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Structural connectivity in schizophrenia and bipolar disorder: Effects of chronicity and antipsychotic treatment

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ABSTRACT

Previous studies based on graph theory parameters applied to diffusion tensor imaging support an alteration of the global properties of structural connectivity network in schizophrenia. However, the specificity of this alteration and its possible relation with chronicity and treatment have received small attention. We have assessed small-world (SW) and connectivity strength indexes of the structural network built using fractional anisotropy values of the white matter tracts connecting 84 cortical and subcortical regions in 25 chronic and 18 first episode (FE) schizophrenia and 24 bipolar patients and 28 healthy controls. Chronic schizophrenia and bipolar patients showed significantly smaller SW and connectivity strength indexes in comparison with controls and FE patients. SW reduction was driven by increased averaged path-length (PL) values. Illness duration but not treatment doses were negatively associated with connectivity strength, SW and PL in patients. Bipolar patients exposed to antipsychotics did not differ in SW or connectivity strength from bipolar patients without such an exposure. Executive functions and social cognition were related to SW index in the schizophrenia group. Our results support a role for chronicity but not treatment in structural network alterations in major psychoses, which may not differ between schizophrenia and bipolar disorder, and may hamper cognition.

1. Introduction

The mental functions altered in major psychoses are likely sustained by the coordinated activity of distributed cerebral regions. Thus, analyses of global connectivity patterns are potentially relevant for the assessment of the underpinnings of psychoses. Analyses derived from graph-theory combined with structural and functional imaging techniques have been helpful in describing global connectivity in the normal brain (Sporns et al., 2004) and its alterations in major psychoses (van den Heuvel et al., 2010; Wang et al., 2012).

Among parameters derived from graph-theory, the small-world index (SW) is useful to summarize properties of the global brain network. This index, in reference to the small-world architecture of the human brain (Bassett et al., 2008), measures the balance between local connectivity or specialization of neuronal assemblies and the optimal communication between distant brain regions in a functional way. Since it is believed that the brain architecture must simultaneously coordinate the information transfer of local specialized networks and global functioning, SW can be seen as a measure of overall efficiency of the functional brain network. Thus, SW is the ratio between clustering coefficient (CLC) and characteristic path length (PL), as indexes of the local and long-range connectivity, respectively. High SW values are therefore associated with efficient coordination of distributed cerebral subnetworks. Additionally, the connectivity strength parameter can estimate the average connective density among the network nodes. Thus, SW and connectivity strength indexes respectively allow for more qualitative and quantitative depictions of the structural connective architecture of the brain.

When applied to structural connectivity in schizophrenia, graph-based analyses have revealed a pattern of decreased integration secondary to higher PL (van den Heuvel et al., 2010), associated with altered SW properties (Suo et al., 2018). Other connectivity alterations

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described in this syndrome included increased CLC (Bassett et al., 2008) and reduced global efficiency (Wang et al., 2012).

Most of these studies were performed in chronic patients. Therefore, a role for chronicity and/or treatment in these connectivity alterations cannot be discarded. To our knowledge, only one study evaluated complex network organization in medication-naïve, first episode schizophrenia patients (Zhang et al., 2015), revealing longer PL but conserved SW values.

Besides, global characteristics of structural networks have not been directly compared between schizophrenia and other major psychoses using graph parameters. Such comparisons could inform about the possible specificity of global network dysconnectivity in schizophrenia. In bipolar disorder, reduced overall CLC and increased PL of structural connectivity have been described in comparison to healthy subjects (Leow et al., 2013). Later studies used different methods and measurements, such as modelling cortical and subcortical areas and testing connections between these areas (Forde et al., 2015) and assessing rich-club connectivity (Collin et al., 2016). The diversity of parameters across studies is a further difficulty for the assessment of the effects of syndrome and chronicity. To our knowledge, the only published face to face comparison of brain networks between schizophrenia and bipolar disorder of structural connectivity is based on correlations of cortical thickness (Wheeler et al., 2015). Other studies have compared cerebral connectivity between schizophrenia and bipolar disorder, although not using graph theory. In a recent preprint, Ji et al. showed widespread fractional anisotropy (FA) reductions in schizophrenia and bipolar disorder as well as higher FA in schizophrenia in areas overlapping the default mode network. Moreover, functional data revealed both increased and decreased connectivity across cerebral regions in schizophrenia compared with control subjects, with intermediate differences in bipolar patients (Skatun et al., 2016).

Therefore, we decided to compare global structural connectivity properties in schizophrenia (chronic and first episode), bipolar patients and control subjects, using diffusion magnetic resonance imaging (dMRI) and the same graph parameters in all groups. Our objectives were to assess the specificity and the possible effects of chronicity and antipsychotic treatment on structural connectivity networks. Thus, we selected schizophrenia and bipolar patients with comparable illness duration (to assess specificity) and compared FE and chronic schizophrenia patients (to assess chronicity effects). Since a proportion of bipolar patients receive long-term antipsychotic therapy, we planned to compare patients with and without such treatment (to assess possible effects of these drugs on global networks). Our hypotheses were that (i) network alterations would be more evident in schizophrenia than in bipolar patients, (ii) similar alterations would be found in chronic and FE schizophrenia patients and (iii) antipsychotic treatment would be unrelated to these alterations.

