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Reduced dorso-lateral prefrontal cortex in treatment resistant schizophrenia

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ABSTRACT

Background: Treatment resistance affects up to one third of patients with schizophrenia (SCZ). A better understanding of its biological underlying processes could improve treatment. The aim of this study was to compare cortical thickness between non-resistant SCZ (NR-SCZ), treatment-resistant SCZ (TR-SCZ) patients and healthy controls (HC).
Methodology: Structural MRI scans were obtained from 3 groups of individuals: 61 treatment resistant SCZ individuals, 67 non-resistant SCZ and 80 healthy controls. Images were analyzed using cortical surface modelling (implemented in freesurfer package) to identify group differences in cortical thickness. Statistical significant differences were identified using Monte-Carlo simulation method with a corrected p-cluster < 0.01.
Results: Patients in the TR-SCZ group showed a widespread reduction in cortical thickness in frontal, parietal, temporal and occipital regions bilaterally. NR-SCZ group had reduced cortex in two regions (left superior frontal cortex and left caudal middle frontal cortex). TR-SCZ group also showed decreased thickness in the left dorsolateral prefrontal cortex (DLPFC) when compared with patients from NR-SCZ group.
Conclusions: The reduction in cortical thickness in DLPFC indicates a more severe form of the disease or a specific finding for this group. Alterations in this region should be explored as a putative marker for treatment resistance. Prospective studies, with individuals being followed from first episode psychosis until refractoriness is diagnosed, are needed to clarify these hypotheses.

1. Introduction

Schizophrenia (SCZ) is a chronic psychotic disorder associated with significant impairment in social and occupational functioning that is estimated to affect 0.3 to 1.6% of the population (Kessler et al., 2005; Tandon et al., 2008).

In spite of recent advances in development of new antipsychotics, failure to achieve expected response is rather common, and 20–33% of patients with SCZ show limited response to standard medications (Lieberman et al., 1989; Lieberman, 1993; Wiersma et al., 1998). Treatment resistance to neuroleptic agents is more frequent in male than female, patients with poorer premorbid functioning, and earlier age of onset (Meltzer, 1997).

After the robust evidence of the superiority in efficacy of clozapine over other antipsychotics (Kane et al., 1988; Wahlbeck et al., 1999; Chakos et al., 2001; Iqbal et al., 2003), there was a recent trend to move to broader definitions of treatment resistance so that more patients are offered treatment with clozapine (Bondolfi et al., 1998; Pantelis and Lambert, 2003; The British Psychological Society and The Royal College of Psychiatrists, 2010). In fact, clozapine appears to have a positive effect even in symptoms traditionally considered resistant, such as negative symptoms and cognitive disturbances, particularly in domains of attention, verbal fluency and executive functions (Meltzer and McGurk, 1999). Nevertheless, due to its severe adverse effects clozapine prescription is recommended only after the patient being considered as treatment resistant (i.e.: failure to two adequate trial with antipsychotics) (Moore et al., 2007; The British Psychological Society and The Royal College of Psychiatrists, 2010). In contrast with the significance of refractoriness in clinical setting, there are only few studies investigating possible neurobiological correlates or consequences of lack of response to neuroleptic agents. To date there are no putative biological marker that could help clinicians to propose an earlier introduction of clozapine.

Regarding structural abnormalities in SCZ, one of the most replicated findings is that individuals with this disease show reductions

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in brain volume and cortical thickness in several regions (e. g.: prefrontal and temporal cortices) (Kuperberg et al., 2003; Cotter et al., 2004; Wiegand et al., 2004; Narr et al., 2005; Hamilton et al., 2007; Narayan et al., 2007; Yoon et al., 2007; Nesvag et al., 2008; Schultz et al., 2010). Disease duration, severity and medication use (Staal et al., 2001; Woods et al., 2005; Haijma et al., 2012) have been associated with these reductions. In addition, poorer treatment response has been linked to gray matter reduction (Harvey et al., 1993; Lieberman, 1999), but there are no studies evaluating brain thickness in treatment resistant SCZ and in comparison to non-treatment resistant patients. Cortical thickness is thought to better represent an endophenotype for a disorder than volume (which is cortical thickness and area measures combined) (Panizzon et al., 2009).

The objective of this study is to compare cortical thickness between non-resistant schizophrenia, treatment-resistant schizophrenia and healthy controls. We hypothesize that TR-SCZ group will have greater reduction in cortical thickness, which would be compatible with a more severe disease process.

