

Title page

Text: 3742 words

Abstract: 172 words

Figures: 3

Table: 2

Functional EEG Network Analysis in Schizophrenia: Evidence of Larger Segregation and Deficit of Modulation

Short title: Network modulation deficit in Schizophrenia

Javier Gomez-Pilar¹, Alba Lubeiro², Jesús Poza^{1,3,4}, Roberto Hornero^{1,3,4}, Marta Ayuso⁵, César Valcárcel^{6,7}, Karim Haidar^{6,7}, José A. Blanco⁸, Vicente Molina^{4,8}

¹ Biomedical Engineering Group, Department TSCIT, ETS Ingenieros de Telecomunicación, University of Valladolid, Spain.

² Psychiatry Department, School of Medicine, University of Valladolid, Spain.

³ Instituto de Investigación en Matemática (IMUVA), University of Valladolid, Spain.

⁴ Neuroscience Institute of Castilla y León (INCYL), University of Salamanca, Spain.

⁵ Clinical Neurophysiology Service, University Hospital of Valladolid, Valladolid, Spain.

⁶ Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM).

⁷ Psychiatry Service, University Hospital of Alava, Spain.

⁸ Psychiatry Service, University Hospital of Valladolid, Valladolid, Spain.

*** Corresponding author**

Email: vicente.molina@uva.es

Tel: +34 983 423 200

Abstract

Background: Higher mental functions depend on global cerebral functional coordination. Fast modulation of functional networks in schizophrenia has not been previously assessed.

Methods: Graph-theory was used to analyze the electroencephalographic (EEG) activity during an odd-ball task in 57 schizophrenia patients (18 first episode patients, FEPs) and 59 healthy controls. Clustering coefficient (*CLC*), characteristic path length (*PL*) and small-worldness (*SW*) were computed at baseline ([-300 0] ms prior to stimulus delivery) and response ([150 450] ms post-stimulus) windows. Clinical and cognitive assessments were performed.

Results: *CLC*, *PL* and *SW* showed a significant modulation between baseline and response in controls but not in patients. Patients obtained higher *CLC* and *SW* at baseline, lower *CLC* and higher *PL* at response, and diminished modulation of *CLC* and *SW* as compared to controls. In patients, *CLC* and *SW* modulation were inversely associated to cognitive performance in executive tasks and directly associated to working memory. Similar patterns were observed in FEPs. *CLC* and *SW* during the baseline were inversely associated to their respective modulation magnitudes.

Conclusions: Our results are coherent with a hyper-segregated network at baseline (higher *CLC*) and a decreased modulation of the functional connectivity during cognition in schizophrenia.

Key words: Complex Network Theory, Schizophrenia, Electroencephalography, Evoked Response.

Significant outcomes

- A deficit in fast modulation of functional network properties (clustering coefficients, path-length and small-worldness) during an odd-ball task was found in schizophrenia patients.
- This deficit was also found in first-episode patients
- There was a significant association between network modulation deficits and cognition in the patients

Limitations

- Spatial resolution of EEG is low and cannot assess possible contributions of subcortical structures.
- The number of electrodes in our study.
- We did not perform source analyses.

Text

1. Introduction

Mental functions depend on global dynamic coordination of cerebral networks^{1,2}, whose characteristics can be assessed using methods derived from graph-theory. Previous studies in the normal brain revealed structural and functional small-world properties as an efficient way to balance local specialization and integration^{3, 4}. These network properties can be jointly summarized in the “small-worldness” parameter (SW), which is defined as the ratio between the global clustering coefficient (CLC) and the characteristic path length (PL) of the network. In a binary network, local CLC is the ratio between the number of triangles in which a given node participates and the maximum possible number of triangles including that node. This measure, averaged across the nodes of the entire network, can be used as an indicator of the network segregation and of local efficiency of information transfer, probably related to specialization. PL is the average of shortest distances for all possible pairs of nodes. It is usually interpreted as a metric of information integration across areas. Both parameters are of interest in the study of schizophrenia, given the abnormal integration of cerebral networks observed in this psychiatric disorder⁵⁻⁸.

Quickly evolving patterns of interaction (in the order of hundreds of milliseconds) are likely to underlie cognitive function in real time^{9,10}. Considering such rapid modulation of cortical activity^{1,11}, the high temporal resolution of electroencephalography (EEG) and magnetoencephalography (MEG), combined with a complex network analysis, can be useful for assessing global connectivity dynamics in normal and altered cognition. In healthy subjects, a MEG study showed that the cognitive effort drives normal brain networks to a less clustered configuration and more long-range synchronization¹². Using the EEG we observed in healthy subjects a significant SW increase from baseline (-300 to 0 ms prior to stimulus onset) to response (150 to 450 ms post-stimulus) windows during an odd-ball task¹³.

However, most EEG or MEG network analyses published in schizophrenia did not take into account that temporal dynamics or compared parameters during different tasks.

Using resting EEG, lower *CLC* and shorter *PL* were reported in schizophrenia¹⁴. Also, a lower *SW* index was reported in 20 chronic patients at rest, whereas decreased *CLC* and increased *PL* values were appreciated during a working memory test¹⁵. More recently, globally reduced segregation and integration were described in 34 schizophrenia patients during an odd-ball task¹⁶, without discriminating between windows in the task. In a functional magnetic resonance (fMRI) study, a lower *SW* index in schizophrenia patients when compared to controls was reported both at rest and during an odd-ball task¹⁷. Shorter *PL* values during task performance were also observed in 20 schizophrenia patients performing a contextual paradigm {Fogelson, 2013 #6983}.

