RELATIONS BETWEEN STRUCTURAL AND EEG-BASED GRAPH METRICS IN HEALTHY CONTROLS AND SCHIZOPHRENIA PATIENTS

Running title: MRI and EEG networks in schizophrenia

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SUMMARY

Objective: To assess using graph-theory properties of both structural and functional networks in schizophrenia patients, as well as the possible prediction of the latter based on the former. Abnormal structural and functional network parameters have been found in schizophrenia, but the dependence of functional network properties on structural alterations has not been described yet in this syndrome.

Experimental design: We applied averaged path-length (PL), clustering coefficient (CLC) and density (D) measurements to structural data derived from diffusion magnetic resonance and functional data derived from electroencephalography in 39 schizophrenia patients and 79 controls. Functional data were collected for the global and theta frequency bands with subjects performing an odd-ball task, both prior to stimulus delivery and at the corresponding processing window. Connectivity matrices were constructed respectively from (i) tractography and registered cortical segmentations (structural) and (ii) phase-locking values (functional).

Principal observations: In both groups, we observed a significant EEG task-related modulation (change between pre-stimulus and response windows) in the global and theta bands. Patients showed larger structural PL and pre-stimulus density in the global and theta bands, and lower PL task-related modulation in the theta band. Structural network values predicted pre-stimulus global band values in controls and global band task-related modulation in patients. Abnormal functional values found in patients *(pre-stimulus density in the global and theta bands and task-related modulation in the theta band)* were not predicted by structural data in this group. Structural and functional network abnormalities respectively predicted cognitive performance and positive symptoms in patients.

Conclusions: *Taken together, the alterations in the structural and functional theta networks in the patients and the lack of significant relations between these alterations, suggest that these types of network abnormalities exist in different groups of schizophrenia patients*.

Key words: schizophrenia, dysconnectivity, network, graph-theory, electroencephalography, diffusion magnetic resonance.

1. INTRODUCTION

Mental functions depend on global dynamics of cerebral networks (Dehaene and Changeux, 2011; Varela, et al., 2001), whose functional and structural characteristics can be assessed in vivo using methods derived from graph-theory (Bullmore and Sporns, 2009). In this context, underpinnings of syndromes like schizophrenia likely involve distributed networks rather than regional alterations, as supported by studies using functional magnetic resonance imaging (fMRI) that revealed network alterations in the resting state (Lo, et al., 2015; Yu, et al., 2011) and during task performance (Ma, et al., 2012; Shim, et al., 2014) in this syndrome. However, considering the rapid and transient change of functional integration of diverse cerebral regions in cognition in humans (Varela, et al., 2001) and animals (Bressler, et al., 1993), assessing fast change of cerebral networks in schizophrenia holds a great interest. Techniques with high temporal resolution are useful to this purpose: change of network properties using EEG during a cognitive task was significantly decreased in schizophrenia patients (Gomez-Pilar, et al., 2017a). Using relative power analyses, we also reported lower EEG task-related change in theta but not in faster bands during an odd-ball task in schizophrenia (Bachiller, et al., 2014).

As mentioned, methods derived from graph-theory are useful to assess the properties of cerebral networks, which can be summarized in parameters such as clustering coefficient (CLC) and characteristic path length (PL). 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. When CLC is averaged across the nodes of a network, it quantifies network segregation and local efficiency of information transfer. In turn, PL is the average of shortest distances for all possible pairs of nodes; it is likely related to information integration across areas. These network parameters provide complementary information about the properties of the whole brain network. Therefore, the use of these parameters instead of their corresponding nodal versions, allows to characterize the global and predominant changes of the network. A recent meta-analysis of functional graph-analytical studies in schizophrenia revealed significant decreases in measures of local organization (CLC) with preservation in short communication paths (PL) (Kambeitz, et al., 2016).

Abnormalities in structural connectivity are also prevalent in schizophrenia (Ellison-Wright and Bullmore, 2009). These abnormalities are likely reflected in structural network properties, since longer structural PL values were found in schizophrenia at frontal and temporal regions using dMRI (van den Heuvel, et al., 2010) and may be associated to genetic liability to this disorder (Bohlken, et al., 2016). Thus, the possibility exists that functional network alterations might be secondary to structural abnormalities in schizophrenia. Indeed, in this syndrome, a relationship has been

reported between a reduction in "rich-club density" (i.e., connections among high-degree hub nodes) and global efficiency of functional connectivity in the resting state using fMRI (van den Heuvel, et al., 2013). Similarly, connectivity deficits in rich-club hubs have been described in young offspring of schizophrenia patients associated to disruption of the functional connectome (Collin, et al., 2017). However, functional connectivity alterations in schizophrenia are not necessarily determined by structural connectivity, since functional connections in the resting state can be found between regions without direct anatomical connections (Honey, et al., 2009).

The application of graph-theory parameters to functional and structural measurements can yield complementary information and help uncovering hidden relationships (Sui, et al., 2012). Using diffusion magnetic resonance imaging (dMRI), graph-theory parameters may inform about structural connectivity differences between anatomical structures, revealing highly connected hubs (Honey, et al., 2010). Graph-theory parameters applied to functional analysis may reveal baseline network characteristics and its dynamic modulation during cognition of signals such as synchrony of the bold-oxygen level dependent signal between regions, or magneto-electrical signals between sensors. Considering the millisecond-scale of modulation of cortical activity during cognition (Bressler, et al., 1993; Dehaene and Changeux, 2011), the combination of network analyses with temporal resolution of electroencephalographic (EEG) recordings can be useful to assess this task-related modulation. Indeed, using EEG in healthy subjects, we reported a significant task-related modulation of network parameters from pre-stimulus (from -300 to 0 ms prior to stimulus onset) to response (from 150 to 450 ms post-stimulus) windows (Martin-Santiago, et al., 2016) during an odd-ball task.