2. Methods

2.1. Subjects

Forty-three schizophrenia (25 males) and 24 euthymic type I bipolar (13 males) patients, and 28 healthy subjects (19 males) were included. The schizophrenia sample included 25 stable and 18 first-episode patients (11 males).

Two of the psychiatrists in the group (VM and PdV) diagnosed the patients according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition. Diagnoses were based on full interviews with patients and other relevant sources of information, such as interviews with relatives.

Schizophrenia patients received stable doses of atypical antipsychotics, 31 of them in monotherapy (12 of them also received antidepressants and 7 benzodiazepines). FE patients had been receiving stable doses of antipsychotics for < 15 days. All the bipolar patients receiving stable treatment: 13 were treated with antipsychotics, and 11 were not receiving this treatment nor had received it for at least the last six months (none of the latter had ever received antipsychotics for more than one month). Fifteen bipolar patients were being treated with lithium, seven with anticonvulsants and nine with antidepressants at the time of inclusion. In total, four bipolar patients were treated in monotherapy with lithium, and 20 received a combination treatment. Antipsychotic doses were individually transformed to chlorpromazine equivalents in mg/d, and adherence was assessed by means of the percent of antipsychotic prescriptions withdrawn during the last six months from pharmacy offices according to the regional register system.

Positive symptoms were scored using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and negative symptoms with the Brief Negative Symptoms Scale (Mané et al., 2014). All schizophrenia patients showed positive and negative psychotic symptoms, while in the bipolar group five cases showed positive symptoms and twelve showed negative symptoms at the time of inclusion. 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, any other psychiatric disorder, and (v) for controls, any current psychiatric or neurological diagnosis or treatment.

The population here included overlaps in part with that of previous reports of our group in schizophrenia on functional networks based on evoked response (Gomez-Pilar et al., 2017), graph complexity (Gomez-Pilar et al., 2018) and structural connectivity of specific tracts of the prefrontal region (Molina et al., 2017).

We obtained written informed consent from all participants after full printed information. The ethical committees of the Clinical University Hospital of Valladolid approved the study.

2.2. Cognitive assessment

We assessed cognition in patients and controls using the Wechsler Adult Intelligence Scale, WAIS-III (IQ); 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) (Segarra et al., 2011). In this battery, verbal memory is assessed using word lists, working memory using digit span tests, motor speed by simultaneously placing with both hands two small tokens in a recipient, verbal fluency as the average of words beginning by “s” and “f” and belonging to a semantic category, performance speed with a digit/symbols tests and problem solving with a Tower of London test. Social cognition was assessed using Mayer, Salovey and Caruso Emotional Intelligence Test (MSCEIT), which scores the dimensions of emotional perception, facilitation, understanding and management (Mayer et al., 2003).

2.3. MRI acquisition and processing

All the acquisitions were performed at a Philips Achieva 3 Tesla MRI unit (Philips Healthcare, Best, The Netherlands) located at the University of Valladolid. The protocol (total acquisition time was 18 min) included an anatomical T1-weighted image and a diffusion acquisition. For the T1-weighted images, a turbo field echo (TFE) sequence was employed, using a spatial resolution of $1 \times 1 \times 1\,mm^3$ and a matrix size of 256×256. 160 sagittal slices were acquired, covering the whole brain.

With regard to the diffusion weighted images (DWIs), an EPI acquisition was employed, obtaining 61 images with different gradient directions (b-value = $1000s/mm^2$) and one baseline image. Matrix size was 128×128, with a voxel size of $2 \times 2 \times 2\,mm^3$. 66 axial slices were acquired.

From the raw data, a processing pipeline was applied in order to extract a connectivity matrix from each subject. The pipeline, which is