2. Methods

2.1. Participants

A total of 208 participants, being 61 TR-SCZ, 67 NR-SCZ, 80 HC participated in this study. Subjects were recruited from an outpatient unit for treatment of SCZ. Diagnosis was confirmed according to DSM-IV criteria using The Structured Clinical Interview for DSM-IV (SCID I). Trained psychiatrists conducted all interviews. All patients were being followed for at least one year. Healthy controls were recruited from a governmental employment agency, among individuals without any current or lifetime psychiatric diagnosis or 1st degree relative with a major psychiatric condition. Subjects in the NR-SCZ and TR-SCZ were also assessed with the positive and negative syndrome scale (PANSS) (Kay et al., 1987) and global assessment of functioning (GAF) (Jones et al., 1995). Medication doses were standardized using defined daily dose (DDD), following the guidelines available in http://www.whocc.no/atc_ddd_index.

Treatment resistance was defined as a failure to respond to 4–6 week trials of at least two different antipsychotic medications in adequate doses (equivalent to at least 400 mg/day of chlorpromazine or 5 mg/day of risperidone). Additionally, 6 month period without remission was required (i.e.: score of 4 or more in eight PANSS items: delusions, unusual thought content, hallucinatory behavior, mannerisms/posturing, blunted affect, social withdrawal, and lack of spontaneity). These criteria follow the recommendation of the International Psychopharmacological Algorithm Project [www.ipap.org].

This study was approved by the Research Ethics Committee of UNIFESP [CEP No. 0661/11], and a written informed consent was obtained from all recruited participants. Clinical and laboratory investigations were strictly conducted according to the principles expressed in the Declaration of Helsinki.

2.2. MRI Protocol

Images were acquired in a Siemens 1.5 T scanner using a 3DSPGR sequence for volumetric analysis (TE = 3.4 ms; TR = 2000 ms; FoV = 256 mm; flip angle: 15°; matrix size: 256 × 256; slice thickness: 1 mm).

2.3. Data analysis

Cortical reconstruction and volumetric segmentation were performed with the Freesurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications (Fischl and Dale, 2000; Fischl, 2012).

For statistical analysis we used the general linear model in order to identify the main effect of group (TR-SCZ vs SCZ; TR-SCZ vs control; SCZ vs control), controlling for age and gender and a surface Gaussian smoothing (FWHM = 15 mm). Statistical significant differences were identified using Monte-Carlo simulation method with a corrected p-cluster < 0.01 (vertex-z-threshold = 2.0). For the comparison between patient groups we used the PANSS total score as a nuisance factor in order to reduce the influences of symptom severity. Additional analyses were carried out with duration of illness and DDD as nuisance factor. In patients receiving clozapine, DDD was correlated to thickness co-varied for age and gender.

For demographics and clinical characteristics we used one-way ANOVA or chi-square test (when appropriated) using SPSS 20.0 for Mac. Statistical significance was set in 0.05.

3. Results

Demographics and clinical characteristics of the sample are described in Table 1. All subjects with schizophrenia from both treatment groups were receiving antipsychotic medication. The majority of patients in TR-SCZ group were receiving clozapine (clozapine: 72.1%, olanzapine: 19.7%, quetiapine: 3.3%, haloperidol: 1%, risperidone: 1% and aripriprazole: 1%). NR-SCZ received olanzapine more frequently (55.2%) followed by quetiapine (13.4%), risperidone (13.4%), haloperidol (6%), aripriprazole (6%), ziprasidone (1.5%), trifluoperazine (1.5%), paliperidone (1.5%) and, zuclopenthixol (1.5%).

3.1. Non-resistant schizophrenia vs healthy control

NR-SCZ exhibited significant decrease in the left superior frontal cortex (Fig. 1) (coordinates (x,y,z): −11, 19.2, 35.4, cluster size: 1222 mm^2, $p < 0.01$) and left caudal middle frontal cortex (coordinates (x,y,z): −38, 13.7, 32.5, cluster size: 1005 mm^2, $p \leq 0.01$).

Table 1
Clinical and demographic characteristics of the sample.

	HC (n = 80)	TR-SCZ (n = 61)	NTR-SCZ (n = 67)	Test-value	P
Age in years (mean/SD)	33.46/8.67	33.80/8.54	35.81/8.76	F = 1.48	0.229
Male (%)	66	65	67	X^2 = 0.80	0.914
PANSS positive (mean/SD)	–	14.10/4.52	11.61/3.66	F = 11.99	0.001*
PANSS negative (mean/SD)	–	18.67/5.75	15.39/4.68	F = 12.63	0.001*
PANSS general (mean/SD)	–	30.39/7.62	27.73/6.84	F = 4.33	0.03*
PANSS total (mean/SD)	–	63.41/14.82	54.58/12.63	F = 13.21	<0.001*
GAF (mean/SD)	–	47.77/10.95	55.42/12.88	F = 12.63	<0.001*
Duration of illness in years (mean/SD)	–	12.9/6.72	12.21/7.29	F = 0.310	0.57
DDD (mean/SD)	–	1.71/.68	1.34/0.63	F = 10.43	0.002*

PANSS: positive and negative syndrome scale; GAF: global assessment of functioning scale; DDD: antipsychotic defined daily dose.
* $p < 0.05$.