To our knowledge, no previous study has assessed the relationship between structural and EEG networks in schizophrenia. Such investigation may help identifying the substrate of the cortical dysfunction in schizophrenia. Therefore, the present study was aimed at characterizing the properties of structural and EEG-based functional networks in schizophrenia and assessing the relationships between properties of those networks in this syndrome, particularly between structural connectivity and EEG modulation.

2. SUBJECTS AND METHODS

2.1 Subjects

Thirty-nine schizophrenia (19 stable chronic and 20 first-episode, FE) patients and 78 healthy controls with normal hearing were included. Demographic, clinical, cognitive and EEG data were collected for each participant (Table 1). In addition, dMRI data were also available in 33 patients (16 FE) and 27 controls (Table 1). One of the psychiatrists in the group (VM) diagnosed the patients according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition. Chronic patients received atypical antipsychotics, 30 of them in monotherapy (12 received antidepressants and 7

benzodiazepines). FE patients were receiving stable doses of antipsychotics for less than 15 days, with a wash-out period of 24 hours prior to EEG acquisition. Symptoms were scored using the Positive and Negative Syndrome Scale (PANSS) (Kay, et al., 1987). 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 process, 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., 2017a), graph complexity (Gomez-Pilar, et al., 2017b) 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 University Hospital of Valladolid approved the study.

2.2. Cognitive assessment

Cognitive data from patients and controls were collected 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).

2.3. MRI acquisition and processing

Acquisitions were carried out using a Philips Achieva 3 Tesla MRI unit (Philips Healthcare, Best, The Netherlands) at the MRI facility at Valladolid University, including anatomical T1-weighted and diffusion-weighted images. For the T1-weighted images, acquisition parameters were: turbo field echo (TFE) sequence, 256 x 256 matrix size, 1 x 1 x 1 mm^3 of spatial resolution and 160 slices covering the whole brain. About the diffusion weighted images, the acquisition protocol parameters were: 61 gradient directions and one baseline volume, b-value = 1000 s/mm^2, $2 \times 2 \times 2$ mm^3 of voxel size, 128×128 matrix and 66 slices covering the entire brain. Total acquisition time was 18 minutes.

The processing pipeline of the acquired MRI volumes is designed to obtain structural connectivity matrices by using both the anatomical (T1-weighted) and diffusion images (Fig. 1).

First, non-brain structures were removed from the T1 images, using BET, the brain extraction tool from the FSL software suite (http://fsl.fmrib.ox.ac.uk) (Smith, 2002). After that, the segmentation of 84 cortical structures was performed employing Freesurfer (https://surfer.nmr.mgh.harvard.edu) (Desikan, et al., 2006; Fischl, et al., 2004). From the same T1 images, gray matter, white matter and cerebrospinal fluid (CSF) were also segmented, and subcortical gray matter structures were obtained using FAST

and FIRST utilities from FSL, respectively (Patenaude, et al., 2011; Zhang, et al., 2001), and combined into a volume called 5tt (5-tissue-type) image.

In parallel, the brain was extracted from the diffusion weighted images (DWI) using DWI2MASK tool from MRtrix (www.mrtrix.org) (Dhollaner and Connelly, 2016). Also employing MRtrix, orientation distribution functions were estimated from the diffusion data using spherical deconvolution(Tournier, et al., 2007), which were later employed to generate anatomically-constrained tractography using both the diffusion data and the 5tt image (after registration). Two million streamlines were generated for each subject.

In order to characterize diffusion at each voxel, diffusion tensors were estimated using a least squares method (Salvador, et al., 2005), and scalar Fractional Anisotropy (FA) volumes were computed from the diffusion tensors. FA quantifies the amount of anisotropy in the diffusion tensor, that is, how much it deviates from a totally isotropic diffusion. FA is usually interpreted as a descriptor of white matter integrity, and decreases in FA have been related to alterations in the white matter due to several factors (demyelination and axonal destruction, among others).

Finally, connectivity matrices were constructed from the tractography results and the (registered) cortical segmentations. When a streamline between two cortical segmentations was found, the averaged FA was computed. Thus, 84x84 connectivity matrices were obtained using FA as connectome metrics (Fig. 2). A threshold was not applied to the obtained matrices; however, some matrix coefficients were equal to zero when a streamline was not found.

Similar connectomics analyses have been reported in schizophrenia (Di Biase, et al., 2017) and other neurocognitive conditions (Jones, et al., 2015)

2.4. EEG recordings and processing

2.4.1 EEG acquisition and preprocessing

EEG recordings were obtained following MRI scans, after a resting period of 30 minutes. Participants performed a 13 minutes three-tone P300 oddball task (for a detailed description see (Gomez-Pilar, et al., 2017a). Electrode impedance was always kept under 5 kΩ. Ground was placed at Fpz electrode and each channel was referenced over Cz electrode and re-referenced to the average activity of all active sensors (Bledowski, et al., 2004; Gomez-Pilar, et al., 2017b), yielding a total of 29 channels.

The P300 task has several advantages for assessing functional network modulation in schizophrenia. In addition to its widespread previous use in the field: (i) it is easy to perform, thus decreasing bias related to lack of subject's cooperation; (ii) its performance activates a large cerebral network (Linden, et al., 1999; Bledowski, et al., 2004); and (iii) differences in EEG global activation patterns have been reported in schizophrenia using this paradigm (Gomez-Pilar, et al., 2017a).

