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Alterations in prefrontal connectivity in schizophrenia assessed using diffusion magnetic resonance imaging

Vicente Molina [a,d,e,f,*], Alba Lubeiro [a], Oscar Soto [a], Margarita Rodriguez [c], Aldara Álvarez [d], Rebeca Hernández [d], Rodrigo de Luis-García [b]

[a] Psychiatry Department, School of Medicine, University of Valladolid, Av. Ramón y Cajal, 7, 47005 Valladolid, Spain
[b] Imaging Processing Laboratory, University of Valladolid, Paseo de Belén, 15, 47011 Valladolid, Spain
[c] Radiology Service, Clinical Hospital of Valladolid, Ramón y Cajal, 3, 47003 Valladolid, Spain
[d] Psychiatry Service, Clinical Hospital of Valladolid, Ramón y Cajal, 3, 47003 Valladolid, Spain
[e] Neurosciences Institute of Castilla y León (INCYL), Pintor Fernando Gallego, 1, 37007, University of Salamanca, Spain
[f] CIBERSAM (Biomedical Research Network in Mental Health), Instituto de Salud Carlos III, Spain

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ABSTRACT

Background: Spatial and biological characteristics of structural frontal disconnectivity in schizophrenia remain incompletely understood. Simultaneous streamline count (SC) and fractional anisotropy (FA) analyses may yield relevant complementary information to this end.
Methods: Using 3T diffusion magnetic resonance imaging both SC and FA were calculated for the tracts linking lateral and medial subregions of prefrontal cortex (PFC) to cingulate, hippocampus, caudate and thalamus in 27 schizophrenia patients (14 first-episodes) and 27 controls. Relationships of these parameters with cognition, symptoms, treatment doses and illness duration were assessed where significant between-groups differences were detected.
Results: Patients showed lower SC and FA in the tracts linking lateral and medial PFC to thalamus (likely corresponding to anterior thalamic peduncle) and lower FA in those linking PFC to caudate (likely through internal capsule), right caudal anterior cingulate and left hippocampus (likely corresponding to hippocampal-prefrontal pathway). Moreover, patients showed greater SC values for the tracts linking medial PFC and left caudal anterior cingulate. SC and FA values for the tracts linking PFC and caudal anterior cingulate were positively related to motor speed, executive function, problem solving and completed categories in WCST. FA for the tract linking right lateral PFC and caudate was directly related to positive symptoms and FA for the tract linking left medial PFC and left thalamus was inversely related to negative symptoms. Treatment doses were not associated with SC or FA values in any tract. Illness duration was negatively associated with SC and FA in the tracts linking PFC and subcortical areas.
Conclusions: Widespread alterations in frontal structural connectivity of PFC can be found in schizophrenia, and are related to cognition, symptoms and illness duration.

1. Introduction

Disconnectivity in schizophrenia is supported by analyses using diffusion magnetic resonance imaging (dMRI) revealing fractional anisotropy (FA) deficits, in white matter tracts (Ellison-Wright and Bullmore, 2009; Patel et al., 2011). Available evidences support that such disconnectivity may be particularly evident for the prefrontal cortex (PFC) (Wheeler and Voineskos, 2014) (Pettersson-Yeo et al., 2011). However, two questions concerning this alteration remain to be clarified. First, which are the specifically affected connections of PFC (i.e., with which particular regions is PFC connectivity more affected). Second, whether connectivity deficits identified in dMRI studies are secondary to impaired myelination or decreased number of axons (Alba-Ferrara and de Erausquin, 2013; Kochunov et al., 2007).

In order to investigate these possibilities, dMRI offers potentially useful complementary connectivity descriptors. FA is generally thought to reflect myelin integrity in the corresponding WM tracts, therefore its deficits likely reflecting myelination impairments. Besides, streamline count (SC) quantifies the number of streamlines connecting selected pairs of regions and its value may be associated to the number of

Abbreviations: BACS, Brief Assessment in Cognition in Schizophrenia Scale; CACC, caudal anterior cingulate cortex; dMRI, diffusion magnetic resonance imaging; DWIs, diffusion weighted images; FA, fractional anisotropy; FE, first-episode; HC, healthy controls; PANSS, Positive and Negative Syndrome Scale; PFC, prefrontal cortex; RLPF, rostral lateral prefrontal cortex; SC, streamline count; SMPF, superior-medial prefrontal cortex; TFE, turbo field echo sequence; WCST, Wisconsin Card Sorting Test; WM, white matter.

* Corresponding author at: Dept. of Psychiatry, University Hospital of Valladolid, Av. Ramón y Cajal, 7, Valladolid 48005, Spain.
E-mail address: viente.molina@uva.es (V. Molina).

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axons directly linking these regions (Jones et al., 2015). SC is the result of extracting the streamlines connecting two particular regions generated by a whole-brain tractography algorithm. Since the total number of generated streamlines is a fixed parameter, differences in SC values (for instance, between patients and controls) for a certain connection reflect differences in the connection strength of that connection relative to the total amount of connections in the brain. Thus, SC is complementary to FA, since it can provide information about subtle changes in the connectivity pattern that may not be identified using FA alone.

