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ORIGINAL ARTICLE

# Analysis of the functional EEG network in an Ecuadorian schizophrenia sample

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**Abstract**
*Background and objectives:* Higher mental functions depend on global functional coordination of the brain. Our aim was to study the baseline condition and modulation of functional networks in a previously unevaluated clinical population, compare the results with a population from another country, and analyze their relationship with cognitive functioning.
*Methods:* We evaluated the functioning of brain networks by EEG in 24 patients with schizophrenia and 32 healthy Ecuadorian controls. EEG recordings were made at rest and while performing a P300 task. Small world (SW), Path Length (PL), clustering coefficient (CLC) and connective strength (CS) values were calculated in both conditions. The values obtained were compared between groups, with the results of Spanish patients, and the relationship between the connective parameters and the cognitive performance of the participants was analyzed.
*Results:* Higher PL, CLC and CS values were identified in patients diagnosed with schizophrenia compared to controls (in basal condition) and lower SW values in this same condition. Ecuadorian patients obtained higher values than Spanish patients in the PL and CLC parameters and lower values for the SW parameter, despite these differences, the pattern of alteration in both samples followed the same trend. Finally, the alteration of CS, SW, CLC and PL parameters at baseline was related to cognitive performance.

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*Conclusion:* The connective alterations identified in Ecuadorian schizophrenic patients are consistent with those found in another sample with different genetic, environmental and cultural conditions. In addition, these alterations were associated with worse performance in different cognitive domains.



## Introduction

The synchronization of oscillatory patterns is fundamental to the understanding of brain activity underlying cognitive processes, which require the integration of dispersed neuronal activity through short- and long-distance communication established by structural and functional connections. Perception, cognition, emotion and behavior seem to be determined more by the interaction between different neuronal assemblies distributed in the brain than by the local activation of an area.[1] For this reason, the study of the functioning of oscillatory patterns is central to the understanding of mental activity.[2]

One of the connective parameters used in the analysis of the organization of oscillatory processes is the Small World (SW) properties of the functional connective network they form. This type of configuration is characterized by presenting a high degree of local clustering, which facilitates regional specialization, and a short average path length, which facilitates the integration of the activity of different neuronal populations.[3,4] Graph theory analyses applied to electrophysiological measurements[5,6] allow to identify this type of configuration. It has been proposed that the presence of higher values in this type of brain network properties translates into a greater capacity for integration and specialization and favors the efficient distribution of information.[7,8] The SW measure is defined as the ratio between the clustering coefficient (CLC), i.e., how interconnected a node is with adjacent nodes (and these with each other) and the characteristic path length (PL), the proximity with which a node is connected to each of the other nodes in the network.[9] Thus, the local CLC index represents an indicator of segregation and local efficiency of information transfer, probably related to regional specialization. The PL is interpreted as a metric of information integration in all areas,[10] this being more efficient the shorter the PL is. Since one of the conditions observed in some patients diagnosed with schizophrenia is the abnormal integration and segregation of neural networks,[11,12,13] the study of these parameters could be important for the better understanding of the etiopathogenic mechanisms of the syndrome.[14]

Another type of parameter relevant to functional alterations in schizophrenia is the Connectivity Strength (CS) measure. CS measures the relationships between a given voxel and the whole brain connectivity matrix rather than relationships with individual regions or networks.[15] For this purpose, this measure summarizes the average connection value of all nodes in the network and can be calculated from phase-locking values (PLV), which in the case of EEG indicate the degree of synchronization between sensors.[16]

Associations between alteration in the described parameters and cognitive performance have been reported.[17,18,19] Previous work based on both graph theory applied to EEG parameters[20,21] and functional magnetic resonance imaging (fMRI)[11,22] identify these types of networks as determinants in cognitive functioning, because a change in their pattern is observed between the resting state and during the performance of cognitive tasks in both schizophrenic patients and healthy individuals. Some results point to dysfunction of these networks in schizophrenia,[9,23,24] however in others no correlation is demonstrated between the clinical severity of psychosis and the disorganization of these networks.[25,26]

The study of brain connectivity in schizophrenia and its relationship with cognitive performance has a long tradition in developed countries; however, in the Andean region (Ecuador, Peru, Bolivia and Colombia) no research of this type has been conducted to date in schizophrenia, so it is necessary to analyze the possible role of functional network organization in these populations and whether there is any particularity that could be linked to genetics or other environmental and cultural conditions.