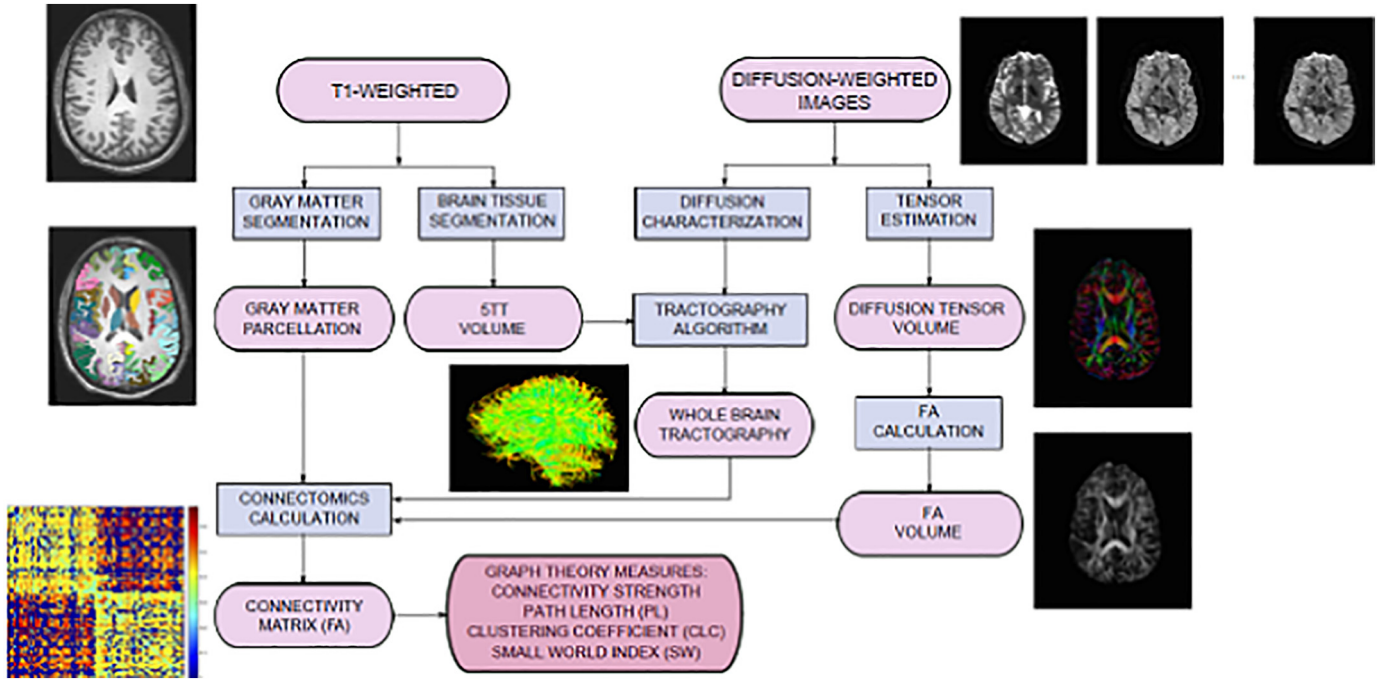

Fig. 1. Schematic depiction of the processing pipeline. Pink boxes indicate initial data, as well as intermediate and final processing outputs. Blue boxes indicate procedures that are applied to the data. From the T1-weighted images, different gray matter structures were segmented to obtain a gray matter parcellation. Also, gray matter, white matter and CSF were separated, and further combined to form the so-called "five-tissue-type" image (5tt), which is employed to guide the anatomically constrained tractography algorithm. Tractography is performed also using the diffusion MRI data, which is employed as well to create fractional anisotropy (FA) maps. All this information (gray matter parcellation, whole-brain tractography and FA map) is taken into account to perform the connectomics calculation, which yields a connectivity matrix. From this matrix, different graph theory parameters are extracted that characterize the connectivity network. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

explained in deeper detail elsewhere (Molina et al., 2017), makes use of freely available research-oriented software (FSL, Freesurfer and MRtrix) in order to first obtain a tissue-type segmentation, a cortical parcellation and a segmentation of subcortical gray matter structures from the T1-weighted images. This information is combined with the diffusion acquisition to obtain a whole brain, anatomically-constrained tractography (2 million streamlines were generated for each subject).

Finally, connectivity matrices were constructed from the tractography results and the (registered) cortical parcellation. Connectivity between any two cortical regions is described in terms of the averaged FA (fractional anisotropy) found along the streamlines connecting them. FA is a commonly employed diffusion metric, and quantifies how much the diffusion is predominantly oriented along one direction. FA is usually interpreted as a descriptor of white matter integrity, as several alterations (axonal destruction or demyelination, for instance) have been described to yield lower FA values.

Image processing is summarized in Fig. 1.

As 84 regions were employed for cortical parcellation, 84 × 84 symmetric connectivity matrices were obtained. No threshold was applied to the matrices, but matrix coefficients can be equal to zero if no streamlines are found between any two cortical regions.

2.4. Graph-theory parameters

From the structural connectivity matrices, we calculated three graph parameters (Rubinov and Sporns, 2010): (i) connectivity strength (i.e. mean network node degree), (ii) network segregation using CLC, and (iii) network integration by means of PL. In addition, SW index was also computed as a useful description of the topology of the whole network. Thus, whereas connectivity strength is as a quantitative marker of global connectivity, SW gives a measure of the network efficiency, yielding complementary information of the structural network.

In order to obtain results independent of network size and network strength, SW index was computed as the ratio between normalized CLC and PL. For that purpose, an ensemble of 50 surrogate random networks was obtained by random reshuffling of the connections (Stam et al., 2009). Then, CLC_n and PL_n were defined as follows (Stam et al., 2009):

$$CLC_n = \frac{\mathrm{CLC}}{\mathrm{C}^{\mathrm{random}}}, \quad (1)$$

$$PL_n = \frac{\mathrm{PL}}{\mathrm{L}^{\mathrm{random}}}, \quad (2)$$

where $\mathrm{C}^{\mathrm{random}}$ and $\mathrm{L}^{\mathrm{random}}$ represent the average of the CLC and PL values over the 50 surrogate networks. Finally, SW index is the ratio between the aforementioned CLC_n and PL_n.

It is noteworthy that the weights of the connectivity matrices represent the averaged FA along the streamlines connecting two brain regions.

2.5. Statistical analyses

As a general strategy, to reduce type I errors risk we analyzed a parameter summarizing network architecture (SW) and another one summarizing connective density (connectivity strength). If SW showed significant between-groups differences, we carried out further analyses (PL and CLC) to characterize network alterations. We chose non-parametric statistics given the subgroups sample sizes. Therefore, in the study, p values $< .05$ were taken as significant since independent analyses with one or a small number of comparisons were carried out to test a priori hypothesis, as follows:

Our first aim was to analyze the specificity of structural network alterations described in schizophrenia. For this purpose, we compared two values (SW and connectivity strength) values between chronic schizophrenia and bipolar patients and healthy controls using a single Kruskall-Wallis test. Only if a significant effect of group was detected,

pots-hoc comparisons using Mann-Whitney tests were performed to identify which groups differed in SW and connectivity strength values. Next, since SW is the ratio between CLC_n and PL_n, we planned to compare these values between the groups showing significant SW differences.