Thus, deficits in the fast modulation of network properties might be found in to schizophrenia. In particular, our working hypotheses were that (i) patients would exhibit altered modulation of functional network properties with cognitive activity across the brain; and (ii) such modulation would correlate with patient's symptoms and/or cognitive performance. We analyzed stimulus-evoked oscillations given its association with "top-down" cognitive processing¹⁸.

Aims of the study: To assess the fast dynamic modulation of brain network properties during a cognitive task in schizophrenia, not addressed in previous studies, using network parameters summarizing segregation and integration of this network.

2. Materials and Methods

2.1. Participants

Fifty-nine healthy controls and 57 schizophrenia patients (39 chronic and 18 first-episode (FE) patients) with normal hearing were included in the study. Exclusion criteria were: (i) any neurological illness; (ii) history of cranial trauma with loss of consciousness longer than one minute; (iii) past or present substance abuse, except nicotine or caffeine (iv) total intelligence quotient (IQ) smaller than 70; and (iv) for patients, presence of any other psychiatric process, and (v) for controls, any current psychiatric or neurological diagnosis or treatment.

Patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. They were on antipsychotic monotherapy. Chronic patients received stable doses of atypical antipsychotics. FEP only received antipsychotics for less

than 72 hours prior to EEG acquisition followed by a wash-out period of 24 hours. Hence, the possible bias due to the selection of acutely ill patients able to cooperate during EEG acquisition without any prior treatment was avoided. Symptoms were scored using the Positive and Negative Syndrome Scale (PANSS)¹⁹. Healthy controls were recruited through newspaper advertisements. Demographic and clinical characteristics are shown in Table 1.

Cognitive data from patients and controls were collected using: the Wechsler Adult Intelligence Scale, WAIS-III (IQ); the Trail-Making Test, TMT ((time part B – time part A)/time part A); the Wisconsin Card Sorting Test (WCST; completed categories and percentage of perseverative errors); and the Spanish version of the Brief Assessment in Cognition in Schizophrenia Scale (BACS)²⁰.

Written informed consent was obtained from all participants after full printed information. The ethical committees of the participating hospitals approved the study.

2.2. Electroencephalographic recordings

EEG data were recorded using a 17-channel EEG system (BrainVision®, Brain Products GmbH). Active electrodes were placed in an elastic cap at Fp1, Fp2, F3, F4, F7, F8, C3, C4, P3, P4, O1, O2, T5, T6, Fz, Pz and Cz (international 10–20 system). Impedance was kept under 5 kΩ. Thirteen minutes of eyes-closed EEG was obtained during an auditory odd-ball 3-stimulus paradigm, which consisted of 600 random sequences of target (500 Hz-tone, probability 0.2), distractor (1000 Hz-tone, probability 0.2), and standard (2000 Hz-tone, probability 0.6) tones. The tone duration was 50 ms, rise and fall time being 5 ms and intensity being 90 dB. Inter-stimulus interval between tones randomly jittered between 1.16 and 1.44 s. The participants were asked to press a button whenever they detected the target tones. Target tones were considered ‘attended tones’ when they were followed by a button press. Only ‘attended’ target tones were taken into account for further analysis²¹. Alertness differences across groups were controlled by comparing accuracy of target responses.

EEG signals were recorded using a sampling frequency of 500 Hz and referenced over Cz electrode. EEG recordings were subsequently re-referenced to the average activity of all

sensors in order to minimize the effect of microsaccadic artifacts²². Data were filtered using a finite impulse response (FIR) band-pass filter (1–70 Hz, Hamming window) and a notch filter to remove the power line frequency interference (50 Hz, Butterworth filter). Artifact rejection was conducted following a three-step approach^{21, 23}. Firstly, an independent component analysis (ICA) was carried out to decompose each EEG recording into a total of 17 components²⁴. After a visual inspection of the scalp maps and the temporal activation, components related to eye-blinks and muscle artifacts were discarded. Secondly, continuous EEG data were segmented into 1s-length trials ranging from -300 ms before target stimulus onset to 700 ms after onset. Thirdly, trials with artifacts were automatically rejected if their amplitude exceeded a statistical-based local adaptive threshold²³.

2.3 Signal similarity across sensors: Event-Related Coherence

Continuous wavelet transform (CWT) was computed to obtain a time-frequency representation of EEG recordings. Complex Morlet wavelet was used because it provides a biologically plausible fit to the signal being modeled²⁶. The scaling factor was set to include frequencies from 1 to 70 Hz^{21,23,27}. Thus, 1s-length evoked responses ([-300 - 700] ms) were decomposed using CWT into two windows: (i) baseline ([-300 0] ms to stimulus onset); and (ii) response ([150 450] ms after stimulus onset)^{21,23}. These windows were chosen to summarize the underlying temporal dynamics between resting (inter-stimulus) and the cognitive processing (centered around the usual P300 peak) windows. We previously showed a significant modulation of graph parameters between these windows in healthy subjects¹³. It is noteworthy that edge effects are not negligible, since EEG trials are finite and short-time recordings. Hence, two cones of influence (COIs) were defined around baseline and response windows to avoid border distortion²⁸.