Signals were band pass filtered between 1 and 70 Hz. In addition, a zero-phase 50 Hz notch filter was used to remove the power line artifact. A three-step artifact rejection algorithm was applied to minimize electroculographic and electromiographic contamination (Bachiller, et al., 2015a): (i) an Independent Component Analysis (ICA) was carried out to discard noisy ICA components; (ii) after ICA reconstruction, EEG signals were divided into trials of 1 second length (ranging from 300 ms before to 700 ms after stimulus onset); and (iii) an automatic method was applied to reject trials whose amplitude exceeded an adaptive statistical-based threshold, which consists of two stages. First, the mean and standard deviation of each channel was computed. Then, trials that exceeded mean $\pm\, 4 \times$ standard deviation in at least two channels were discarded (Nunez, et al., 2017). *After this adaptive artifact rejection, 91.21 ± 11.28 trials for controls and 86.33 ± 14.13 for patients were left for further analyses.*

In order to describe the event-related potential (ERP) waveforms, Figure 1S has been include in the Supplementary material. ERPs in the midline electrodes are shown in Figure S1.A. Figure S1.B shows the channel grand average waveforms. Finally, Figure S1.C depicts scalps maps with the P300 peak amplitude for both groups.

2.4.2 EEG brain graphs

The functional brain network was characterized using EEG graphs. Electrodes were used to represent network nodes, whereas network edges were set by computing the neural coupling between pairs of electrodes. Specifically, neural coupling was established using the phase locking value (PLV) across successive trials (Lachaux, et al., 1999). PLV in sensible to small oscillations of the EEG (Spencer, et al., 2003) and takes into account nonlinearities (van Diessen, et al., 2015), which is an intrinsic feature of EEG recordings. PLV can be computed using different approaches. In this study, the continuous wavelet transform (CWT) was used to extract the phase information from each trial (Bob, et al., 2008). Edge effects in CWT were considered by computing the cone of influence (COI) for pre-stimulus and response time windows. Only wavelet coefficients inside the respective COI were considered for the analyses to avoid edge effects. We refer to our previous studies (Gomez-Pilar, et al., 2017b) for detailed explanations about how wavelet coefficient were computed, the wavelet parameters were configured and the COIs were applied to the CWT decomposition in order to minimize edge effects. After using CWT approach to perform filtering and phase extraction in one operation (Bob et al., 2008), the PLV between two signals x(t) and y(t) can be obtained evaluating the variability of the phase difference across successive trials:

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

where N_t is the number of trials, $\Delta\varphi_{xy}$ is the instantaneous phase difference between x and y signals, k is the time interval, and s the scaling factor of the mother wavelet (see (Bachiller et al., 2015) for details).

Thus, functional connectivity matrices based on PLV ranged between 0 and 1, where a value of 1 is obtained with completely synchronized signals and a value of 0 implies an absence of synchronization. Following the same methodology as in the structural data, functional connectivity matrices were not thresholded.

2.4.3 Segmentation of the EEG response

In order to assess the task-related modulation of the graph parameters along the odd-ball task, two time windows were considered for comparison. On the one hand, the pre-stimulus window (i.e. a period of expectation before the stimulus onset) ranges from -300 ms to the stimulus onset. On the other hand, the response window was selected to capture the P3b response. In order to take into account the inter-individual variability of the P3b response, the response window was adaptively set for each participant. Firstly, the event-related wave was computed for each subject by the synchronized averaging of all the trials corresponding to attended target tones. Secondly, a low-pass finite impulse response filter with cut-off frequency of 8 Hz was applied to the evoked wave in order to obtain only the components related to delta and theta frequency bands. It is noteworthy that this filter was only applied to estimate the time window related to the EEG response. Thirdly, the maximum amplitude of the low-pass filtered evoked wave in the Pz channel was located into a window ranging from 250 to 550 ms from the stimulus onset (Bachiller, et al., 2015b). The corresponding sample to the maximum amplitude was used as a central time sample of the response window. Finally, the response window was set on ±150 ms around the central time sample.

2.5. Graph-theory parameters

From both the structural and functional connectivity matrices, we calculated three graph-theory parameters to characterize global properties of the brain network: (i) connectivity strength (i.e. mean network degree) by means of network density (D), also named network strength (ii) network segregation using CLC, and (iii) network integration by means of PL (Rubinov and Sporns, 2010). For the sake of comparability and to obtain results independent of network size and network strength,, CLC and PL were computed over an ensemble of 50 surrogate random networks, which were used to normalize CLC and PL values obtained from the original networks (Stam, et al., 2009).

Therefore, normalized CLC and PL can be defined:

$$\mathrm{CLC} = \frac{\mathrm{C}}{\mathrm{C^{random}}}, \tag{2}$$

$$\mathrm{PL} = \frac{\mathrm{L}}{\mathrm{L^{random}}}, \tag{3}$$

where C and L can be defined as follows:

$$C = \frac{1}{N}\sum_{i=1}^{N} \frac{\sum_{\substack{i\neq j}}\sum_{\substack{i\neq l \\ j\neq l}} w_{ij}w_{il}w_{jl}}{\sum_{\substack{i\neq j}}\sum_{\substack{i\neq l \\ j\neq l}} w_{ij}w_{il}}, \tag{4}$$

$$L = \frac{N(N-1)}{\sum_{i=1}^{N}\sum_{j\neq i}^{N}\frac{1}{L_{ij}}}, \tag{5}$$

In equation (4), w_{ij} can be referred to PLV between nodes i and j (for functional analyses) or the structural connectivity between two regions using the streamlines from MRI. N is the total number of nodes of the network (29 in EEG analyses, 84 in MRI). Finally, L_{ij} is defined as the inverse of the edge weight (Stam et al., 2009).