In order to investigate both possibilities (decreased myelination and/or number of axons) and its spatial distribution, we determined both SC and FA for the most relevant connections of the PFC. Since PFC is directly linked to a large number of regions in the normal brain we chose candidate connections by selecting regions directly connected to PFC and also meeting these criteria: i) prior findings supporting its involvement in schizophrenia and ii) having a role in functions deemed to be relevant to this syndrome.

Among the regions strongly linked to the PFC via direct connections and previously reported to be involved in schizophrenia are anterior cingulate (Baiano et al., 2007), hippocampus (Harrison, 2004), thalamus (Pergola et al., 2015) and caudate (Simpson et al., 2010). Besides, these regions play a role in cognitive functions deemed to be altered in schizophrenia, such as working memory, executive functions and social cognition (Barch and Ceaser, 2012; Sui et al., 2015). Given the different physiological roles of medial prefrontal and dorsolateral prefrontal cortices (Fuster, 1999), and the reported involvement of both medial (Fornito et al., 2009; Whitfield-Gabrieli et al., 2009) and lateral (Callicott et al., 2000; Fischer et al., 2012) prefrontal cortices in schizophrenia, we studied the tracts connecting both subregions of PFC with the above mentioned regions of interest.

Therefore, the aim of this study is to analyze both the spatial distribution and characteristics of PFC connectivity alterations in schizophrenia. To this end, the differences between patients and controls in SC and FA in relevant WM tracts were assessed. We hypothesized that deficits in SC and/or FA should be found in patients, independently of their treatment and chronicity and be related to clinical symptoms and/or cognitive deficits.

2. Subjects and methods

2.1. Patients

Our sample included 27 schizophrenia patients (14 of them were first-episode (FE) and 27 age and sex-matched healthy controls (HC; Table 1)). Participants were fully informed about the study and provided written informed consent.

Inclusion criteria for patients were (i) schizophrenia diagnosis according the Diagnostic and Statistical Manual of Mental Disorders, 5th edition criteria; and (ii) for the FE patients, illness duration of less than one year. The diagnosis were made or confirmed by an expert clinician (V.M.). All patients were receiving stable doses of atypical antipsychotic treatment at the time of MRI scans. Symptoms were scored using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

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 1 min; (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 intelligence quotient (IQ) was assessed using a Spanish brief version of the Wechsler Adult Intelligence Scale WAIS-III (Fuentes Dura et al., 2010). Other cognitive assessments included the Spanish version of Brief Assessment in Cognition in Schizophrenia Scale (BACS) (Segarra et al., 2011) and the Wisconsin Card Sorting Test (WCST; number of categories and percent of perseverative errors). Direct scores from the subscales of the Spanish version of the BACS were collected, including: verbal memory (list learning), working memory (digit span), motor speed (token motor task), verbal fluency (FAS), attention and processing speed (symbol coding) and problem-solving (tower of London).

2.3. Diffusion 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 T1-weighted and diffusion-weighted images.

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

With regard to the diffusion weighted images, the acquisition protocol parameters were: 61 gradient directions, one baseline volume, b-value = 1000 s/mm^2, $2 \times 2 \times 2$ mm^3 of voxel size, 128 × 128 matrix and 34 slices covering the entire brain. Total acquisition time was 18 min.

From the anatomical images, non-brain structures were removed in a first step using the brain extraction tool from FSL (http://fsl.fmrib.ox.ac.uk) (Smith, 2002). Next, automatic cortical reconstruction was performed using FreeSurfer (http://surfer.nmr.mgh.harvard.edu). Gray matter, white matter and CSF were also separated, and subcortical gray matter structures were obtained using “fast” and “first” utilities from FSL, respectively (Patenaude et al., 2011; Zhang et al., 2001). These structures were combined to form a “five-tissue-type” image (5tt) using “5ttgen” from MRtrix (www.mrtrix.org).

From the diffusion weighted images (DWIs), brain was then extracted using “dwi2mask” tool from MRtrix v3.12 (Dhollander et al., 2016). Afterwards, employing MRtrix, orientation distribution functions were estimated from the diffusion data using spherical deconvolution

Table 1
Demographic and clinical data shown as mean (sd). First-episode group ($n = 14$) is a sub-sample of the schizophrenia patients group ($n = 27$).

	Schizophrenia (all cases) $N = 27$	First episode schizophrenia $N = 14$	Healthy controls $N = 27$
Age	33.85 (9.13)	29.43 (7.94)	33.85 (10.54)
Sex (M:F)	17:10	9:5	18:9
Educational level (years)	13.79 (3.56)	15.50 (2.78)	15.67 (2.50)
Illness duration (months)	88.68 (123.84)	7.31 (8.30)	–
Chlorpromazine equivalents (mg)	374.80 (193.42)	357.14 (215.82)	–
PANNS positive	11.32 (3.60)	10.14 (2.00)	–
PANSS negative	15.04 (5.04)	13.36 (2.95)	–
PANNS total	47.60 (11.63)	41.00(6.18)	–