From CWT decomposition, event-related Coherence (*ERC*) was computed to assess linear functional interactions²⁹. *ERC* is useful to identify coherent activity between cognitive networks [Yener and Başar 2012], since it is a measure of the degree of coordination between assemblies of neurons triggered by a cognitive task [Başar et al. 2015] In this study, *ERC* was calculated for each pair of electrodes and its values were averaged in the 4-70 Hz frequency band to obtain a global similarity measure for each

time window. Changes in *ERC* between resting and active windows allowed the assessment of task-related modulation in graph parameters for each group. Since we had no a priori hypothesis regarding modulation deficits in any particular band, network analyses were performed in the whole frequency band to avoid an inflation of the number of comparisons.

Further description of CWT and *ERC* is detailed in the Supplementary Material.

2.5 Graph parameters

In order to model a system as a graph, nodes should represent the dynamical units and their links should be the interactions between them³⁰. Thereby, the brain can be assimilated to a complex network with functional connectivity units that can be altered due to a pathological process³¹. The linear interaction between the neural activity in different cerebral regions can be used to represent the brain as a graph. Each electrode would correspond to a vertex (or node) and the relationships between electrodes would be the links (or edges) between them. In the present study, we used *ERC* to set the weights of the links. *ERC* could be useful in patients with cognitive impairment, such as schizophrenia, to study whether sensory and cognitive networks are manifested in topologically different places and in different frequency windows [Yener y Basar 2012]. Completely filled *ERC* matrices were then used as adjacency matrices. Hence, the generated fully connected network was composed of $N=17$ nodes, corresponding to the electrodes, and network weights set by the *ERC* values between electrodes.

Networks can be described by several parameters. The present study focused on two complementary features of the brain network: segregation and integration, together with their fast modulation during a cognitive task. In order to characterize the segregation of the network, we computed *CLC*³². In the case of weighted networks, *CLC* has been generalized as follows in order to avoid the influence of the mean edge weight:

$$CLC = \binom{N}{3} \sum_{i \in n, j, h \in n} (w_{ij}^b w_{ih}^b w_{jh}^b)^{\frac{1}{3}}, \quad (1)$$

where w_{xy} denotes the edge weight between electrodes i and j .

To quantify the integration of the network, we computed *PL*. It is defined as the average shortest path length between all pairs of nodes in the network³²:

$$PL = \frac{1}{N} \sum_{i \in n} \frac{\sum_{j \in n, j \neq i} d_{ij}}{n-1}, \quad (2)$$

where d_{ij} indicates the minimum distance (i.e. the inverse of *ERC*) between electrodes i and j . It is noteworthy that the previous definition takes into account that some of the paths with minimum distance can be formed of multiple edges.

To facilitate the comparison with previous research, the balance between *CLC* and *PL* was computed. This ratio (known as *SW*) is useful to assess the small-world properties of the network. Small-world networks are defined as those significantly more clustered than random networks, yet have approximately the same *PL* as random networks³². *SW* index is defined as the ratio between segregation and integration, where *CLC* and *PL* have been normalized in order to eliminate the dependence on basic parameters of the network, such as network size, or density³³:

$$\gamma = \frac{CLC}{\langle CLC \rangle_{random}}, \quad (3)$$

$$\lambda = \frac{PL}{\langle PL \rangle_{random}}, \quad (4)$$

$$SW = \frac{\gamma}{\lambda}, \quad (5)$$

where $\langle CLC \rangle_{random}$ and $\langle PL \rangle_{random}$ denote *CLC* and *PL* averaged over an ensemble of 50 surrogate networks, which were computed from a randomization of the original network by reshuffling its connections³³.

2.6 Parameter baseline correction (modulation)

The baseline correction process was applied to achieve a stimulus-independent characterization²³ and to quantify the dynamical changes during the evoked response (i.e. modulation). Network parameters were computed for each temporal window (baseline and response), providing meaningful information about the temporal evolution of network properties²³. Modulation in each parameter (P^c) was assessed as the result of the following baseline correction procedure:

$$P^C = P^{RES} - P^{BL}, \quad P = \{\gamma, \lambda, SW\}, \quad (6)$$

where P^{BL} and P^{RES} represent the parameter averaged for the baseline and the response windows. Negative or positive values indicate decreases or increases from baseline to response, respectively.

Figure 1 summarizes the whole signal processing procedure carried out in the study.

2.7. Statistical analyses

After testing normality and homoscedasticity of the distribution of network parameters, the following analyses were performed:

- i. Network parameters at baseline and response windows were compared between groups using a multivariate analysis of covariance ('group' as fixed factor, and 'sex' and 'age' as covariates) with Bonferroni correction. Using a similar multivariate analysis of covariance, modulation of network parameters (γ , λ and SW changes between baseline and response windows) were compared between groups. Effect sizes were assessed using Cohen's d when statistically significant differences were found. This was followed by univariate within-group analyses of network parameters using paired t -tests (significance level: $\alpha=0.009$).
- ii. The statistical significance of possible associations between baseline network parameters and the corresponding modulation values in patients, (only where significant between-group differences in modulation were detected) was assessed using Pearson correlation. In order to discard a major role for long-term treatment and chronicity, these and the previous analyses were repeated only for FEP.
- iii. We also assessed the significance of the association between modulation of network parameters (only those that showed significant between-group differences) and clinical and cognitive data. Spearman's correlation was used, since cognitive data distribution did not meet parametric assumptions.
- iv. Finally, spatial analyses of the network changes (within- and between-group comparisons) were performed using nodal CLC .