Our second aim was to assess the role of chronicity in these structural connectivity alterations. This effect was tested using a single Mann-Whitney U test between chronic and FE patients for SW and connectivity strength. Then, Spearman's rho coefficients were calculated between graph parameters and, duration of illness (in months).

Finally, to further assess the possible effects of antipsychotics on brain connectivity, we compared with a Mann-Whitney test the network values in the bipolar group between patients receiving ($n = 13$) or not ($n = 11$) antipsychotics during at least the last six months. Moreover, we calculated in the Spearman's rho coefficients between current antipsychotic dosage and network values.

Finally, we calculated the Spearman's rho coefficients between SW values and cognitive performance (BACS, perseverative errors in WCST and social cognition) and symptoms scores (PANSS positive and total, and BNSS total).

For the sake of interpretability of network values, we assessed the Pearson's correlation coefficients with Bonferroni adjustment between structural SW and the average FA values in white matter tracts connecting prefrontal cortex (PFC) with other relevant regions in accordance with the methodology employed in a previous study (Molina et al., 2017).

A database with the main data supporting the present results is freely available (Mendeley Data, v2 http://dx.doi.org/10.17632/y93pffg4zd).

3. Results

Demographic data are shown in Table 1. Sex distribution did not differ between groups ($\chi^2 = 1.428$, df = 3, $p = .699$). Both schizophrenia groups and bipolar patients showed a generalized cognitive deficit as compared to controls. Negative symptoms scores were significantly higher in schizophrenia as compared to bipolar patients (Table 1),

Mean values are shown with the corresponding standard deviation. Where not otherwise indicated, values correspond to raw clinical or cognitive scores. Significant differences are shown for clinical values between patients groups and for cognitive values with respect to controls (*$p < .05$; **$p < .01$; Mann-Whitney U tests).

There was a significant difference in age between groups ($\chi^2 = 27.13$, df = 3, $p < .001$), bipolar patients being significantly older than FE SZ (U = 34.5, z = 4.53, $p < .001$) and healthy controls (U = 139, z = 3.47, $p < .001$). Chronic SZ patients were also significantly older that FE SZ patients (U = 84.5, z = 3.22, $p < .001$), but both SZ groups did not differ significantly in age from healthy controls.

Illness duration was significantly longer in chronic schizophrenia (U = 14.5, z = 4.66, $p < .001$) and bipolar (U = 14, z = 4.68, $p < .001$) as compared to FE patients, but did not differ between the former two groups (U = 204, z = 0.891, $p = .372$).

Treatment adherence was deemed to be good in patients. All groups withdrew > 70% of prescription from pharmacy offices during the last six months.

3.1. SW values in specific tracts

SW values were directly related to FA in the following tracts linking homolateral regions ($n = 85$; in all cases $p < .001$): right superior frontal with superior parietal ($r = 0.429$); right rostral middle frontal with hippocampus ($r = 0.330$) and superior temporal ($r = 0.351$); left superior frontal with superior parietal ($r = 0.332$); left middle frontal with caudate ($r = 0.318$) and superior parietal ($r = 0.429$). Therefore, higher SW values were associated with higher FA values in the tracts

Table 1
Demographic, clinical and cognitive data in patients and controls.

	Age (yr.)	Illness duration (months)	GAF score	Positive symptoms (PANSS score)	Negative symptoms (BNSS (total score)	Total PANSS score	Verbal memory	Working memory	Motor speed	Verbal fluency	Performance speed	Problem solving	Total IQ	Perseverative errors (percent)	MSCEIT (total)
First episode schizophrenia patients	29.14 (8.10)	22.09 (53.80)	63.16 (13.87)	10.88 (2.73)	32.75 (20.27)	53.07 (21.72)	35.97* (12.70)	16.24* (4.41)	55.61* (15.75)	17.66* (5.39)	46.28* (15.24)	14.89* (5.12)	85.41** (12.55)	17.14* (9.83)	100.20* (20.09)
Chronic schizophrenia patients	39.19 (10.35)	163.67 (117.64)	50.77 (14.98)	12.81 (4.25)	39.07 (17.25)	64.28 (20.49)	34.17** (12.20)	15.96** (5.39)	48.99* (18.66)	18.61* (5.46)	35.42** (15.30)	14.21* (5.32)	92.75** (16.39)	24.51** (35.08)	96.83* (25.79)
Bipolar patients	45.60 (11.70)	177.82 (110.09)	66.05 (11.25)	10.53 (3.79)	14.00** (16.51)	33.56* (10.03)	34.62** (12.13)	17.35* (3.84)	67.40* (15.90)	21.29* (5.80)	42.60* (12.54)	15.90 (3.19)	98.10** (9.96)	24.42** (16.92)	100.40* (21.15)
Healthy controls	33.09 (10.53)	NA	NA	NA	NA	NA	54.06 (8.40)	33.44 (3.72)	70.33 (15.06)	26.53 (5.41)	66.55 (12.74)	17.95 (4.40)	110.70 (12.38)	10.03 (5.62)	122.72 (14.23)

Table 2
Structural connectivity parameters for patients and controls.