With regard to the EEG functional network, parameters were computed into two frequency ranges. They were selected based on their relevance for the task-related modulation of the EEG during P300 tasks shown in schizophrenia in previous studies: the global band (from 1 to 70 Hz) (Gomez-Pilar, et al., 2017a) and the theta band (from 4 to 8 Hz) (Bachiller, et al., 2014; Doege, et al., 2009). A diminished task-related modulation of theta activity during an oddball task was found in schizophrenia, but not in faster frequency bands (Bachiller et al., 2014). In addition, the assessment of the theta band showed abnormalities in the brain network reconfiguration in the secondary functional pathways in schizophrenia (Gomez-Pilar et al., 2017b). On the other hand, the global band could be also useful to assess the specificity of the theta band.

Functional network parameters during pre-stimulus and its corresponding task-related modulation (i.e. difference between the response and the pre-stimulus windows) were used for statistics.

Structural connectivity network parameters will be referred to as dMRI-PL, dMRI-D and dMRI-CC, and functional network parameters as EEG-PL, EEG-D and EEG-CLC.

2.6. Statistics

We compared socio-demographic data (age, sex, education years and parental education) between patients and controls (t or χ^2 tests when appropriate). Each subgroup of patients (i.e., those with only EEG and those with EEG plus dMRI data) was compared to the corresponding controls.

2.6.1 Comparisons of graph-theory parameters

After testing normality and homoscedasticity of data distribution using Kolmogorov-Smirnov and Levene tests, we compared functional (EEG-based) and structural (dMRI-based) graph-theory parameters between patients and controls using Student´s t-tests. Within-group changes in functional network parameters were assessed using t-tests for related samples. After Bonferroni adjustment, p level was set to 0.05/15=0.003.

For the sake of interpretability, we studied the relationship between structural connectivity parameters (dMRI-PL, dMRI-D and dMRI-CLC) and the average FA values in identifiable relevant white matter tracts. *With this analysis, it could be easier to interpret the results of graph-theory data in terms of integrity of white matter tracts.* To do this, we used the methodology employed in a previous study (Molina, et al., 2017), in which FA was assessed in tracts connecting prefrontal cortex (PFC) with other relevant regions. Correlation coefficients between structural connectivity network parameters and FA values in these tracts were computed, with Bonferroni adjustment with p set to 0.001.

When statistically significant differences in network parameters were found between patients and controls, we compared the corresponding values between FE and stable chronic patients using Mann-Whitney U-tests for independent samples, to discard a major effect of chronicity in those differences.

2.6.2 Association between structural and functional networks

The main hypothesis of the study was that the structural connectivity of the brain network would determine the pre-stimulus functional network properties and/or its task-related modulation. This was studied using stepwise multivariate regression models. Since significant correlations between different structural variables were found, to avoid collinearity effects we performed principal component analyses (PCA) separately with structural (dMRI) and functional (EEG) variables for global and theta bands. This allowed a priori reducing the number of comparisons for further analyses, thus reducing the Type I errors risk. Individual structural and functional network factor scores were introduced respectively as independent and dependent variables in the regression model aimed to predict functional properties from structural network data.

2.6.3 Clinical and cognitive correlates

Next, we studied the cognitive and clinical correlates of graph-theory parameters for the patients using stepwise multivariate regression models (for structural and functional data). To calculate a global score summarizing cognition, individual cognitive scores were introduced in a PCA. The resulting individual scores were saved and introduced as dependent variables in the model. Possible associations between graph-theory parameters and symptoms were similarly assessed.

To discard major confounders, correlation coefficients were calculated between graph-theory parameters and both illness duration and current treatment doses.

3. RESULTS

There were no statistically significant differences between patients and controls in age and sex distribution in the whole sample, nor between patients and controls with dMRI data. Patients had fewer study years and a generalized cognitive deficit (Table 1).

3.1. Comparison of graph-theory parameters

3.1.1 Structural parameters

Patients showed statistically significant longer mean dMRI-PL values than controls (t=2.20, df=58, unadjusted p=0.03; Figure 3).

Values of dMRI-PL were inversely associated to FA values in relevant tracts linking PFC with anterior cingulate, superior temporal, insular and superior parietal cortices and hippocampus and caudate. Moreover, dMRI-CLC and dMRI-D values were directly associated to FA values in these tracts (3.2.3 section).

3.1.2 Functional parameters

Both EEG-PL and EEG-CLC in the global band and EEG-D in the theta band showed a significant increase from pre-stimulus to response within patients and control groups, which remained significant only in the controls after Bonferroni adjustment (table 2). Controls, but not patients, showed a significant increase in EEG-CLC and EEG-PL values in the theta band from pre-stimulus to response (Table 2). Therefore, a significant positive task-related modulation of EEG-CLC and EEG-PL values was found in this band only in controls.

In the global band, pre-stimulus window EEG-D was significantly higher for patients (t=2.52, df=115, unadjusted p=0.03; Figure 3; Table 2), without significant differences in the corresponding task-related modulation.

In the theta band, pre-stimulus EEG-D was higher (t=2.637, df=115, p=0.010), and EEG-PL task-related modulation was lower (t=-2.128, df=115, p=0.035) for patients (Figure 3; Table 2).