3. Results

3.1. Between- and within group differences in network parameters

3.1.1 Between-groups differences at baseline and response windows

There was a significant multivariate effect for 'group' (Wilk's lambda=0.87; $F=2.24$; $df=6,109$; $p=0.045$) but not for 'age' or 'sex'. The inter-subject effects tests (Table 2) revealed statistically significant differences for SW and γ at baseline (with larger values in patients) and γ and λ at response (smaller γ and larger λ in patients). There were no statistically significant differences between FEP and chronic patients in mean network parameters

3.1.2 Between- and within-group differences in network modulation

There was a significant multivariate effect for 'group' but not for 'age' or 'sex' on mean network modulation (Wilk's lambda=0.98; $F=3.64$; $df=3,112$; $p=0.040$). The inter-subject effects tests revealed statistically significant differences with moderate effect sizes for γ^c , λ^c and SW^c (smaller values in patients; Table 2).

Controls showed statistically significantly positive changes for γ^c (i.e. a statistically significant increase from baseline to response windows) ($t=3.38$, $df=58$, $p=0.001$), λ^c ($t=2.84$, $df=58$, $p=0.006$) and SW^c ($t=3.27$, $df=58$, $p=0.002$). In patients, non-significant changes were observed for γ^c ($t=-0.96$, $df=56$, $p=0.340$), λ^c ($t=0.74$, $df=56$, $p=0.460$) and SW^c ($t=-0.34$, $df=56$, $p=0.700$). FEP showed similar deficits of modulation in γ^c ($t=-0.85$, $df=17$, $p=0.410$), λ^c ($t=-1.07$, $df=17$, $p=0.30$) and SW^c ($t=0.37$, $df=17$, $p=0.720$) (Table 2).

3.2. Association between baseline parameters and modulation

In patients, baseline parameters were negatively associated with the corresponding γ^c (all patients $r=-0.569$, $p<0.0001$; FEP $r=-0.535$, $p=0.022$), λ^c (all patients $r=-0.602$, $p<0.0001$; FEP $r=-0.821$, $p<0.001$) and SW^c (all patients $r=-0.525$, $n=57$, $p<0.0001$; FEP $r=-0.647$, $n=18$, $p=0.004$). Therefore, higher values at baseline were associated with smaller task-related modulation of the corresponding network parameter (Fig. 2).

3.3. Association between network modulation and cognitive performance

In patients, γ^c was inversely associated to completed categories (all patients: $\rho=-0.348$, $p=0.015$; FEP $\rho=-0.325$, $p=0.219$) and directly to the percent of perseverative errors in WCST (all patients: $\rho=0.316$, $p=0.029$; FE: $\rho=0.022$, $p>0.05$). SW^c was inversely associated to performance in the Tower of London test (all patients: $\rho=-0.338$, $p=0.004$; FEP $\rho=-0.382$, $p=0.118$) and completed categories in WCST (all patients: $\rho=-0.373$, $p=0.009$; FE: $\rho=-0.389$, $p=0.0136$). Consequently, higher increases in SW and γ^c from baseline to response can be related to a poorer performance in schizophrenia patients, although this was not confirmed in the FEP subgroup (Fig. 2).

γ^c was inversely related to normalized scores in TMT (all patients; $\rho=-0.298$, $p=0.044$; FE: $\rho=-0.512$, $p=0.043$), suggesting a direct association with working memory performance (Fig. 2).

In controls, no significant associations were found for network modulation or cognitive performance.

There was no association between symptom scores and network modulation.

3.. Spatial analyses

Controls showed bilateral frontal and right temporoparietal γ increases from baseline to the response window, γ not found in patients. Patients showed a statistically significantly lower widespread γ value during the response window (Fig. 3).

4. Discussion

In our study, a modulation deficit in all network parameters was found in schizophrenia patients during a P300 task. Moreover, CLC and SW values were higher at baseline and lower in response windows, whereas PL was higher in the response window for patients during the task. In this group, an inverse relationship between positive modulation of CLC and SW and performance in executive function tests was found.

Previous evidences in humans² and animals¹¹ showed that rapid and transient modulation of coherence and functional integration play a role in cognition, which may be hampered in schizophrenia patients according to the present data. Our analyses

support the notion that schizophrenia can be associated with a deficit to reconfigure the brain network during a cognitive task. The particular brain sources driving such deficit may be further explored.

The larger baseline *CLC* in patients may reflect more segregated cortical activity in comparison to controls prior to stimulus onset. Previous results on clustering in schizophrenia using graph analyses are discrepant. In the resting state, a larger clustering was observed with fMRI in 19 schizophrenia patients³⁴, as well as non-significant differences in clustering using MEG³⁵. By means of EEG, a reduced clustering was seen in 34 schizophrenia patients performing an odd-ball task¹⁶ and in 40 patients looking at a stationary dot¹⁴. Ma et al¹⁷ reported with fMRI a reduced clustering in schizophrenia both at rest and during an odd-ball task, with shorter path length at rest but longer during the task. Our findings support the notion that both increased (larger *CLC* values during the baseline) and reduced (smaller *CLC* values during the response) clustering may be found in schizophrenia patients at different temporal points depending on the time of cognitive processing. This result could correspond to respectively increased and decreased functional segregation in patients during baseline and response windows.