## Material and methods

### Subjets

Twenty-four patients diagnosed with schizophrenia (17 men) and thirty-two healthy controls (22 men) were included. Written informed consent was obtained from all participants after full printed information. The ethical committees of the Universidad San Francisco de Quito approved the study.

Patients were diagnosed by the psychiatrists in charge of their treatment according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, based on complete interviews and all available evidence. Healthy controls were recruited through contacts of university research staff. Sociodemographic and clinical characteristics are presented in Table 1.

Current treatment dose was converted to mg/d in chlorpromazine equivalents.

Exclusion criteria for patients and controls included history of neurological disease (including head trauma with loss of consciousness), past or present substance dependence (except nicotine and caffeine), not having completed elementary school. In addition, controls with any current psychiatric diagnosis or treatment were excluded.

All patients with schizophrenia were receiving stable doses of atypical antipsychotics.

### Cognitive assessment

The following tests was used in the cognitive assessment process:

Brief Assessment in Cognition in Schizophrenia (BACS)[27] using the Spanish adaptation of the battery.[28]

**Table 1** Sociodemographic, clinical, and cognitive data of patient and controls.

| | Ecuador | | | Schizophrenia patients | | | Healthy controls | | |
|---|---|---|---|---|---|---|---|---|---|
| | Schizophrenia patients | Healthy controls | $T/X^2$ | España | Ecuador | $T/X^2$ | España | Ecuador | $T/X^2$ |
| M:F Ratio | 17:07 | 22:12 | 0.24 | 13:07 | 17:07 | 0.17 | 17:11 | 12:05 | 0.45 |
| Age (years) | 37.96(1.76) | 36.56(11.48) | 0.44 | 38.4(13.09) | 37.95(12.76) | 0.11 | 36.71(11.83) | 37.82(9.23) | -0.33 |
| Education (years) | 12.75(3.19) | 16.55(3.44) | -3.79*** | 13.85(4.04) | 12.75(3.19) | 0.91 | 16(2.2) | 16.53(3.73) | -0.37 |
| Positive PANSS | 15.64(6.32) | NA | 1.11 | 12.44(4.59 | 15.63(6.32) | -1.72 | NA | NA | |
| Negative PANSS | 17.95(7.01) | NA | 1.27 | 18.56(7.99) | 17.95(7.01) | 0.25 | NA | NA | |
| Verbal memory | 32.83(7.39) | 45(11.19) | -4.62*** | 36.67(9.21) | 32.83(7.39) | 1.43 | 49.21(9.38) | 41.56(10.86) | 2.46* |
| Working memory | 14.57(4.23) | 19.63(3.52) | -4.79*** | 15.87(4.09) | 14.66(4.22) | 0.87 | 21.78(3.52) | 17.81(3.05) | 3.77*** |
| Motor speed | 35.04(13.26) | 65.31(11.72) | -9.04*** | 44.2(14.75) | 35.04(13.26) | 2.01 | 66.46(14.28) | 61.5(7.65) | 1.284 |
| Verbal Fluency | 16.96(5.47) | 21.40(9.59) | -2.03* | 18.61(8) | 16.95(5.47) | 0.76 | 23.93(11.45) | 22.71(3.77) | 0.41 |
| Processing speed | 46.58(14.46) | 67.25(10.58) | -6.18*** | 65.67(13.51) | 46.58(14.46) | 4.11*** | 68.64(14.12) | 68.62(9.7) | 0.01 |
| Tower of London | 11.38(4.55) | 16.94(3) | -5.51*** | 15.87(3.66) | 11.37(4.54) | 3.22** | 16.92(3.38) | 16.37(3.22) | 0.53 |

Note: T= student's T, $X^2$=Chi-square used for M:F Ratio only,
* =p<0.05,
** =p<0.01,
*** =p<0.001

## EEG recording

### EEG data acquisition and preprocessing

EEG recordings were obtained using Brain Recorder® software (Brain Products Gmbh; Munich, Germany), a 64-channel BrainAmp® amplifier (Brain Products Gmbh; Munich, Germany).