Between-group differences in functional and structural graph-theory parameters had medium effect sizes (Cohen´s d; Table 2), although these differences would not survive after Bonferroni adjustment.

3.1.3 Comparison between FE and chronic patients

As compared to the FE subgroup, we found larger structural PL in the chronic patients, while no differences were obtained between patient subgroups in global and theta band pre-stimulus density nor in theta band modulation (Supplementary material, Table S3).

3.2. Association between structural and functional networks

3.2.1 Correlations among graph-theory parameters: PCA

Correlations were high among graph-theory parameters based on structural (dMRI-CLC vs. dMRI-D r=0.802, p<0.001; dMRI-CLC vs. dMRI-PL r=-0.515, p<0.001) and functional data in the global (EEG-CLC vs. EEG-PL r=0.791, EEG-CLC vs. EEG-D r=0.512, p<0.001) and in the theta bands (EEG-CLC vs. EEG-PL r=0.919, p<0.001; EEG-CLC vs. EEG-D r=0.631,

p<0.001). Therefore, independent variables for the regression models were calculated from PCAs. Eigenvalues higher than the unit and scree-plots were used to select the number of factors, saving individual factor scores. PCA results are summarized in Table S2.

The PCA for structural parameters yielded one factor explaining 73.07% of variance (eigenvalue 2.192), with positive coefficients for dMRI-CLC and dMRI-D and negative for dMRI-PL. Factor scores were statistically significant lower for patients (mean -0.235, sd 1.125) than for controls (mean 0.294, sd 0.769; df=54, t=2.01, p=0.049).

PCA of EEG graph-theory parameters in the global band yielded a three factors solution explaining 88.49% of variance, respectively contributed by EEG-CLC, EEG-PL and EEG-D task-related modulation (42.40% variance, eigenvalue 2.544), pre-stimulus EEG-PL and EEG-CLC (25.39% variance, eigenvalue 1.52) and both pre-stimulus and task-related modulation of EEG-D (20.70% variance, eigenvalue 1.242). Scores for the third factor were significantly larger for patients (mean 0.300, sd 1.138) than for controls (mean -0.134, sd 0.893, t=2.26, df=115, p=0.026).

In the theta band, a two-factor solution was found. The first was positively related to task-related modulation of EEG-CLC, EEG-PL and EEG-D (53.07% variance, eigenvalue 3.18), whereas the second factor was positively related to pre-stimulus EEG-CLC, EEG-PL and EEG-D (23.55% variance, eigenvalue 1.41). Scores for the first factor were smaller at trend level for patients (mean -0.294, sd 0.759) than for controls (mean 0.119, sd 1-090, t=-1.86, df=115, p=0.065).

3.2.2 Prediction of functional scores based on structural scores

For the healthy controls, structural factor scores predicted functional global band pre-stimulus (EEG-PL and EEG-CLC) scores (R^2=0.222, df=1,24, F=6.86, β=-0.472, p=0.015). This relation was not significant for patients (R^2=0.008, df=1,29, F=0.23, β=-0.090, p=0.606).

In the patients, structural factor scores inversely predicted values of the first factor in the global band (task-related modulation of EEG-PL and EEG-CLC) (R^2=0.172, df=1,29, F=6.03, β=-0.415, p=0.02; Figure 4a). Therefore, in the patients, larger dMRI-CLC and dMRI-D values were associated to smaller task-related modulation of EEG-PL and EEG-CLC. Since dMRI-PL contributed negatively to the structural factor, that negative association between structural and functional factors implies that shorter dMRI-PL will predict larger EEG-PL and EEG-CLC task-related modulation.

In the patients structural factor scores did not predict functional parameters that had shown significant differences with controls: task-related modulation in the theta band (R^2=0.001, df=1,29, F=0.006, β=0.015, p=0.93), pre-stimulus EEG-D in the global band (R^2=0.024, df=1,29, F=0.075, β=-0.15, p=0.42) and pre-stimulus (EEG-CLC, EEG-PL and EEG-D) in the theta band (R^2=0.008, df=1,29, F=0.244, β=0.091, p=0.34).

For the sake of interpretability, we calculated Pearson´s correlations between individual d-MRI and EEG graph parameters. dMRI-CLC was negatively associated in the patients to task-related modulation of EEG-PL (r=-0.383, p=0.03) and EEG-PL (r=-0.495, p=0.005) in the global band. There were no significant correlations between task-related modulation in theta band parameters and individual dMRI-based graph parameters (-0.28>r>0.166).

3.2.3 Structural networks and specific tracts

Structural PL was inversely associated to FA (n=55) in the tracts linking homolaterally dorsolateral PFC with right cingulate (r=-0.299, p=0.028), left cingulate (r=-0.357, p=0.008), right hippocampus (r=-0.499, p<0.001), left caudate (r=-0.446, p=0.001), left parietal (r=-0.394, p=0.003), left superior temporal (r=-0.359, p=0.007), right superior temporal (r=-0.478, p<0.001), left insula (r=-0.322, p=0.016) and right insula (r=-0.359, p=0.007). No positive correlations were found between structural PL and FA values.

Structural CLC was directly related to FA in the tracts linking homolaterally dorsolateral PFC with right hippocampus (r=0.508, p<0.001), left parietal (r=0.392, p=0.003) and right parietal (r=0.273, p=0.044). Similarly, structural density was directly related to FA in the tracts linking homolaterally dorsolateral PFC with left hippocampus (r=0.328, p=0.016), right hippocampus (r=0.404, p=0.002), left thalamus (r=0.337, p=0.013), left caudate (r=0.268, p=0.050), left parietal (r=0.542, p<0.001), right parietal (r=0.435, p=0.001), left superior temporal (r=0.331, p=0.014), right superior temporal (r=0.475, p<0.001), left insula (r=0.316, p=0.019) and right insula (r=0.424, p=0.001).