The temporal resolution of fMRI would not allow discriminating between resting and active windows as defined in the present study. This may contribute to the discrepancies with previous reports of reduced clustering in schizophrenia using fMRI³⁶. However, information from fMRI studies may help to explain the reconfiguration deficit observed in our study. Fewer hubs (i.e. highly connected nodes) have been reported with fMRI in schizophrenia in the resting state³⁷ and during an odd-ball task¹⁷, along with a significant randomization of global network metrics³⁷. Such reduction in the number of highly connected nodes may explain the network reconfiguration deficit and the larger *PL* in the response window in our patients. Likewise, it would be also coherent with the less globally coordinated mode of brain connectivity in schizophrenia, reported with fMRI³⁶.

Additional increases of *CLC* over baseline levels predicted worse performance on executive tasks in patients but not in controls. This result indicates that a larger basal (i.e. pre-stimulus) segregation hinders cognition in schizophrenia. Thus, larger increases

in clustering above a hyper-segregated basal state could hamper the more complex cognitive capacities, for which a larger integration of cortical activity among distant brain regions is needed^{1,2}. Hypothetically, this might be related to the fewer number or strength of hubs, which could hamper cortical integration. Cognitive demands of the P300 task are low, but more demanding tasks drive the transitory formation of long-range integrative networks¹². However, *CLC* modulation was directly related to working memory. Therefore, larger segregation could provide some advantage for working memory performance when network modularity was more important than integration. In a previous fMRI study modularity, but not *SW*, predicted working memory performance³⁸.

Patients also showed larger *PL* values in the response window, which might result from the structural long-range connectivity deficits reported in schizophrenia³⁹. Such deficits in network integration might also conceivably contribute to the deficit of modulation in functional clustering.

The investigation of baseline hyper-clustering in patients is beyond our research, but speculatively might be related to inhibitory deficits in schizophrenia^{40, 41}. *CLC* quantifies the linear similarity degree between the neighbors of each node and most short-range cortico-cortical⁴² and recurrent⁴³ connections are excitatory. As a consequence, inhibitory cortical deficits might drive a basal hyper-synchronization secondary to mutual excitation among pyramidal neurons, which could be reflected in larger local phase and power coupling (and therefore in larger *CLC* values). This possibility seems consistent with previous EEG studies in schizophrenia that showed an increased neural noise (i.e. the amount of spontaneous, non-task evoked EEG power)⁴⁴⁻⁴⁷. In this context, spontaneous neural activity is not stochastic noise, but rather exhibits patterns largely conditioning by evoked responses⁵².

Husserl's phenomenology (and Aristotle's "koine aesthesis" *κοινὴ αἰσθησις*) proposes the "synthesis" of multiple mental processes as the basis of conscious experience. Conscious and subliminal perception seem to be different by a larger extension of synchronization in the former¹. Therefore, a dysfunction in that integrative process (suggested in our cases by the larger basal *CLC* and the modulation deficits in *CLC* and

PL) may disturb the conscious experience in patients with schizophrenia. The neural representation of internal and external events may be based on the transitory conformation of distributed synaptic assemblies⁵³. Thus, network deficits, such as those found in our study, might contribute to schizophrenia. This possibility seems to be in line with phenomenological accounts, such as “disturbed ipseity”, one of whose facets is hyper-reflexivity. It is defined as “exaggerated self-consciousness, a tendency to objectifying attention towards processes and phenomena that would normally be ‘inhabited’ or experienced as part of oneself”⁵⁴. An excess of functional segregation accompanied by a deficit in network modulation might be compatible with increased consciousness of these phenomena. Cortical hyper-segregation may hamper an adequate phenomenological integration of elements of mental life, leading to misinterpretation or hindered cognition.

Our study has strengths and limitations. The sample size is larger than previous network studies. Furthermore, this is the first study that assesses fast network modulation during cognitive activity in schizophrenia. However, EEG recordings are hampered by the shared variance among contiguous sensors, though the comparison of different conditions may help to overcome this problem. In addition, our analyses are based on low-density EEG recordings; nonetheless, functional characteristics of dynamic brain networks can be explored using low-density EEG recordings⁵⁵. Larger *CLC* at baseline in patients may reflect a more segregated brain (i.e. diffuse hyperconnectivity). Measures of network segregation may help to elucidate these possibilities by balancing the density between intra- and inter-module connections⁵⁶. Finally, EEG activity was recorded with eyes closed. Thereby, a larger contribution of alpha rhythms can be expected, but this should not have influenced the results on modulation between windows.

In conclusion, our findings support a relevant decrease in the ability to integrate cortical networks in schizophrenia, which may be based on a hyper-segregated basal state and a deficit of network modulation during cognitive activity.

Acknowledgements

This work was supported by the Instituto Carlos III (PI11/02708, PI11/02203 and PI15/00299) and the Gerencia Regional de Salud de Castilla y León (GRS 932/A/14 and GRS 1134/A/15) grants; the 'MINECO and FEDER (TEC2014-53196-R), 'Consejería de Educación de la Junta de Castilla y León' (VA037U16); and predoctoral fellowships to A. Lubeiro ('Consejería de Educación Junta de Castilla y León') and to J. Gomez-Pilar (University of Valladolid).

Financial disclosures

None.