	First episode schizophrenia patients	Chronic schizophrenia patients	Bipolar patients	Healthy controls
Clustering coefficient	0.996 (0.001)	0.994 (0.003)	0.994 (0.004)	0.996 (0.002)
Path Length	1.014 (0.005)	1.021 (0.011)*	1.018 (0.010)*	1.014 (0.005)
Small-worldness	0.982 (0.005)	0.974 (0.012)*	0.976 (0.012)*	0.982 (0.006)
Connectivity Strength (Density)	0.341 (0.019)	0.311(0.037)**	0.304(0.035)**	0.343 (0.030)

Significant differences in comparison to healthy controls *$p < .05$; **$p < .01$.

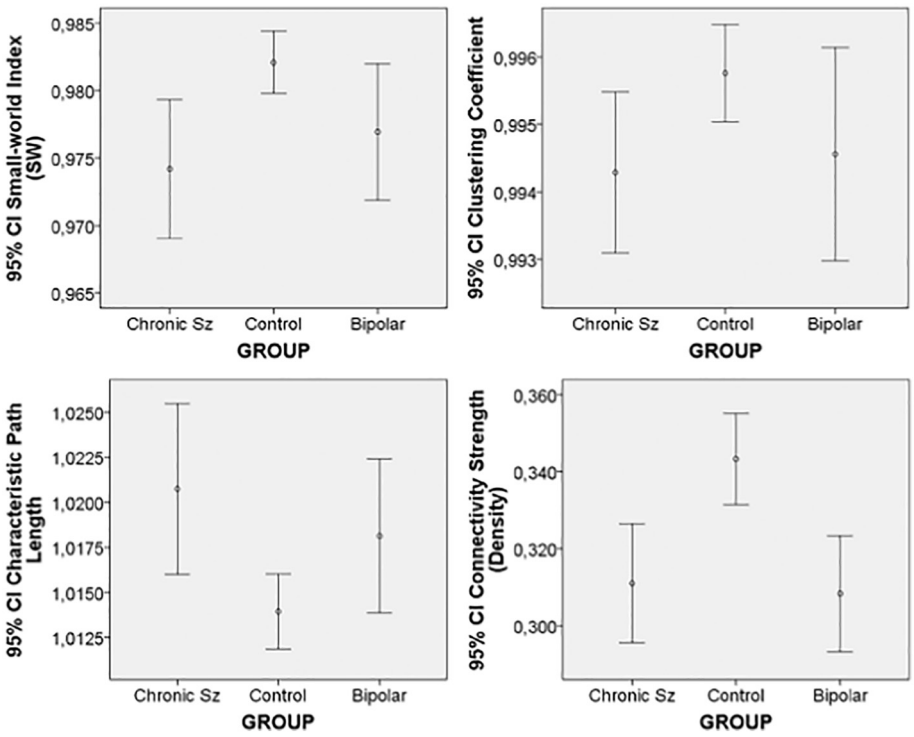

Fig. 2. 95% CI intervals of network parameters for structural connectivity in the chronic schizophrenia and bipolar and healthy control groups. Both patients groups showed smaller SW and larger PL values than controls, without significant differences in CLC as compared to controls. There were no significant differences in any parameter between chronic Sz and bipolar patients.

linking prefrontal cortex with other regions.

3.2. Specificity analyses

A significant effect of group (chronic SZ, bipolar, control) was found on SW ($\chi^2 = 6.096$, df = 2, $p = .042$). Post-hoc Mann-Whitney tests showed significantly lower SW values in chronic SZ as compared to controls (U = 212, z = −2.459, $p = .014$), without significant differences in SW between chronic SZ and bipolar patients (U = 255, z = −0.900, $p = .368$; Table 2 and Fig. 2).

A larger PL_n in chronic SZ as compared to controls (U = 227, z = 2.192, $p = .014$) seems to be driving the SW differences. There were no significant differences in CLC_n or PL_n between chronic SZ and bipolar patients. CLC_n did not differ significantly between chronic schizophrenia with respect to bipolar patients and controls.

Similarly, a highly significant effect of group was found for connectivity strength ($\chi^2 = 16.391$, df = 2, $p < .001$). Post-hoc Mann-Whitney tests showed significantly lower connectivity strength in chronic SZ as compared to controls (U = 161, z = −3.367, $p = .001$), without significant differences between chronic SZ and bipolar patients (U = 279, z = −0.420, $p = .368$; Fig. 2).

3.3. Chronicity analyses

Significantly lower SW values were found in chronic SZ as compared to FE patients (U = 128, z = −2.388, $p = .017$), as well as significantly longer PL_n (U = 143, z = 2.043, $p = .04$) and smaller CLC_n (U = 135, z = −2.21, $p = .027$) (Fig. 3). There were no significant SW differences between FE patients and controls.

Moreover, chronic patients showed significantly lower connectivity strength than FE patients (U = 103, z = −3.003, $p = .003$). FE patients did not differ in connectivity strength from healthy controls (U = 231, z = 0.473, $p = .636$).

Illness duration was inversely associated with SW values (rho = −0.374, $p = .004$) and connectivity strength (rho = −0.336, $p = .004$) in all patients. In the schizophrenia patients alone, this correlation was still significant for SW (rho = −0.515, $p = .001$) and connectivity strength (rho = −0.422, $p = .009$), but not in the bipolar group (SW: rho = −0.179, $p = .427$; (rho = −0.007, $p = .976$) (Fig. 4).