Only associations at p≤0.001 were significant after Bonferroni adjustment.

3.3 Cognitive and clinical correlates

The factor analysis of cognitive scores yielded a single factor (eigenvalue 3.449), with positive coefficients for all but percent of perseverative errors, explaining 54.11% of the total variance.

Scores of the first factor in the theta band (modulation) directly predicted cognitive performance in the patients (R^2=0.312, df=1,28, β=0.558, F=12,22, p=0.002; Figure 4b). Structural values were not associated to cognition in patients.

Positive symptoms were inversely associated to structural network factor scores (R^2=0.329, df=1.29, F=13.21, β=-0.573, p=0.001; Figure 4c), therefore positively associated to dMRI-CLC and dMRI-D and inversely to dMRI-PL. The first factor in the global band (task-related modulation of EEG-PL and EEG-CLC) positively predicted positive symptoms (R^2=0.235, df=1,35, F=10,74, β=-1.274, p=0.002; Figure 4d). *To further clarify this point, we calculated the partial correlation coefficients between positive symptoms and structural factor scores controlling for global band task-related*

modulation (r=-0.459, p=0.006) and between positive symptoms and global band task-related modulation controlling for structural network values (r=0.432, p=0.01), supporting the independence of the associations.

3.4 Confounding factors

Duration of illness was inversely associated to structural factor scores (r=-0.599, p=0.001). Thus, larger duration would imply smaller dMRI-CLC and dMRI-D as well as longer dMRI-PL. Current antipsychotic dose was not significantly related to structural (-0.069<r<0.148, p=n.s.) nor functional (-0.040<r<0.183, p=n.s.) graph-theory parameters.

4. DISCUSSION

Global band network characteristics a baseline in control and its task-related modulation in patients were predicted by structural network parameters. EEG-PL and EEG-CLC in the global band and EEG-D in the theta band showed a significant task-related modulation only in controls after adjustment for multiple comparisons. Although unadjusted, patients showed larger dMRI-PL, higher pre-stimulus EEG-D at both global and theta bands and reduced functional task-related modulation of EEG-PL at the theta band, without any significant association between these structural and functional alterations. In patients, structural connectivity and theta task-related modulation respectively predicted positive symptoms and cognition.

Network parameters have been calculated from scalp sensors in the present work. Therefore, the connectivity estimates are not derived from true sources of the corresponding activity involved in task processing. Volume conduction effects imply that signals from different sources arrive to different sensors, hampering the estimation of the connectivity among the original activity sources (Brunner, et al., 2016; Van de Steen, et al., 2016). Our functional estimates are therefore to be considered just a global outline of the functional network characteristics and their modulation with cognitive activity. However, this outline may contain useful information regarding characteristics such as local clustering, mean path length and density of functional connections. They can be relevant to understand differences between patients and controls in terms of pre-stimulus network organization and their change with cognition. Source estimates using procedures such as Low Resolution Tomography (LORETA) might allow identifying activity sources from which PLV values could be calculated and among which structural connectivity could be assessed. This approach would be useful to describe effective connectivity relations among these sources, which can be of interest for the pathophysiology of psychosis. Those procedures, however, are not completely reliable, and the inverse solution problem remains unsolved. Therefore, the functional global outline here describe can hold a significant value, in particular its fast modulation with cognition; although only indirectly reflecting the characteristics of the underlying sources.

We calculated structural connectivity parameters using FA values from white matter tracts linking anatomical regions and functional connectivity using phase similarity of EEG signals between sensors. Both measurements summarized the same properties of the respective networks, and the prediction of global band pre-stimulus (controls) and task-related modulation (patients) functional values from structural scores supports the relation of both kinds of networks. Caution is necessary when considering these relations, given the above mentioned possible influence of volume conduction effects. Remarkably, abnormalities in structural and functional networks were unrelated in the patients.

The lower factor scores in the patients for structural connectivity (positively loaded for dMRI-CLC and dMRI-D and inversely related to dMRI-PL), suggest a reduced integrity of white matter connectivity in schizophrenia among nearby (reflected in lower CLC) and distant (longer PL) regions. The larger dMRI-PL in our patients is coherent with reports of reduction of global communication paths (Griffa, et al., 2015; van den Heuvel, et al., 2013) and lower FA in schizophrenia, likely reflecting alterations of long-range tracts (Ellison-Wright and Bullmore, 2009; Patel, et al., 2011).

To our notice, no previous study has explored the structural underpinnings of alterations of fast task-related modulation in functional networks in schizophrenia. Odd-ball task performance involves the coordination of different brain regions (Linden, et al., 1999). For both groups, EEG-PL and EEG-CLC in the global band increased from pre-stimulus to response windows, which implies that widespread local task-related activations elongate mean EEG-PL and increase EEG-CLC. In our cases, factor scores summarizing structural network (positively associated to dMRI-CLC and dMRI-D, and negatively to dMRI-PL) inversely predicted EEG-PL and EEG-CLC task-related modulation in the global band in patients. Thus, patients with smaller dMRI-CLC and dMRI-D, and larger dMRI-PL, would show a smaller global-band EEG-CLC and EEG-PL modulation. However, as compared to controls, patients did not show a deficit of functional EEG-PL task-related modulation in the global band, raising doubts about the significance for schizophrenia of that association between structural connectivity and global band modulation.

