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Parkinsonism is associated to fronto-caudate disconnectivity and cognition in schizophrenia

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ABSTRACT

The present work studies the possible relation of parkinsonism and fronto-caudate dysconnectivity, as well as its relation to cognition in schizophrenia patients. We assessed parkinsonism using Simpson-Angus scale and pre-fronto-caudate connectivity using diffusion magnetic resonance in 22 schizophrenia patients (11 first-episodes) and 14 healthy controls. Fractional anisotropy was calculated for the white matter tracts directly linking rostral middle prefrontal (RMPF) and superior medial prefrontal (SMPF) regions with caudate nucleus. Cognition was assessed using the Brief Assessment of Cognition in Schizophrenia Scale (BACS). Total parkinsonism scores were negatively related to fractional anisotropy in the right SMPF-caudate tract in patients, which was also found in the first-episode patients alone, but not in controls. Parkinsonism was also inversely associated in patients to performance in social cognition, verbal memory, working memory and performance speed tests. In conclusion, our data support the involvement of fronto-striatal dysconnectivity in parkinsonism in schizophrenia.

1. Introduction

Motor abnormalities exist in schizophrenia (Peralta and Cuesta, 2001), not only in antipsychotic –treated patients (Compton et al., 2015; Hirjak et al., 2015; Peralta et al., 2010). Several types of motor abnormalities are found in this syndrome, classified according to different criteria into neurological soft signs, abnormal involuntary movements (AIMs; including tardive dyskinesia, akathisia, dystonia and spontaneous parkinsonism) and catatonic phenomena (Compton et al., 2015); into motor poverty, agitation, stereotypy/mannerisms, proskinetic, negativistic and dyskinetic dimensions (Peralta and Cuesta, 2001); and into catatonic, soft and hard neurologic and extrapyramidal signs (Cuesta et al., 2014). Among motor abnormalities, parkinsonism is the most frequently found in neuroleptic-naïve patients (Hirjak et al., 2015; Peralta et al., 2014). Nevertheless, in antipsychotic-treated patients it is very difficult to attribute parkinsonism either to drug or disease in cross-sectional assessments.

The cerebral substrates of motor abnormalities have been investigated using structural and functional imaging in schizophrenia (Hirjak et al., 2015; Walther, 2015). AIMs (mostly, tardive dyskinesia) have been related to morphological abnormalities in different regions of basal ganglia, largely in caudate (Altshuler et al., 1988; Bartzokis et al., 1990; Sarro et al., 2013), but also in right putamen (Elkashef et al., 1994) and globus pallidus (Elkashef et al., 1994). However, a role for cortical regions in AIMs has been also described, including prefrontal cortex (Heinz et al., 1988; Li et al., 2013) and its connections with basal ganglia (Bai et al., 2009). Therefore, a role for structurally altered fronto-subcortical connectivity can be hypothesized in AIMs in schizophrenia. In support of this, motor activity levels were inversely associated with fractional anisotropy (FA, a measure derived from diffusion magnetic resonance related to integrity of myelin) in white matter tracts underneath the right supplemental motor area, the right precentral gyrus and posterior cingulum in patients, such as internal and external capsule (Walther et al., 2011).

Since the underpinnings of parkinsonism in schizophrenia are much less investigated than those of tardive dyskinesia, we decided to focus in the former. To this end, our aim was to investigate the association between parkinsonism and specific cortico-basal ganglia connections

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meeting two conditions: (i) linking regions with reported involvement in schizophrenia and (ii) previously found to be abnormal in schizophrenia patients. Motor, premotor and prefrontal cortices send projections to the basal ganglia (Graybiel, 1997; Groenewegen, 2003), but prefrontal rather than motor/premotor regions seem involved in schizophrenia (Callicott et al., 2000; Fischer et al., 2012; Fornito et al., 2009; Whitfield-Gabrieli et al., 2009). Moreover, direct connections linking dorsolateral and superior frontal cortex to caudate were reported to show decreased FA in a recent study using connectomics to assess FA for the tracts linking pairs of regions of interest (Molina et al., 2017). Thus, we predicted an association between tracts linking prefrontal cortex and caudate to parkinsonism in schizophrenia. Since these tracts likely correspond to the dorsolateral frontal-subcortical circuit (Chow and Cummings, 1999), which has a role in both motor and cognitive functions, and parkinsonism may be associated to cognitive deficits in schizophrenia (Cuesta et al., 2014), we also assessed the cognitive correlates of AIMs in our sample. Spontaneous parkinsonism was not assessed in this sample, as patients were receiving antipsychotic treatment. Therefore, potential associations between cortico-subcortical connectivity and parkinsonism should be confirmed in neuroleptic-naïve samples.