3.4. Treatment effects

Correlation coefficients between current antipsychotic doses and network parameters were not statistically significant, neither for the whole sample (−0.059 < rho < 0.060) nor for SZ and bipolar patients separately considered (0.103 < rho < 0.114; Fig. 5).

There were no significant differences in SW values between bipolar patients with (0.977, sd 0.008) and without (0.975, sd 0.018) antipsychotic treatment exposure (Mann-Whitney, U = 57, z = −0.194, $p = .875$). Similarly, connectivity strength did not differ between bipolar patients previously treated (0.259, sd 0.033) and untreated (0.320, sd 0.037) with AP (U = 46, z = −1.178, $p = .257$).

Further comparisons of CLC_n (with antipsychotics (0.994, sd 0.003);

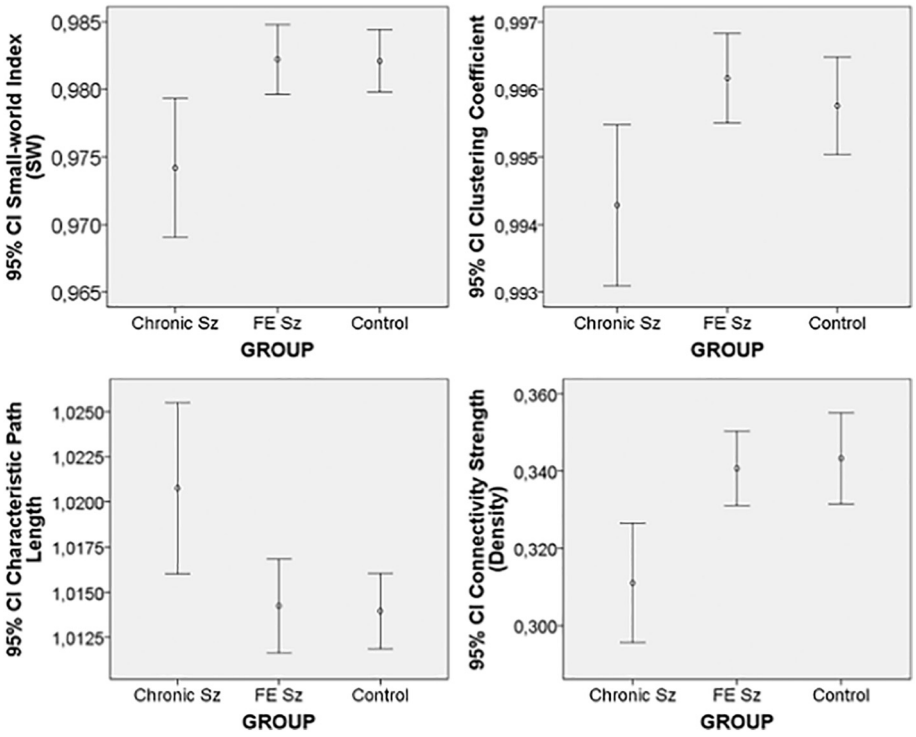

Fig. 3. 95% CI intervals of network parameters for structural connectivity in the chronic and FE schizophrenia and healthy control groups. There were no significant differences in any parameter between FE schizophrenia and healthy controls.

without antipsychotics (0.994, sd 0.005)) and PL_n (with antipsychotics (1.017, sd 0.007); without antipsychotics (1.019, sd 0.014)) showed non-significant differences related to exposure to antipsychotics in this group. Illness duration was not significantly different in bipolar patients treated (210.9, sd 96.60 months) or not (65.29, sd 128.67) with antipsychotics (U = 35, z = −1.04, p = .32).

3.5. Clinical correlates

In all patients considered together, SW values were directly associated with problem solving performance (Tower of London; rho = 0.289, p = .040) and inversely to the percent of perseverative errors in WCST (rho = −0.321, p = .025). Connectivity strength was directly associated with working memory performance (rho = 0.291, p = .039).

In the SZ group, SW values were directly associated with problem solving (rho = 0.332, p = .048), and inversely with percent of perseverative errors (rho = −0.358, p = .035). Moreover, in this group SW values were directly associated with social cognition performance (MSCEIT total score, rho = 0.372, p = .047) (Fig. 6). There was a marginal association between total PANSS scores and SW values in this group (rho = −0.281, p = .087).

In this group, connectivity strength was not significantly associated with cognitive nor clinical values.

In bipolar patients, there were not significant correlations between network parameters and general cognition, but SW values were inversely related to positive symptoms (rho = −0.661, p = .001), and connectivity strength was related to social cognition (rho = 0.547, p = .028).

4. Discussion

According to our data, the global architecture (SW) and density (connectivity strength) of the structural network is altered in both chronic schizophrenia and bipolar disorder, but not in FE schizophrenia. The higher PL values in chronic SZ and bipolar patients are likely to be driving their alterations of the SW.