Instead, we found task-related modulation deficits in patients in the theta band. *However, modulation in the global band was not decreased in patients, which may relate to the relatively larger involvement of theta oscillations in P300 performance as shown by relative power and median frequency analysis during this task (Bachiller, et al., 2014).* Using different methodologies, smaller increases of theta power have been found for schizophrenia patients during P300 tasks (Bachiller, et al., 2014; Doege, et al., 2009). *Taken together, this suggests a higher impact on theta than global band connectivity in schizophrenia.* Since theta oscillations have a role in synchronization between distant regions (von Stein, et al., 2000), the task-related modulation deficit in theta suggests a decreased capacity for integrating activity across cortical regions in schizophrenia, which

would be not closely associated to anatomical connectivity deficits according to our results.

Such relative independence of structural and functional connectivity alterations surprised us, but could be explained by data showing that functional connectivity exists between regions without direct anatomical connection (Adachi, et al., 2012; Honey, et al., 2009). Thus, deficits of functional integration (in the theta band) would not require altered structural substrates. Coordination of activity between distant regions may be established indirectly, since functional connectivity is high among regions with common efferences to third regions, which may convey information to higher regions and may also receive similar afferences (Adachi, et al., 2012). Therefore, the alteration in relevant cortical hubs reported in schizophrenia (van den Heuvel, et al., 2013) may hamper the synchronization of regions not directly linked via with matter tracts. Although other data using anatomical and functional MRI show a substantial correspondence between the corresponding networks (Hagmann, et al., 2008), this relation had not been assessed yet with EEG data. Considering all this, we must underline that structural deficits were found in our patients (larger dMRI-PL and lower factor scores) and were predictive of positive symptoms. This suggests the coexistence of alterations in both structural and functional networks (in the theta band) within schizophrenia, but not necessarily in the same cases. In other words, either both unrelated functional and structural networks alterations are found in schizophrenia or they are characteristics of different schizophrenia subgroups. The latter possibility seems favored by recent reports supporting that structural connectivity values can segregate biologically valid clusters within schizophrenia (Lubeiro, et al., 2016; Sun, et al., 2015; Wheeler, et al., 2015). Using EEG, both no difference (Jhung, et al., 2013; Rubinov, et al., 2009) and a decrease (Micheloyannis, et al., 2006) of CLC at rest were reported in schizophrenia, which may be coherent with that possibility.

Remarkably, pre-stimulus EEG-D is higher in the patients. The density is the mean network degree (i.e. a measure of the network strength), implying a functional over-connectivity at rest in schizophrenia. This result is in agreement with the increased prefrontal functional connectivity reported in schizophrenia (Anticevic, et al., 2015). The different patterns of dMRI-D and EEG-D in patients, and the lack of a significant relation between them, support the independence of the alterations in both networks. Speculatively, the increased EEG-D might relate to the deficit in GABA function observed in schizophrenia (Gonzalez-Burgos, et al., 2011; Thakkar, et al., 2017), which could lead to hyper-synchronization. *In our study, functional connectivity is based on PLV values; thus, larger pre-stimulus theta EEG-D values suggest and excess of synchronization in the patients in this band, which could have a ceiling effect on task-related synchronization and might hamper theta EEG-D modulation. Therefore, an inhibitory transmission deficit could justify both the increased baseline D values and the lower modulation in the theta band, given its large implication in P300 task performance (Bachiller, et al., 2014; Doege, et al., 2009). This possible dependence on inhibitory function might also justify the lack of a significant prediction of theta modulation by structural connectivity.*

The increase in theta task-related modulation values (i.e., larger functional density, CLC and PL in this band) predicted better cognition in the patients. There was only one cognitive factor, which is not surprising since the assessment instrument (BACS) included the dimensions where performance was previously found decreased in schizophrenia. That predictive relationship suggests that cognitive deficit is secondary to the decreased capacity of modulating the functional network in the theta band, perhaps indicating a lesser capacity to integrate the activity of different areas in a task.

Our study is limited by the sample size of patients with both structural and functional network data available. A larger sample would be needed to test the hypothesis of distinct schizophrenia clusters based on structural connectivity. In addition, the assessment of nodal parameters could be of interest. However, connectivity analysis at the sensor level is very problematic due to effects of field spread (Schoffelen and Gross, 2009). Therefore, future studies should also be focused on increasing the number of EEG electrodes to provide more accurate results. Moreover, we cannot rule out an effect of treatment, although antipsychotic doses were unrelated to structural and functional graph parameters. It must be also noted that all EEG measures are influenced by volume conduction. In order to minimize this effect, a well-known strategy is based on the assumption that volume conduction affects the connectivity estimates in a similar way in two different experimental contrasts, such as pre-stimulus and response conditions (Bastos and Schoffelen, 2016). With regard to the use of dMRI-based connectivity, the accuracy of the cortical segmentation and the choice of the tractography method influence the obtained connectivity matrices. Although FA is the most usual dMRI descriptor for white matter integrity, it cannot identify the ultimate origin of connectivity alterations.

We may conclude that task-related modulation deficit in the theta band in schizophrenia is independent from deviation from normal structural network properties. This, considered together with the different correlates of functional and structural connectivity alterations, might support different clusters within the schizophrenia syndrome.

Conflicts of interest: None

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Table 1: Demographic, clinical and cognitive data in patients and controls. Significant differences with respect to controls are shown for patients   * $p<0.05$; **$p<0.001$; ***$p<0.001$.