The International System 10-20 was used for electrode placement, in addition to a ground electrode at the AFz site. During recording, the reference was taken over the Cz electrode, allowing the final inclusion in the study of a total of 62 recording channels. The impedance of the electrodes was kept below 5 KΩ at all times. The sampling rate was 250 Hz and the signal was recorded continuously.

Two electrodes were extracted to record the possible noise source derived from eye movements.

### Odd-ball paradigm

Electrophysiological evaluation in the presence of cognitive stimulation was performed using an auditory odd-ball paradigm (with unexpected target stimulus). All participants listened to 600 binaural tones presented in random order with an inter-stimulus interval that fluctuated randomly between 1.16 and 1.44 s; the paradigm extended for 13 min. Three types of tones were presented: target tone (500 Hz tone; probability; 0.2), distractor tone (1000 Hz tone; probability; 0.2), and standard tone (2000 Hz tone; probability; 0.6).

Subjects who responded correctly to at least 50% of the stimuli included in the paradigm were included in the study. Only the response to correctly attended target tones was used for subsequent EEG analyses.

## EEG processing

The time-frequency representation of the EEG was calculated using the continuous wavelet transform (CWT), including frequencies from 1 to 70 Hz. In this way, two windows derived from the division of the 1s evoked responses [(-300-700) ms] were generated: 1) pre-stimulus [(-3000) ms before the onset of the target stimulus]; and 2) response [(300) ms centered around the response peak].

In order to systematize artifact rejection, a three-step approach developed by the group in previous studies[29,30] was used.

The parameters included in the analyses were the following; 1) path length, 2) clustering coefficient, 3) small world and 4) connectivity strength and their respective modulations upon realization of the odd-ball paradigm.

For the construction of graphs derived from the EEG analysis, the measurements recorded at the 62 electrodes used in the study were taken. The activity of each electrode was interpreted as representing a node of the network, while the links were calculated based on the phase-locking between each pair of electrodes.[31] To estimate the signal synchrony between electrodes, the phase-locking values (PLV) in successive trials were used.[32] CWT was used in the PLV calculation,[33] using the analyses developed by the research group in previous studies,[16,34] represented in the following formula:

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

where N is the number of attempts, $\Delta\varphi_{xy}$ is the phase difference between the x and y signals, k is the time interval and s is the wavelet scaling factor.

The network segregation was analyzed using the CLC parameter.[35] This analysis is expressed as follows:

$$CLC = \binom{N}{3} \sum_{\substack{i,j,h \in n \\ i \neq j,\ i \neq h, j \neq h}} \left(w_{ij} w_{ih} w_{jh}\right)^{1/3}$$

where wxy denotes the weight of the connection between electrodes i and j. The task-associated CLC modulation was defined as the change in CLC values between the prestimulus and response windows.

For the analysis of network integration, the PL parameter[35] was used. The following equation was used for this purpose:

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

where dij indicates the minimum distance between electrodes i and j. The PL modulation associated with the task was defined as the change in PL values between the prestimulus and response windows.

The balance between segregation and integration was calculated using the SW parameter.[35] The SW modulation associated with the task was defined as the change in SW values between the pre-stimulus and response windows.

$$SW = \frac{CLC}{PL}$$

The CS was calculated using the following formula:

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

where Wij refers to PLV between nodes i and j, and N is the total number of nodes in the network.[34] Task-associated CS modulation was defined as the change in CS values between the pre-stimulus and response windows.[16]

The EEG recording and analysis equipment and procedures were identical to those used in,[9,36] in order to be able to compare the results in the corresponding samples.

## Statistical analyses

Demographic, cognitive, clinical and neurophysiological data were compared between the groups into which the sample was divided using Kruskal-Wallis tests; in cases where a significant group effect was identified, the Mann-Whitney test was used to make comparisons between pairs of groups. Analyses were also performed to assess the effects of drug treatment on altered connective parameters in patients using Spearman's Rho.

### Analysis of connective parameters

The parameters; Small World, Path Length, clustering coefficient, connectivity Strength, modulation in path length, modulation in small world parameter, modulation in clustering coefficient parameter and modulation in connectivity strength parameter were included in the analyses. The Kruskal-Wallis test was used for overall sample comparison and the Mann-Withney test for pairwise comparison when a significant effect was detected for the group.