This finding is consistent with previous reports in schizophrenia

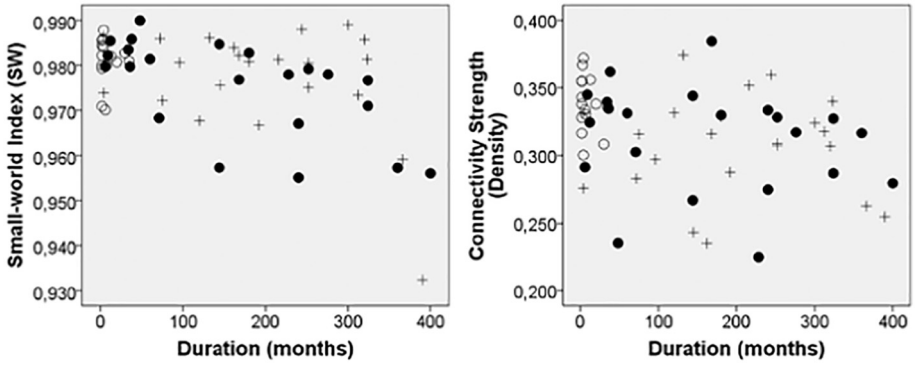

Fig. 4. Association between illness duration and SW indexes and connectivity strength values. The relation was significant in the schizophrenia for both SW and connectivity strength, but not in the bipolar group. Solid dots: chronic SZ; open circles: FE schizophrenia; crosses: bipolar patients.

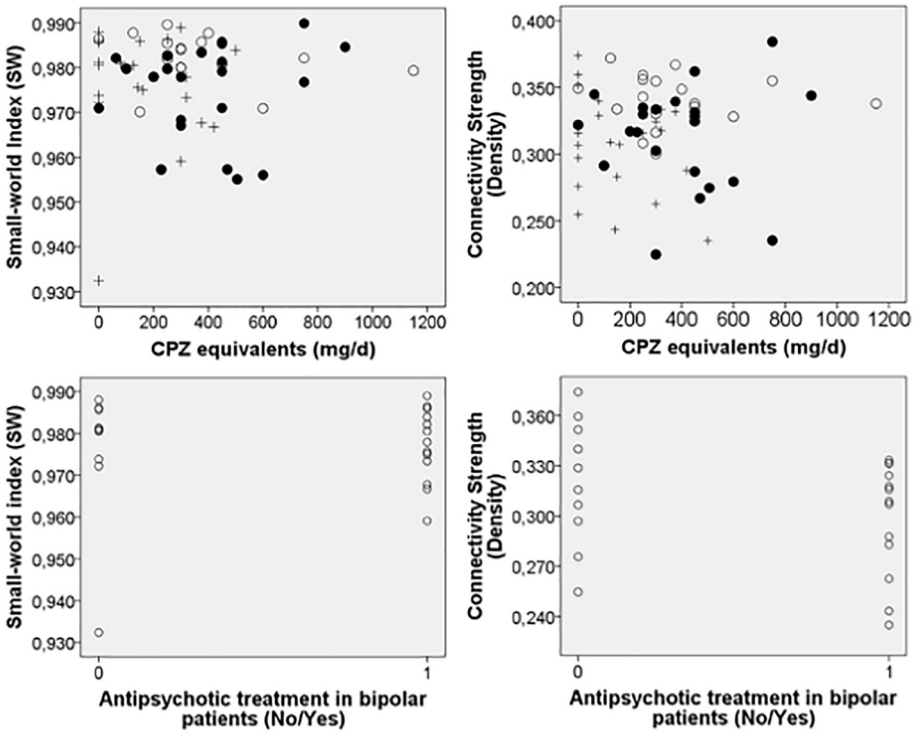

Fig. 5. In the upper row, scatterplot showing the lack of association between antipsychotic dose and SW and connectivity strength values. (Solid dots: chronic SZ; open circles: FE schizophrenia; crosses: bipolar patients). In the lower row, comparison of SW and connectivity strength values between bipolar patients with or without antipsychotic treatment.

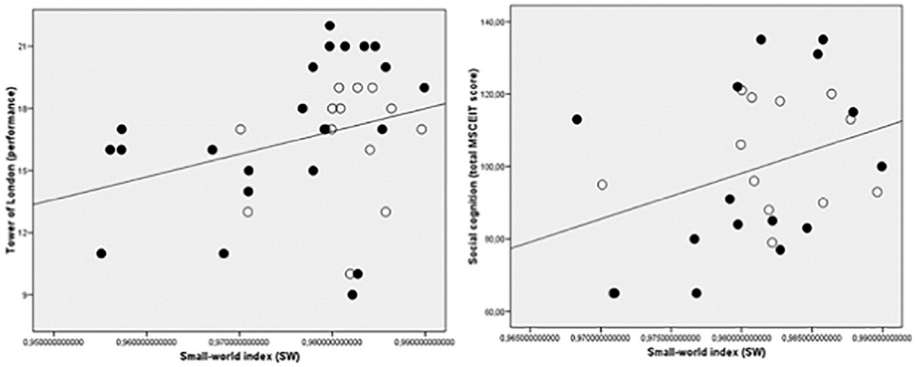

Fig. 6. Association in the schizophrenia group between SW index of strcutural connectivity and problem solving (left) and social cognition (right). Solid dots: chronic schizophrenia; open circles: FE schizophrenia.

(Suo et al., 2018; van den Heuvel et al., 2010) and, according to our data, seems not to be explained by antipsychotic treatment, since there was no correlation between current antipsychotic dosage and network values, and network parameters did not differ between bipolar patients receiving or not this treatment.