References

1. Dehaene S, Changeux JP. Experimental and theoretical approaches to conscious processing. *Neuron* Apr 28 2011;70(2):200-227.
2. Varela F, Lachaux JP, Rodriguez E, Martinerie J. The brainweb: phase synchronization and large-scale integration. *Nat Rev Neurosci* Apr 2001;2(4):229-239.
3. Sporns O, Chialvo DR, Kaiser M, Hilgetag CC. Organization, development and function of complex brain networks. *Trends Cogn Sci* Sep 2004;8(9):418-425.
4. Latora V, Marchiori M. Efficient behavior of small-world networks. *Phys Rev Lett* Nov 5 2001;87(19):198701.
5. Friston KJ. The disconnection hypothesis. *Schizophr Res* Mar 10 1998;30(2):115-125.
6. Kaufmann T, Skatun KC, Alnaes D, et al. Disintegration of Sensorimotor Brain Networks in Schizophrenia. *Schizophr Bull* Nov 2015;41(6):1326-1335.
7. Touskova T, Bob P. Consciousness, awareness of insight and neural mechanisms of schizophrenia. *Rev Neurosci* 2015;26(3):295-304.
8. de Jong JJ, de Gelder B, Hodiament PP. Sensory processing, neurocognition, and social cognition in schizophrenia: towards a cohesive cognitive model. *Schizophr Res* May 2013;146(1-3):209-216.
9. Bressler SL, Tognoli E. Operational principles of neurocognitive networks. *Int J Psychophysiol* May 2006;60(2):139-148.
10. Sporns O. Networks for Cognition. *Networks of the Brain*. Cambridge, Massachusetts: MIT Press; 2011:182.
11. Bressler SL, Coppola R, Nakamura R. Episodic multiregional cortical coherence at multiple frequencies during visual task performance. *Nature* Nov 11 1993;366(6451):153-156.
12. Kitzbichler MG, Henson RN, Smith ML, Nathan PJ, Bullmore ET. Cognitive effort drives workspace configuration of human brain functional networks. *J Neurosci* Jun 1 2011;31(22):8259-8270.
13. Martín-Santiago O, Gomez-Pilar J, Lubeiro A, et al. Modulation of brain network parameters associated with subclinical psychotic symptoms. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* in press.
14. Rubinov M, Knock SA, Stam CJ, Micheloyannis S, Harris AW, Williams LM, Breakspear M. Small-world properties of nonlinear brain activity in schizophrenia. *Hum Brain Mapp* Feb 2009;30(2):403-416.
15. Micheloyannis S, Pachou E, Stam CJ, Breakspear M, Bitsios P, Vourkas M, Erimaki S, Zervakis M. Small-world networks and disturbed functional connectivity in schizophrenia. *Schizophr Res* Oct 2006;87(1-3):60-66.

16. Shim M, Kim DW, Lee SH, Im CH. Disruptions in small-world cortical functional connectivity network during an auditory oddball paradigm task in patients with schizophrenia. *Schizophr Res* Jul 2014;156(2-3):197-203.
17. Ma S, Calhoun VD, Eichele T, Du W, Adali T. Modulations of functional connectivity in the healthy and schizophrenia groups during task and rest. *Neuroimage* Sep 2012;62(3):1694-1704.
18. Makeig S, Debener S, Onton J, Delorme A. Mining event-related brain dynamics. *Trends Cogn Sci* May 2004;8(5):204-210.
19. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13(2):261-276.
20. Segarra N, Bernardo M, Gutierrez F, et al. Spanish validation of the Brief Assessment in Cognition in Schizophrenia (BACS) in patients with schizophrenia and healthy controls. *Eur Psychiatry* Mar 2011;26(2):69-73.
21. Gomez-Pilar J, Poza J, Bachiller A, Gómez C, Molina V, Hornero R. Neural Network Reorganization Analysis During an Auditory Oddball Task in Schizophrenia Using Wavelet Entropy. *Entropy* 2015;17:5241-5256.
22. Bledowski C, Prvulovic D, Hoechstetter K, Scherg M, Wibral M, Goebel R, Linden DE. Localizing P300 generators in visual target and distractor processing: a combined event-related potential and functional magnetic resonance imaging study. *J Neurosci* Oct 20 2004;24(42):9353-9360.
23. Bachiller A, Poza J, Gomez C, Molina V, Suazo V, Hornero R. A comparative study of event-related coupling patterns during an auditory oddball task in schizophrenia. *J Neural Eng* Feb 2015;12(1):016007.
24. Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods* Mar 15 2004;134(1):9-21.
25. Blanco S, García H, Quiroga R, L. R, O.A. R. Stationarity of the EEG series. *IEEE Eng Med Biol Mag* 1995;14:395-399.
26. Roach BJ, Mathalon DH. Event-related EEG time-frequency analysis: an overview of measures and an analysis of early gamma band phase locking in schizophrenia. *Schizophr Bull* Sep 2008;34(5):907-926.
27. Tallon-Baudry C, Bertrand O, Delpuech C, Pernier J. Stimulus specificity of phase-locked and non-phase-locked 40 Hz visual responses in human. *J Neurosci* Jul 1 1996;16(13):4240-4249.
28. Torrence C, Compo G. A practical guide to wavelet analysis. *Bulletin of the American Meteorological Society* 1998;79:61-78.
29. Nunez PL, Srinivasan R, Westdorp AF, Wijesinghe RS, Tucker DM, Silberstein RB, Cadusch PJ. EEG coherency. I: Statistics, reference electrode, volume conduction, Laplacians, cortical imaging, and interpretation at multiple scales. *Electroencephalogr Clin Neurophysiol* Nov 1997;103(5):499-515.