### Comparison of connective parameters between Ecuadorian and Spanish clinical population

We analyzed whether the alterations in the functional connective network were similar between patients with schizophrenia in the Ecuadorian and Spanish samples. For this purpose, comparisons were made using U-Mann Whitney tests for the altered parameters.

### Relationship between connective disorders and cognitive performance

Multiple stepwise linear regressions were performed using as dependent variables the scores obtained in the cognitive battery by all participants in the study sample and as independent variables the connective parameters that showed a significant alteration in the previous analyses were taken into account. (see Figure 2a). These same analyses were performed in the Ecuadorian cohort (see Figure 2b).

## Results

The age and sex of the patients were balanced in both samples. No significant differences were found in the sex distribution between the group of patients diagnosed with schizophrenia and the controls, ($x^2$=4.93, df=2, p=0.09) $x^2$ and age (K=0.831, df=2, p=0.66).

Shapiro-Wilk test was performed to test the normality of the connective parameters found that the variables PL (modulation), (W=0.96, p=0.02), SW (pre-stimulus), (W=0.94, p<0.001), CLC (pre-stimulus) (W=0. 88, p<0.001), PL (pre-stimulus) (W=0.92, p<0.001), and CS (pre-stimulus), (W=0.96, p=0.02) do not exhibit normality so nonparametric tests were used for statistical analyses.

No significant correlations were found between antipsychotic treatment dose and the studied parameters: CLC (pre-stimulus), (rho= -0.247, S=1921, p=0.279); PL (pre-stimulus), (rho=-0.179, S=1816.4, p=0.284); CS (pre-stimulus), (rho=- 0.157, S=1782.3, p=0.496); SW (pre-stimulus), (rho=0.151, S=1307.8, p=0.514), CLC modulation (rho= 0.08, S=1410.3, p=0.717); PL modulation (rho=-0.019, S=1569.2, p=0.935); CS modulation (rho=- 0.086, S=1408.3, p=0.713); SW modulation (rho=0.039, S=1480.7,p=0.868)

## Brain connectivity patterns

For the calculation of connectivity metrics the mean number of segments used in patients was 80.79 (sd 20.96) and 88.88 (sd 13.78) in controls.

Significantly higher values were found in schizophrenia patients than in controls in the parameters Clustering coefficient (U=239, p<0.008); Path Length (U=223, p<0.003; Connectivity Strength (U=270, p<0.029); connectivity strength modulation (U=280, p<0.043 and lower values of Small World (U=226, p<0.004). See Table 2.

## Comparison of connective parameters between the Spanish and Ecuadorian clinical population

The experimental protocol was applied identically in the Spanish and Ecuadorian samples.

No differences were found in sex ($x^2$=0.034,df=1,p=0.853) or age (K=0.28, df=1,p=0.6) between the Spanish and

**Table 2** Values of connective parameters in basal state and modulation for Ecuadorian patients and controls.

| | Healthy controls | Schizophrenia patients |
|---|---|---|
| SW (pre-stimulus) | 0.9281 (0.014) | 0.9082 (0.025)** |
| SW (modulation) | -0.0004 (0.005) | -0.0005 (0.01) |
| CS (pre-stimulus) | 0.3141 (0.020) | 0.3226 (0.043)* |
| CS (modulation) | 0.0021 (0.007) | 0,0020 (0.009)* |
| CLC (pre-stimulus) | 1.0061 (0.002) | 1.0086 (0.004)** |
| CLC (modulation) | 0.0003 (0.001) | 0.0003 (0.002) |
| PL (pre-stimulus) | 1.0845 (0.015) | 1.1126 (0.035)** |
| PL (modulation) | 0.0002 (0.007) | 0.0011 (0.015) |

Significant differences:
* p <0.05 in the schizophrenia group compared to the control group.
** p <0.01 in the schizophrenia groups compared to the control group.

Ecuadorian populations. Ecuadorian patients showed higher values compared to Spanish patients in the Clustering Coefficient (U=134, p=0.004) and Path Length (U=138, p=0.006) parameters and lower values in the Small World parameter (U=142, p=0.007). These results are illustrated in Figure 1.