As previously mentioned, there are not previous head to head comparisons of structural connectivity between schizophrenia and bipolar disorder using graph parameters and FA (Suo et al., 2018). Direct comparisons of structural connectivity based on graph parameters between these syndromes have been published based on correlations of regional gray matter thickness values, an indirect index of cortical connectivity, revealing alterations in deficit schizophrenia but not in non-deficit schizophrenia or bipolar disorder (Wheeler et al., 2015). A recent review of studies using graph theory and diffusion imaging to assess structural connectivity separately in schizophrenia and bipolar disorder supports frontal dysconnectivity in both syndromes (O'Donoghue et al., 2017).

There is evidence that FA values may be related to myelin integrity, although there are several other factors that can contribute to reductions in FA (Jones and Cercignani, 2010). Therefore, our data in chronic patients are consistent with the lower FA reported in schizophrenia (Ellison-Wright and Bullmore, 2009; Patel et al., 2011), as well as in schizophrenia and bipolar disorder (Hercher et al., 2014). The larger PL in our chronic patients is also consistent with the reported reduction of global communication paths (Griffa et al., 2015; van den Heuvel et al., 2013) in schizophrenia. Moreover, network alterations in the bipolar group also agree with previous report on widespread decease of FA in this syndrome (Barysheva et al., 2013). Taken together, these findings suggest a disruption of white matter tracts in chronic psychoses.

Our analysis reveals an alteration in connective architecture in both schizophrenia and bipolar disorder. Our aim was to assess global properties of such architecture, not considering alteration in specific tracts, but previous literature supports a different regional distribution of connective alterations between these syndromes. A recent review based on gray matter volumes support hyperconnectivity between the default mode and limbic networks in schizophrenia as compared to bipolar disorder, as well as hypoconnectivity between limbic and salience networks (Brandl et al., 2019). We previously described FA alterations in the connections between prefrontal cortex, caudate nucleus, thalamus and anterior cingulate in schizophrenia (Molina et al., 2017), which seems consistent with the former results. Another group reported no effect of group for FA between schizophrenia and bipolar

patients and controls in corpus callosum and cingulum bundle with radial diffusivity and apparent diffusion coefficient elevated in schizophrenia and not bipolar disorder (Nenadic et al., 2017). These regional differences in connectivity may underlie altered global patterns of connectivity in both psychotic syndromes.

If antipsychotic treatment is not the primary reason behind structural connectivity alteration in these syndromes, illness might have a progressively deleterious effect on that connectivity. In other words, chronicity but not antipsychotic treatment could be the primary reason of global network dysconnectivity in these syndromes, which seem consistent with the negative association found in the present sample between illness duration (but not age) and SW in our patients. Moreover, beyond illness duration, other factors might have a negative influence on cerebral connectivity in chronic psychotic patients, such as early drug consumption or social isolation. The corresponding potential effects may be assessed with specific designs.

In the bipolar group, alterations in connectivity might hypothetically be secondary to other treatments than antipsychotics, such as mood stabilizers. This however seems unlikely, since a positive relation has been reported between lithium exposure and FA values (Gildengers et al., 2015), and the majority of the bipolar patients were receiving lithium.

In the schizophrenia group, higher SW values were associated with a better performance in executive (Tower of London and WCST) and social cognition tasks, which seems consistent with the broad cortical involvement in this kind of tasks, given the multiple cognitive demands underlying it. Thus, when connectivity architecture is hampered, performance may decrease due to a lower capacity for harmonizing the activity of the multiple areas involved. In the bipolar group, however, we did not detect a similar relation between network structure and cognition. This could be related to the smaller sample size of this group but may also suggest different underpinnings for the lower SW in bipolar disorder as compared to schizophrenia, which is also suggested by the inverse association in this group but not in schizophrenia with positive symptoms.

According to our data, architecture disruption (SW alterations) seems to have larger consequences for cognition in schizophrenia than quantitative (connectivity strength) deficits. This seems consistent with the data revealing a reduced betweenness centrality for frontal hubs in schizophrenia (van den Heuvel et al., 2010), since a less central role of these structures in the global network could reduce its SW value. Similar data have been reported with functional imaging network analyses (Lynall et al., 2010; van den Heuvel et al., 2013).

Our study has limitations. Bipolar patients were significantly older than chronic schizophrenia patients, but this is likely an effect of the later illness onset of bipolar disorder (Dagani et al., 2017): since we tried to collect samples with similar illness duration, an older age was expected in bipolar patients. Interhemispheric connections were not considered to assess network values. Sample sizes are relatively small, but this size is similar to that in other reports in the field, with the advantage of including bipolar and schizophrenia patients. Our sample did not include first episodes of bipolar disorder, and we lack a completely treatment-naïve schizophrenia sample, which would be necessary to clarify the possible role of treatment in network deficits.

5. Conclusion

Alterations of global structural connectivity were found in both chronic schizophrenia and bipolar syndromes but not in FE schizophrenia; the effect of antipsychotic treatment on structural connectivity seems questionable since no correlation was found between current antipsychotic dosage and connectivity parameters, and these did not differ between bipolar patients receiving antipsychotic treatment and those who do not. Structural connectivity values were positively associated in these syndromes to performance in working memory and problem solving tests. White matter connective alterations may have a pathogenetic role in primary psychotic syndromes.

Conflict of interest

None.

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