published in whole or in part elsewhere;
- The manuscript is not currently being considered for publication in another journal;
- All authors have been personally and actively involved in substantive work leading to the manuscript, and will hold themselves jointly and individually responsible for its content.

## Declaration of Competing Interest

None.

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