2. Methods

2.1. Subjects

Our sample included 22 schizophrenia patients (11 of them were first-episode (FE) and 14 controls (Table 1). Participants were fully informed about the study and provided written informed consent. We have compared elsewhere the connectivity characteristics of the white matter tracts here included between patients and controls (Molina et al., 2017).

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 in a stable phase of illness and receiving stable doses of atypical antipsychotic treatment at the time of MRI scans. FE patients had been treated for one month or less. Treatment doses were converted to chlorpromazine equivalents according to the minimum effective dose method (Leucht et al., 2014). 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); (iii) cranial trauma with loss of consciousness longer than one minute; (iv) for patients, any other mental or neurological diagnosis.

The study complied with the ethical standards of the Helsinki Declaration and was approved by the ethical committee of the University Hospital of Valladolid. Written informed consent was obtained from the participating subjects.

Table 1
Sociodemographic, clinic, cognitive, connectivity and parkinsonism data. Asterisks indicate significant differences with controls: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

	All patients ($n = 22$)	FE patients ($n = 11$)	Healthy controls ($n = 14$)
Sex (M:F)	10:12	8:3	6:8
AP dose (CPZ equivalents)	356.81 (201.89)	328.12 (181.97)	N/A
Illness duration (months)	64.66 (78.98)	37.55 (26.89)	N/A
Age (years)	33.94 (8.09)	31.27 (7.60)	36.7 (10.90)
Education (years)	14.71 (3.53)	14.63 (3.80)	16.67 (2.08)
Parental education (years)	11.92 (4.27)	13 (3.88)	12.50 (4.63)
PANSS-positive	10.70 (2.44)	11 (2.14)	N/A
PANSS-negative	14.29 (3.40)	14.81 (3.62)	N/A
Verbal memory***	35.87 (11.59)	39.5 (9.87)	49.38 (9.44)
Working memory***	17.37 (4.03)	18.2 (4.23)	23.00 (2.51)
Motor speed***	58.5 (12.42)	60.8 (11.08)	85.08 (10.88)
Verbal fluency***	19.31 (4.06)	18.825 (3.89)	30.31 (5.13)
Performance speed***	46.5 (16.80)	50.9 (14.35)	66.92 (10.31)
Problem solving	15.12 (4.96)	15.2 (4.84)	16.08 (3.20)
Total IQ***	93.66 (12.03)	91.7 (11.45)	106.46 (6.87)
Left RMPF-caudate FA	0.36 (0.02)	0.37 (0.02)	0.38 (0.02)
Left SMPF-caudate FA	0.41 (0.02)	0.42 (0.02)	0.43 (0.02)
Right RMPF-caudate FA	0.36 (0.02)	0.37 (0.03)	0.38 (0.04)
Right SMPF-caudate FA	0.41 (0.02)	0.41 (0.02)	0.43 (0.03)
Total SAS score**	0.29 (0.39)	0.25 (0.35)	0 (0.0)
Rigidity-SAS**	0.37 (0.50)	0.31 (0.42)	0 (0.0)
Non-rigidity SAS**	0.098 (0.22)	0.12 (0.26)	0 (0.0)

2.2. Parkinsonism assessment

Parkinsonism was assessed using the Extrapyramidal Side Effects Rating Scale (Simpson and Angus, 1970) by one researcher (J.B.). This scale (henceforth Simpson-Angus Scale, SAS) yields scores in 10 subdomains and a total score. Given our sample size, we only used this total score (sum of item scores divided by 10). The SAS is a valid instrument to assess treatment-induced parkinsonism (Janno et al., 2005).

2.3. 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 dimensions of interest were scores using the Spanish version of Brief Assessment in Cognition in Schizophrenia Scale (BACS) (Segarra et al., 2011). 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).

2.4. Imaging methods

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 × 1 × 1 mm^3 of spatial resolution and 160 slices covering the whole brain.

Given the data supporting a role for caudate in AIM, we assessed caudate volumes using Free-Surfer software (http://surfer.nmr.mgh.harvard.edu).

2.4.1. Diffusion MRI acquisition and processing

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 × 2 × 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 a brain extraction tool from FSL (http://fsl.fmrib.ox.ac.uk) (Smith, 2002). Next, automatic cortical reconstruction was performed using FreeSurfer. 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), the brain was then extracted using "dwi2mask" tool from MRtrix v3.12 (Dhollander et al.,