### Relationship between connective parameters and cognitive performance

The basal CS parameter is a good predictor of performance inversely in the variables working memory ($R^2$=0.07;B=-290; T=4.971;p=0.03)and motor speed ($R^2$=0.24;B=-272;T=9.44; p=0.03). The SW parameter directly predicted performance in the domains processing speed ($R^2$=0.13;B=377;T=8.947; p=0.004) and Tower of London ($R^2$=0.08;B=310;T=5.746; p=0.02). The basal PL parameter inversely predicted performance in the motor speed variable ($R^2$=0.24;B=-361;T=9.44; p=0.005). Finally, the resting state clustering coefficient inversely predicted performance in the verbal memory subcategory ($R^2$=0.08;B=-315;T=5.936;p=0.02). The model showed no predictive ability of any of the connective parameters on the verbal fluency sub-category of the BACS test. See Figure 2a.

## Discussion

Higher CS values were identified in patients diagnosed with schizophrenia compared to healthy controls as well as a significantly higher deficit in the modulation of this parameter. In addition, SW values (in the pre-stimulated condition) were lower in the schizophrenia group. Patients also showed higher PL and CLC values in this condition than controls. Finally, the alteration of CS, SW, CLC and PL parameters was related to performance in neuropsychological tests.

The findings identified in our sample are in line with those reported in other populations such as Spain. A study conducted in a sample with schizophrenia in Spain identified higher CS values at baseline and during an attentional task versus controls.[16,37] For its part, the lower SW index in Ecuadorian patients has been described in a Spanish sample.[38] Finally, in a Spanish sample it was observed that patients showed higher baseline recordings than controls in CLC and PL parameters.[34]

However, significant differences are observed in some of these parameters between both populations (see Figure 1). A possible explanation for the differences found may be determined by the heterogeneity inherent to the condition studied. This heterogeneity may also manifest itself in measures of brain connectivity.[39]

To our knowledge, no previous research had performed a comparative analysis of the presence of these alterations in two populations with different genetic, socioeconomic, and cultural conditions. One of the strengths of this study is that