	Patients		Controls	
	Schizophrenia (EEG, n=39)	Schizophrenia (EEG+dMR; n=33)	Controls (EEG; n=78)	Controls (dMR+EEG; n=27)
Age	33.053(8.801)	33.059(8.951)	30.948 (10.839)	34.668 (11.150)
Sex (M:F)	23:16	19:14	46:32	18:9
CPZ equivalents (mg/d)	377.901(196.934)	374.802(193.419)	NA	
Duration(months)	95.169(117.388)	83.86(117.456)	NA	
Education years	14.191(3.600)	14.882(3.051)	16.561(2.254)	17.427(2.866)

PANSS Positive symptoms	11.702(3.427)	11.388 (3.457)	NA	
PANSS Negative symptoms	17.571(7.309)	15.450 (5.057)	NA	
Total symptoms	53.810(18.892)	53.313 (18.913)	NA	
Total IQ	91.061(14.528) ***	94.701(11.789) ***	113.209(11.088)	109.458 (12.165)
Verbal memory	34.262(12.889) ***	35.315(12.345)***	51.115(8.194)	53.000(7.274)
Working memory	16.151(5.010) ***	17.074(4.148) ***	21.626(3.621)	23.140(2.723)
Motor speed	58.879(13.781) ***	62.538(12.041) ***	72.610(16.583)	85.503(8.154)
Verbal fluency	18.352(5.730) ***	19.613(4.799) ***	27.856(5.155)	28.827(5.177)
Proccessing speed	43.700(15.360) ***	45.641(14.672) ***	69.588(14.378)	69.251(14.841)
Problem solving	15.253(4.622)	16.317(3.418)	17.524(2.571)	17.042(2.641)
WCST perseverative errors (%)	17.921(10.123) ***	21.152 (17.077) ***	9.801(5.141)	8.221(3.573)
WCST completed categories	4.419(1.878) ***	4.812 (1.711) **	5.847(0.610)	5.879 (0.478)

Table 2. Structural and functional graph-theory parameters for patient and controls. Mean values are shown with the corresponding sd per group. Task-related modulation is defined as the difference for the corresponding functional parameter between its value at the response and pre-stimulus windows.

	Structural (dMRI) network			Functional (EEG) network						
					Global band			Theta band		
	Schizophrenia (n=33)	Controls (n=27)	Cohen´s d		Schizophrenia (n=39)	Controls (n=78)	Cohen´s d	Schizophrenia (n=39)	Controls (n=78)	Cohen´s d
CLC	0.995 (0.002)	0.995 (0.001)		Pre-stimulus Modulation	1.006 (0.004) 0.001 (0.001)#	1.007 (0.005) 0.001 (0.002)##		1.009 (0.006) -8.526E-05 (0.004)	1.008(0.004) 0.001 (0.004)#	
PL	1.018(0.009)*	1.013 (0.005)	0.686	Pre-stimulus Modulation	1.087 (0.028) 0.003 (0.008)#	1.088 (0.027) 0.004 (0.013)##		1.104(0.027) -0.001 (0.020)*	1.099 (0.022) 0.009 (0.025)#	-0.432
D	0.329 (0.032)	0.346 (0.030)		Pre-stimulus Modulation	0.326 (0.078)* 0.001 (0.009)	0.297 (0.053) -0.001 (0.013)	0.434	0.361 (0.043)* 0.008 (0.025)#	0.3381 (0.042) 0.020 (0.032)#	0.514

* Statistically significant differences between patients and controls (p<0.05) ; # statistically significant within-group task-related modulation(response minus pre-stimulus; p<0.05; ## idem p<0.001.

Figure legends

Figure 1. Processing pipeline yielding fractional anisotropy values to be used in graph-theory calculations.

Figure 2. (A) The 29 EEG channel labels superposed on the structural ROIs. EEG nodes (filled in white) were used to generate functional connectivity matrices from PLV values between each pair of electrodes. The figure illustrates the approximate placement of the EEG electrodes over the ROIs. *The list of the 29 electrodes used in the study according to international 10-10 system is: Fp1, Fp2, F7, F3, Fz, F4, F8, FC5, FC1, FCz, FC2, FC6, T7, C3, Cz, C4, T8, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, O1, Oz and O2.*

Figure 2. (B) Schematic depiction (axial and sagittal views) of the relevant tracts (streamlines) from which fractional anisotropy (FA) was calculated to generate structural connectivity matrices. Streamlines were calculated between each pair of the 84 nodes corresponding to the cortical segmentation are shown as spheres (their sizes are proportional to the actual size of the corresponding ROI). For the sake of clarity, only tracts linking PFC with anterior cingulate, superior temporal, insular and superior parietal cortices and hippocampus and caudate are drawn.

Figure 3. Error bars corresponding to the graph-theory parameters with statistically significant differences between patients and controls (from left to right, structural PL, functional pre-stimulus D at the global and at the theta bands, and functional PL task-related modulation at the theta band). Circles represent the mean value, while bars indicate the interval of confidence (95%).

Figure 4. Scatterplots showing the association between (a) factor scores resulting from the principal components analysis of structural graph-theory parameters (X axis) and scores of the second factor resulting from the principal components analysis of functional graph-theory parameters in the global band (modulation; Y axis); (b) factor scores for the first factor from the principal components analysis of functional graph-theory parameters at the theta band (modulation) and factor scores from the principal components analysis summarizing cognitive scores; (c) positive PANSS scores and global band PL and CLC task-related modulation and (d) structural network (right) Solid dots represent chronic patients, open dots represent FE patients.