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Biological and cognitive correlates of cortical curvature in schizophrenia

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ABSTRACT

Mean cortical curvature may relate to cortico-cortical connections integrity. We explored the association between prefrontal (PFC) cortical curvature and fractional anisotropy (FA) values for tracts connecting PFC and relevant cortical regions. In schizophrenia Anatomical and diffusion magnetic resonance images were obtained from 34 patients (16 of them first-episodes) and 32 healthy controls. We calculated curvature at rostral lateral prefrontal (RLPF) and superior medial prefrontal (SMPF) areas and mean FA for the tracts respectively connecting RLPF and SMPF areas with anterior caudal cingulate (ACC), superior temporal gyrus (STG) and superior parietal SP regions. Cognitive and clinical data were collected, including baseline symptoms, Clinical Global Impression change scores from baseline to follow-up, illness duration and treatment dosage. Patients showed significantly lower FA values in the tracts linking right RLPF-ACC, right SMPF-SPG and bilaterally PFC-STG. FA values in short-range cortico-cortical connections (linking PFC and ACC) were inversely associated with PFC curvature. In patients, cognitive performance was negatively associated with PFC curvature. Larger curvature values were associated to lack of clinical improvement at follow-up. We conclude that cortical curvature is influenced by integrity in short-range cortico-cortical connections and relates to cognition and clinical outcome in schizophrenia patients.

1. Introduction

The diversity of clinical manifestations of schizophrenia, together with the low replicability of biological findings and the diversity of genetic underpinnings in that syndrome, has led to proposals to divide schizophrenia into biologically homogeneous clusters (Crow, 1985). Recently, hyperdopaminergia (Howes and Kapur, 2014), white matter abnormalities (Sun et al., 2015) and genetic profiles (Arnedo et al., 2014) have been proposed as biological traits identifying distinct clusters of patients within the schizophrenia syndrome. Moreover, using network measurements and cortical thickness, deficit-type schizophrenia patients showed an increased density of connections relative to non-deficit patients (Wheeler et al., 2015). These findings support the relevance of anatomical connectivity for disentangling the variability in biological abnormalities in schizophrenia, since a significant decrease in that parameter might characterize a cluster of patients with a relatively distinct clinical and/or cognitive profile.

In this line, we recently reported the identification of a cluster of schizophrenia patients (including the same proportion of chronic and first episode cases) characterized by larger mean curvature values across most regions of the cortex (Lubeiro et al., 2016). This cluster was also different form the rest of cases in other parameters, i.e: i) lack of the expected increase in striatal glucose metabolism produced by antipsychotics, ii) reduced thalamic and cingulate metabolism and iii) worsening of negative symptoms in the follow-up.

Cortical curvature has been considered a marker related to cortico-cortical connectivity, in particular short-range connections (Ronan et al., 2012). Tracts connecting nearby areas on the cortical surface have U-fibers (short association fibers with a curve shape), while major tracts (such as inferior and superior longitudinal fascicles) have straight cores (Takemura et al., 2016). Although this relationship is still matter of discussion from that hypothesis can be predicted that white matter deficits would be reflected in higher curvature values (Ronan et al., 2011). Therefore, the cluster we identified could be also characterized by a deficit of short-range structural connectivity among relevant cortical regions. It seems thus of interest to test the possible association

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Table 1
Demographic, clinic, cognitive, curvature and FA data are shown for patients. FE and controls.

	Sz (n = 34) Mean (SD)	FE (n = 16) Mean (SD)	C (n = 33) Mean (SD)
Age	34.26 (9.98)	28.56 (7.77)*	35.61 (11.52)
Sex (M:F)	21:14	11:5	22:11
Education (years)	14.00 (3.52)**	15.25 (3.04)	16.62 (2.90)
Parental education (years)	10.41 (4.50)	12.60 (4.37)	12.00 (4.87)
Intelligence coefficient	94.18 (11.90)***	90.58 (11.98)***	115.93 (10.79)
Illness duration (months)	93.59 (118.75)	8.62 (11.09)	–
CZP equivalents (mg)	396.48 (236.55)	393.33 (265.33)	–
PANSS positive	11.47 (3.43)	10.44 (2.1)	–
PANSS negative	15.63 (5.072)	13.88 (3.14)	–
PANSS total	49.09 (12.70)	42.25 (6.7)	–
Verbal memory (L.L)	35.30 (12.12)***	37.38 (13.74)***	50.56 (8.98)
Working memory (D.S)	16.76 (4.41)***	18.08 (4.58)**	22.93 (2.67)
Motor speed (M.T)	61.34 (13.45)***	61.42 (9.44)***	83.93 (11.02)
Verbal fluency	19.30 (4.86)***	18.56 (5.38)***	29.24 (5.41)
Attention and processing speed (S.C)	44.45 (15.78)***	51.75 (12.63)***	69.96 (15.13)
Executive function/problem solving (T.L)	16.14 (16.81)	16.17 (2.76)	16.81 (2.7)
WCST perseverative errors (%)	20.79 (17.58)***	15.99 (9.94)**	9.46 (5.32)
PCA-F1	− 0.22 (0.92)	0.29 (0.61)	0.24 (1.06)
PCA-F2	− 0.17 (1.07)	0.06 (0.89)	0.16 (0.9)
printCG1	− 0.79 (0.72)***	− 0.61 (0.55)***	0.76 (0.51)
Curvature left RLPF (mm^{-1})	0.15 (0.01)	0.15 (0.01)	0.15 (0.01)
Curvature left SMPF (mm^{-1})	0.13 (0.01)	0.13 (0.01)	0.13 (0.00)
Curvature right RLPF (mm^{-1})	0.15 (0.01)	0.15 (0.01)	0.15 (0.01)
Curvature right SMPF (mm^{-1})	0.13 (0.01)	0.13 (0.01)	0.13 (0.00)
FA left RLPF-ACC	0.41 (0.03)	0.42 (0.03)	0.42 (0.03)
FA right RLPF-ACC	0.43 (0.04)*	0.44 (0.04)	0.45 (0.04)
FA left SMPF-ACC	0.37 (0.04)	0.37 (0.04)	0.38 (0.04)
FA right SMPF-ACC	0.4 (0.04)	0.41 (0.05)	0.39 (0.04)
FA left RLPF-SP	0.42 (0.03)	0.43 (0.02)	0.44 (0.02)
FA right RLPF-SP	0.43 (0.03)	0.44 (0.02)	0.44 (0.03)
FA left SMPF-SP	0.46 (0.02)	0.47 (0.02)	0.47 (0.02)
FA right SMPF-SP	0.47 (0.02)*	0.48 (0.02)	0.48 (0.02)
FA left RLPF-STG	0.44 (0.03)*	0.45 (0.02)	0.45 (0.02)
FA right RLPF-STG	0.45 (0.03)*	0.46 (0.03)	0.46 (0.02)
FA left SMPF-STG	0.45 (0.02)	0.46 (0.02)	0.45 (0.02)
FA right SMPF-STG	0.46 (0.02)*	0.46 (0.02)	0.47 (0.02)