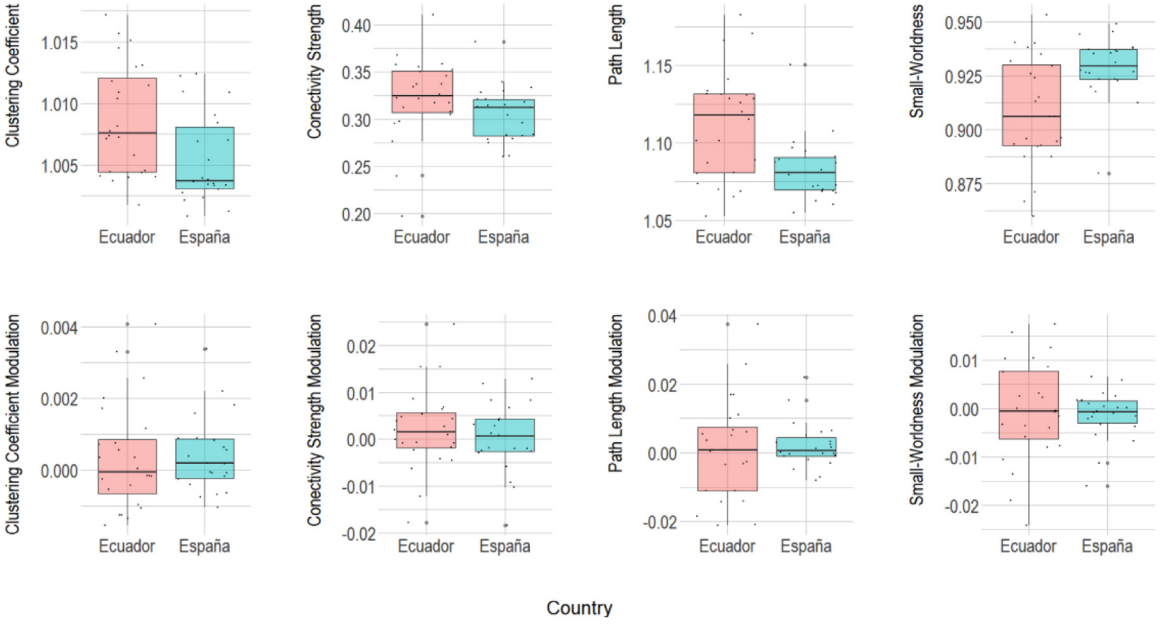


**Figure 1** Differences between Spanish and Ecuadorian patient groups in connective parameters.

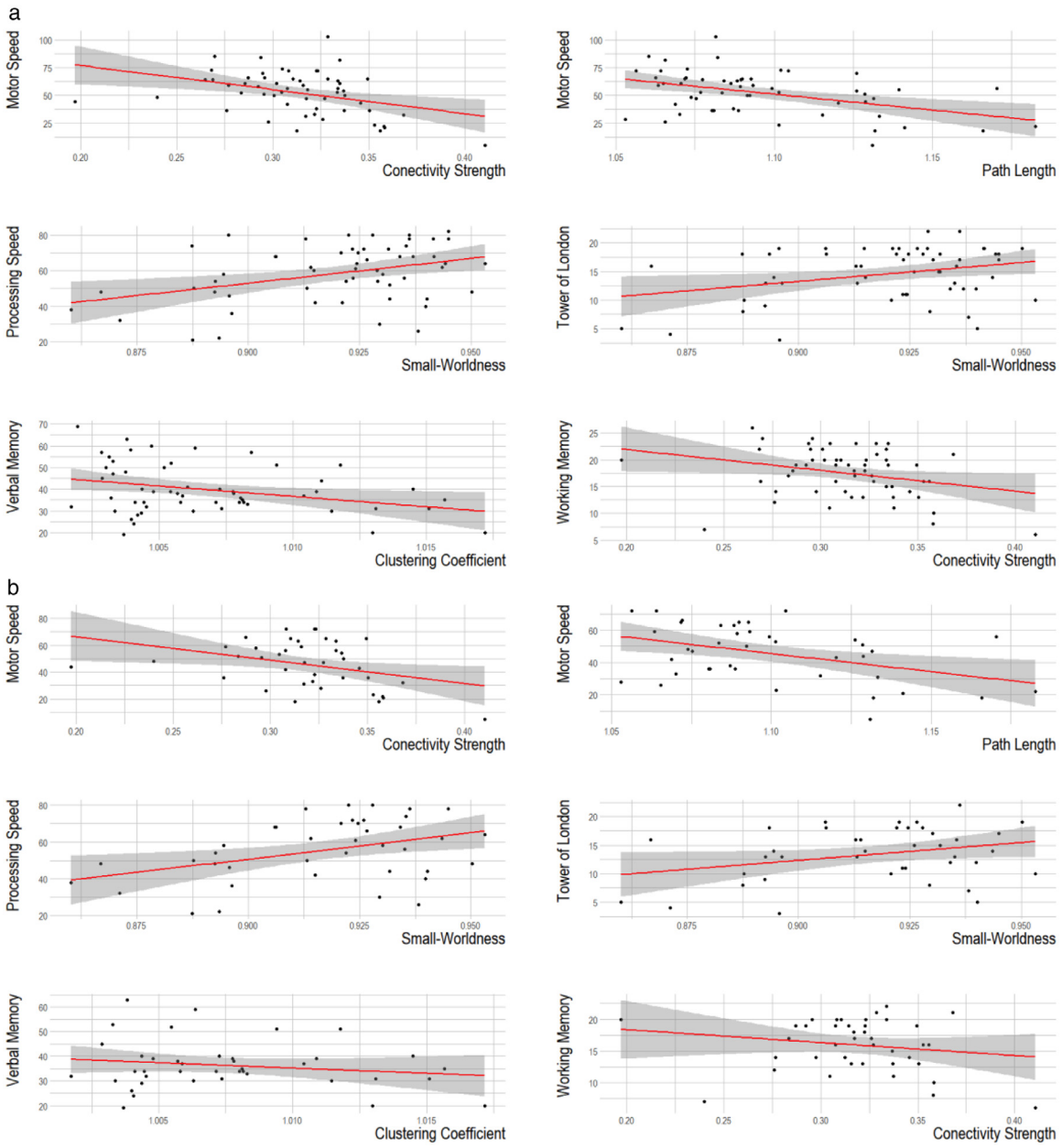


**Figure 2** **a**. Scatter plot depicting the association between connective parameters and cognitive scores in patients with schizophrenia and controls in the study sample. **b.** Scatter plot representing the association between connective parameters and cognitive scores in patients with schizophrenia and controls in the Ecuador cohort.

the results were compared with the results of investigations that applied the same methodology of data processing and analysis, which guarantees the homogeneity of the protocols and allows reinforcing the starting hypothesis regarding the universality of the disease in terms of functional connective alterations.