30. Boccaletti S, Latora V, Moreno Y, Chavez M, Hwang DU. Complex networks: Structure and dynamics. *Physics Reports*, . *Physics Reports* 2006;424:175-308.
31. Stam CJ, van Straaten EC. The organization of physiological brain networks. *Clin Neurophysiol* Jun 2012;123(6):1067-1087.
32. Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. *Neuroimage* Sep 2010;52(3):1059-1069.
33. Stam CJ, de Haan W, Daffertshofer A, et al. Graph theoretical analysis of magnetoencephalographic functional connectivity in Alzheimer's disease. *Brain* Jan 2009;132(Pt 1):213-224.
34. Yu Q, Sui J, Rachakonda S, He H, Gruner W, Pearlson G, Kiehl KA, Calhoun VD. Altered topological properties of functional network connectivity in schizophrenia during resting state: a small-world brain network study. *PLoS One* 2011;6(9):e25423.
35. Rutter L, Nadar SR, Holroyd T, Carver FW, Apud J, Weinberger DR, Coppola R. Graph theoretical analysis of resting magnetoencephalographic functional connectivity networks. *Front Comput Neurosci* 2013;7:93.
36. Lynall ME, Bassett DS, Kerwin R, McKenna PJ, Kitzbichler M, Muller U, Bullmore E. Functional connectivity and brain networks in schizophrenia. *J Neurosci* Jul 14 2010;30(28):9477-9487.
37. Lo CY, Su TW, Huang CC, Hung CC, Chen WL, Lan TH, Lin CP, Bullmore ET. Randomization and resilience of brain functional networks as systems-level endophenotypes of schizophrenia. *Proc Natl Acad Sci U S A* Jul 21 2015;112(29):9123-9128.
38. Stevens AA, Tappon SC, Garg A, Fair DA. Functional brain network modularity captures inter- and intra-individual variation in working memory capacity. *PLoS One* 2012;7(1):e30468.
39. Zalesky A, Fornito A, Seal ML, Cocchi L, Westin CF, Bullmore ET, Egan GF, Pantelis C. Disrupted axonal fiber connectivity in schizophrenia. *Biol Psychiatry* Jan 1 2011;69(1):80-89.
40. Gonzalez-Burgos G, Lewis DA. NMDA Receptor Hypofunction, Parvalbumin-Positive Neurons and Cortical Gamma Oscillations in Schizophrenia. *Schizophr Bull* May 24 2012.
41. Lewis DA, Curley AA, Glausier JR, Volk DW. Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. *Trends Neurosci* Jan 2012;35(1):57-67.
42. Hellwig B. A quantitative analysis of the local connectivity between pyramidal neurons in layers 2/3 of the rat visual cortex. *Biol Cybern* Feb 2000;82(2):111-121.
43. Douglas RJ, Koch C, Mahowald M, Martin KA, Suarez HH. Recurrent excitation in neocortical circuits. *Science* Aug 18 1995;269(5226):981-985.
44. Diez A, Suazo V, Casado P, Martin-Loeches M, Molina V. Spatial distribution and cognitive correlates of gamma noise power in schizophrenia. *Psychol Med* Jun 2013;43(6):1175-1185.

45. Diez A, Suazo V, Casado P, Martin-Loeches M, Perea MV, Molina V. Frontal gamma noise power and cognitive domains in schizophrenia. *Psychiatry Res* Jan 30 2014;221(1):104-113.
46. Winterer G, Coppola R, Goldberg TE, Egan MF, Jones DW, Sanchez CE, Weinberger DR. Prefrontal broadband noise, working memory, and genetic risk for schizophrenia. *Am J Psychiatry* Mar 2004;161(3):490-500.
47. Winterer G, Ziller M, Dorn H, Frick K, Mulert C, Wuebben Y, Herrmann WM, Coppola R. Schizophrenia: reduced signal-to-noise ratio and impaired phase-locking during information processing. *Clin Neurophysiol* May 2000;111(5):837-849.
48. Cortes-Briones JA, Cahill JD, Skosnik PD, et al. The Psychosis-like Effects of Delta(9)-Tetrahydrocannabinol Are Associated With Increased Cortical Noise in Healthy Humans. *Biol Psychiatry* Dec 1 2015;78(11):805-813.
49. Spencer KM. Baseline gamma power during auditory steady-state stimulation in schizophrenia. *Front Hum Neurosci* 2011;5:190.
50. Bachiller A, Diez A, Suazo V, Dominguez C, Ayuso M, Hornero R, Poza J, Molina V. Decreased spectral entropy modulation in patients with schizophrenia during a P300 task. *Eur Arch Psychiatry Clin Neurosci* Sep 2014;264(6):533-543.
51. Molina V, Bachiller A, Suazo V, Lubeiro A, Poza J, Hornero R. Noise power associated with decreased task-induced variability of brain electrical activity in schizophrenia. *Eur Arch Psychiatry Clin Neurosci* Dec 30 2014.
52. Sporns O. Dynamic Patterns in Spontaneous Neural Activity. *Networks of the Brain*. London: The MIT Press; 2011:149-178.
53. Buzsáki G. Diversity of Cortical Functions: Inhibition. *Rhythms of the Brain*. New York: Oxford University Press; 2006:61-79.
54. Saas LA, Parnas J. Explaining schizophrenia: the relevance of phenomenology. In: Cheung Chung M, K.W.M. F, Graham G, eds. *Reconceiving Schizophrenia*. New York: Oxford Univ Press; 2007:63-92.
55. Qin Y, Xu P, Yao D. A comparative study of different references for EEG default mode network: the use of the infinity reference. *Clin Neurophysiol* Dec 2010;121(12):1981-1991.
56. Newman ME. Modularity and community structure in networks. *Proc Natl Acad Sci U S A* Jun 6 2006;103(23):8577-8582.