Significant differences with controls:.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

between cortical curvature and structural connectivity in schizophrenia, which could contribute to further characterize a possible schizophrenia subtype. To do so, we investigated the correlates of cortical curvature in a new schizophrenia sample using diffusion magnetic resonance imaging (dMRI). Cognitive and clinical data were included, and we tested the possible influence of illness duration and antipsychotic treatment upon curvature. We focused on the prefrontal lobe and its more relevant connections, given the previous connectivity and folding alterations reported for this region in schizophrenia (Pettersson-Yeo et al., 2011; Wheeler and Voineskos, 2014; Zhou et al., 2015) and in particular the recent identification of white matter alterations in specific tracts connecting this region (Molina et al., 2017) and the larger gyrification (Nenadic et al., 2015) or curvature values reported for the same region in schizophrenia (Lubeiro et al., 2016).

2. Subjects and methods

2.1. Patients

The sample included 34 schizophrenia patients (16 of them were first-episode (FE) and 33 healthy controls (HC; Table 1). Participants were fully informed about the study and provided written informed consent. None of these subjects were included in our former report on schizophrenia sub-classification (Lubeiro et al., 2016) but they include the subjects that participated in a previous report on structural prefrontal connectivity assessed with dMRI (Molina et al., 2017).

Inclusion criteria for patients were (i) schizophrenia diagnosis made by an expert clinician (V.M.) according the criteria in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition; and (ii) for the FE patients, illness duration of less than one year. All patients were on stable doses of atypical antipsychotic treatment. Symptoms were scored using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Clinical Global Impression (CGI) change was scored to assess the patients global improvement, from 1 (large improvement) to 7 (large worsening). Improvement by this method was scored by the treating psychiatrist, when available, after 3–6 months of follow-up.

Exclusion criteria were: (i) intelligent quotient under 70; (ii) past or present substance abuse (except caffeine and nicotine); (ii) cranial trauma with loss of consciousness longer than one minute; (iv) for patients, any other mental or neurological diagnosis, and (v) for controls, any current neurological or psychiatric diagnosis or any treatment affecting central nervous system.

The study complied with the ethical standards of the Helsinki Declaration and was approved by the ethical committee of the University Hospital of Valladolid.

2.2. Cognitive assessment

Global IQ was assessed using a Spanish brief version of the Wechsler Adult Intelligence Scale WAIS-III (Fuentes Dura et al., 2010). We used the Spanish version of Brief Assessment in Cognition in Schizophrenia Scale (BACS) (Segarra et al., 2011; Wheeler and Voineskos, 2014), to assess performance in verbal memory (list learning), working memory (digit span), motor speed (token motor task), verbal fluency (categories), attention and processing speed (symbol coding) and executive function and problem solving (Tower of London), as well as the Wisconsin Card Sorting Test (WCST; percent of perseverative errors).

2.3. Diffusion MRI acquisition and processing

Acquisitions were carried out using a Philips Achieva 3 T MRI unit (Philips Healthcare, Best, The Netherlands) in the MRI facility at Valladolid University, and consisted of T1-weighted and diffusion weighted images.

For the anatomical T1-weighted images, acquisition parameters included: turbo field echo (TFE) sequence, 256 × 256 matrix size, 1 × 1 × 1 mm^3 of spatial resolution and 160 slices covering the whole brain.

With regard to the diffusion weighted images, the parameters of the acquisition protocol were the following: 61 gradient directions, one baseline volume, b-value = 1000 s/mm^2, 2 × 2 × 2 mm^3 of voxel size, 128 × 128 matrix and 66 slices covering the entire brain. Total acquisition time was 18 min. Both T1 and diffusion weighted images were obtained in the same session and in the same order (T1 followed by diffusion). The total acquisition time refers to the whole T1 + DWI protocol.

MR images were processed in order to obtain connectivity matrices and cortical curvature.

From the anatomical images, non-brain structures were first removed using the brain extraction tool from FSL (http://fsl.fmrib.ox.ac.uk) (Smith, 2002). Next, automatic cortical reconstruction was