The results obtained at baseline in the CS parameter by patients diagnosed with schizophrenia could be reflecting a connective condition contributing to the overload of the neural ensembles. The presence of higher resting-state density values found in patients diagnosed with schizophrenia could hinder the modulatory capacity of neural ensembles in this group.[40] This is consistent with reports of a GABAergic deficit identified in schizophrenia.[41] Dysregulation in the excitatory/inhibitory balance[42] could cause the basal hypersynchronization present in some patients diagnosed with schizophrenia and be reflected through higher CS values.

An increased modulation of the CS parameter was also identified in the group of patients diagnosed with schizophrenia. In the literature we can find several studies that using different imaging techniques in their analysis,[43,44,45] have reported the presence of an increased activity of the default neural network in schizophrenia. The activation of neural mechanisms not associated with the performance of a simple attentional task could be behind the inefficiency shown by some patients to perform such tasks.

Thus, difficulties in modulation could mean that while in controls there is a decrease in global activation before a task (which probably responds to the need to activate more networks involved in cognitive processing), patients increase their activity even more, thus producing a failure in specialization.

The presence of lower values in the SW parameter in basal state with respect to controls identified in the group of patients diagnosed with schizophrenia could be linked to worse processing reflected in cognitive tests. Small-world organization has been shown to be fundamental in information transfer in terms of functional integration and segregation,[46,8,47] efficient levels of information segregation and integration with low energy and wiring costs are linked to a number of benefits for connective functioning, such as, a high degree of short global communication with relatively few connections.[48]

In the cognitive section, our results indicate a predictive relationship linking a higher CS index to worse results in motor speed, which is in line with previous studies suggesting that performance in this cognitive function would depend on the functional hyperactivation shown by patients' networks.[49] Motor speed was also inversely associated with the PL index. This association could reflect the importance of network integration for the correct performance of cognitive tasks that require the activation of different processing levels. From a theoretical point of view, these signs could be a consequence of oscillatory alterations mediated by inhibitory dysregulations identified in the disease.[42]

On the other hand, participants who performed worse in the processing speed domain presented lower resting state SW levels. Slower processing speed could therefore be associated with a less globally integrated and less clustered resting functional organization. This is consistent with evidence reported in preceding studies indicating a reduction in processing speed in patients diagnosed with schizophrenia.[50,51]

A relationship was also found between performance on the verbal memory task and the CLC index. As the clustering values increased the worse the participants' performance was this domain. Previous studies have reported this same relationship[52] which could reflect the dependence of verbal memory on the level of functional segregation shown by the networks in the basal state.

It has been proposed that an excess of cortical activation may result in an overload of working memory processes beyond their capacity.[53,54,55] Our results point in the same line, higher indexes in the CLC parameter are related to worse performance in working memory.

Finally, the magnitude of SW predicted better scores in executive function. The relationship identified in the results between SW measures and this domain could be indicative of the dependence of executive function on the small-world configuration of the networks in the basal state.

Our study has limitations, most of them related to the small sample size. This limitation may have had a special incidence in the comparisons made between the groups of patients diagnosed with schizophrenia from Ecuador and Spain (n=24) and (n=22) respectively, and may have been one of the circumstances that contributed to the differences found between the connective parameters of both populations. On the other hand, significant differences were found in the years of schooling of patients and controls, so we cannot rule out that this factor may explain, at least in part, the differences in the connective patterns of both groups. Nevertheless, the overall pattern of the data in the Ecuadorian population was consistent with that identified in previous studies of similar populations in other countries. The inherent heterogeneity of the syndrome, which has been discussed previously, could also have contributed to the presence of these differences. Moreover, these results should be replicated in samples without neuroleptic treatment.

## Conclusions

Ecuadorian patients diagnosed with schizophrenia present connective alterations similar to those found in other samples with different genetic, environmental and cultural conditions. Moreover, these alterations were related to worse performance in several cognitive domains.

## Ethical considerations

The study protocol was accepted by the ethical committees of the Universidad San Francisco de Quito (2017-042E).

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## Declaration of Competing Interest

The authors have no conflict of interest to declare.

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## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.ejpsy.2021.06.004.

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