Table/figure legends

Table 1. Demographic and clinical characteristics. Significant differences with respect to controls (**, $p < 0.001$).

Table 2. Mean network parameters for each group and summary of the statistical results obtained after comparing schizophrenia patients and controls (*, $p < 0.05$; **, $p < 0.01$). Effect sizes for within- and between-group significant differences are shown (Cohen's d).

Figure 1. Processing steps for evoked response analysis. EEG recordings for each electrode during a single trial of the oddball task for a control (a1) and a schizophrenia patient (a2). Computation of the evoked response (b1 and b2). Similarity matrices calculated by means of *ERP* (c1 and c2). Nodal *CLC* for a control (d1) and a schizophrenia patient (d2).

Figure 2. A) Association between baseline and modulation values in schizophrenia patients for: (a1) *SW*, and (a2) normalized *CLC*. B) Significant relationships between cognitive performance and modulation of network parameters for patients: b1, b2 and b3 depict associations with modulation of *CLC*; b4 depicts an association with *SW* modulation: larger values in Tower of London, completed categories in WCST and less perseverative errors in WCST indicate better executive function. Lower values in adjusted TMT indicate better working memory.

Filled circles: chronic patients; empty circles: FEP.

Figure 3. Nodal clustering maps depicting the spatial distribution of intra- (comparison between baseline and response) and inter-group differences in *CLC* (C: controls; SP: schizophrenia patients; FEP: first episode patients; CP: chronic patients).

Tables

	Schizophrenia patients (n=57)	First episode patients (n=18)	Controls (n=59)
<i>Age (years)</i>	34.1 (8.4)	28.4 (8.5) **	35.0 (11.6)
<i>Sex (Male:Female)</i>	29:28	12:6	29:21
<i>PANSS-Positive</i>	11.6 (4.8)	11.3 (3.7)	NA
<i>PANSS-Negative</i>	18.0 (8.5)	21.2 (9.3)	NA
<i>PANSS-Total</i>	55.2 (22.6)	59.8 (25.6)	NA
<i>Total IQ</i>	88.1 (16.4)	87.7 (16.6)	104.9 (10.0)
<i>BACS list of words</i>	36.0 (11.7)**	34.3 (12.2) **	55.5 (7.7)
<i>BACS digits</i>	16.5 (5.1) **	15.3 (5.7) **	22.8 (3.2)
<i>BACS motor speed</i>	46.5 (19.3) **	40.0 (17.8) **	57.0 (15.4)
<i>BACS verbal fluency</i>	17.2 (6.0) **	17.5 (5.1) **	25.4 (4.6)
<i>BACS execution speed</i>	36.7 (15.6) **	33.9 (14.1) **	67.7 (10.7)
<i>BACS Tower of London</i>	14.1 (5.4) **	12.7 (5.7) **	18.6 (2.6)
<i>WCST completed categories</i>	3.8 (2.0) **	3.5 (2.2) **	5.8 (0.8)
<i>WCST perseverative errors (%)</i>	20.4 (13.3) **	22.9 (9.8) **	9.6 (4.8)
<i>TMT (time B-A/A)</i>	1.9 (1.4) **	2.4 (1.7) **	0.9 (0.6)

Table 1.

	Controls	Schizophrenia patients (<i>n</i> =57)	Type III square sum; <i>F</i> ; <i>p</i>	Effect-size (patients vs controls)	First
<i>SW baseline*</i>	1.021 (0.015)	1.027 (0.013)	0.001; 6.627; 0.011	0.427	1.0
<i>SW response</i>	1.030 (0.019)	1.027 (0.160)	0.000; 1.340; 0.249		1.0
<i>SW modulation**</i>	0.010 (0.020)	0.000 (0.018)	0.003; 7.484; 0.007	0.525	0.0
<i>Effect size (within-group)</i>	0.525	0.000			
<i>CLC baseline*</i>	1.050 (0.022)	1.059 (0.020)	0.003; 5.733; 0.018	0.428	1.0
<i>CLC response*</i>	1.065 (0.030)	1.056 (0.023)	0.002; 3.025; 0.085	0.336	1.0
<i>CLC modulation**</i>	0.015 (0.034)	-0.003 (0.027)	0.009; 10.155; 0.002	0.586	0.0
<i>Effect size (within-group)</i>	0.587	0.139			
<i>PL baseline</i>	1.033 (0.013)	1.030 (0.011)	0.000; 2.432; 0.122		1.0
<i>PL response*</i>	1.028 (0.009)	1.031 (0.011)	0.000; 3.758; 0.055	0.298	1.0
<i>PL modulation*</i>	-0.005 (0.016)	0.002 (0.014)	0.001; 4.635; 0.033	0.456	-0.0
<i>Effect size (within-group)</i>	0.447	0.090			

Table 2.