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Greater clinical and cognitive improvement with clozapine and risperidone associated with a thinner cortex at baseline in first-episode schizophrenia

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ABSTRACT

Cortical thickness may be useful as a treatment response predictor in first-episode (FE) patients with schizophrenia, although this possibility has been scarcely assessed. In this study we assessed the possible relation between cortical thickness in regions of interest selected because of previously reported structural alterations in schizophrenia and clinical and cognitive changes after two years of treatment with risperidone or clozapine in 31 neuroleptic-naïve FE patients with schizophrenia (16 of them treated with clozapine and 15 with risperidone). Using the last-observation-carried-forward (LOCF), a larger improvement in positive, negative and total symptoms was predicted by the amount of baseline cortical thinning in the right prefrontal cortex (pars orbitalis). After two years of treatment, cognitive status was reassessed in the 17 patients (11 on clozapine) who had not dropped out. Working memory improvement after reassessment was associated with a greater baseline cortical thinning in the left prefrontal cortex (pars orbitalis), and verbal memory improvement with a greater baseline cortical thinning in the left pars triangularis. Significant but weak cortical thickness decrease from baseline to follow-up was observed in patients in comparison to controls (left pars triangularis and opercularis, and left caudal middle frontal areas). These results may support a positive predictive role for cortical thinning in the frontal region with regard to clinical and cognitive improvement with clozapine and risperidone in FE patients with schizophrenia.

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1. Introduction

Cortical thinning (mostly at frontal and temporal regions) has been reported in chronic (Goldman et al., 2009) and FE antipsychotic naïve patients with schizophrenia (Xiao et al, 2013; Venkatasubramanian et al., 2008) or FEs treated with antipsychotics for no more than 6 weeks (Crespo-Facorro et al., 2011), although the possibility still exists that some groups of patients are without cortical thinning (Wiegand et al., 2004). Changes in cortical thickness have been reported for global and lobar regions (Crespo-Facorro et al., 2011), automated parcellations of the frontal lobe (Venkatasubramanian et al., 2008) or regions of interest across the brain (Goldman et al., 2009; Xiao et al., 2013).

Significant cortical thinning, if present, may reflect some neurodevelopmental correlate (Bystron et al., 2008) that might modify treatment response. Thus, the possibility that treatment response in FE patients may be different depending on their degree of cortical thinning seems worth exploring. Moreover, cortical thickness may also vary in relation to environmental factors such as early experiences (Whittle et al., 2014), which might also modulate treatment response.

To our knowledge, in FE schizophrenia only one report described significantly larger occipital thickness and greater frontal asymmetry in treatment responders (Szeszko et al., 2012). The association between cognitive improvement and baseline thickness has not been previously assessed. Our objective in the present study was to assess the prediction of clinical and neuropsychological response based on pre-treatment cortical thickness in a group of FE neuroleptic-naïve patients with schizophrenia. Moreover, we re-assessed cortical thickness after two years of antipsychotic treatment with risperidone or clozapine. Our a priori hypothesis was that greater baseline cortical thickness would be associated with greater clinical improvement.

2. Methods and material

The present data stem from an open label, clinical trial on clozapine use in FE patients with schizophrenia, approved by the Ethics

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Committee of the Hospital Doce de Octubre (Madrid), authorized by the Spanish Agency of Medicine and Sanitary Products (AEMPS) and registered in the clinical trials database of the European Medicines Agency as EUDRACT No.: 2006-002000-34. This trial was developed without any commercial interests and was completely financed from public agencies. In this trial, FE neuroleptic naïve patients with schizophrenia or schizophreniform disorder were randomly assigned to risperidone or clozapine and followed for two years in a clinical setting (Hospital Doce de Octubre, Madrid). At inclusion and after two years, magnetic resonance imaging (MRI) studies were obtained to determine cortical thickness. The corresponding clinical assessments during follow-up were periodically performed by one of the authors (JS-F) and cognitive assessments by another author (DT). We have previously reported on clinical outcomes after one year in this sample (Sanz-Fuentenebro et al., 2013); in that paper we described the study design in further detail (Fig. 1).

The patients were included after written acceptance of the corresponding informed consent form. The inclusion criteria were as follows: (i) diagnosis of schizophrenia or schizophreniform disorder (according to DSM-IV-TR criteria and determined by one of the authors: JS-F; experienced psychiatrist) with less than two years of evolution and without any previous treatment; (ii) absence of any other psychiatric disorder (Axis I or focal neurological signs); (iii) absence of psychotropic drug use one month before the study commencement, or antidepressants in the three months prior to inclusion; (iv) absence of cranial trauma or infection of the central nervous system; (v) absence of drug dependency, including alcohol, with the exception of nicotine and caffeine; and (vi) age below 35 years in males and 40 years in females.

Upon inclusion, patients were randomly assigned to clozapine or risperidone according to the order of inclusion in the trial. Out of 59 contacted patients, 35 of them (24 males) agreed to inclusion. Three patients were excluded during follow-up as their condition did not evolve to schizophrenia. Four additional cases were lost to follow-up in the initial four weeks. The 31 remaining patients (22 males) were randomly distributed to clozapine/risperidone (16/15). Of them, seventeen patients who had not dropped out of the study were available for a second MRI study and neuropsychological assessment after two years of treatment (11 on clozapine, 6 on risperidone).

Twenty-three (16 males) healthy controls were also included; of them a second MRI study was available for 11 participants.

For clinical assessment, we employed the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). The dosage of the treatment was prescribed according to the patient's situation as usual in clinical practice (started at 12.5 mg a day, maximum dosage of 900 for clozapine; started at 2 mg, maximum dosage of 10 for risperidone). The mean dosage employed at week 12 was 5.22 (SD: 0.97; range: 4–6) for risperidone and 226.66 (SD: 97.95; range: 100–400) for clozapine; and after one year: 5.43 (SD: 1.51; range: 4–8) for risperidone and 220.45 (SD: 112.26; range: 25–350) for clozapine. All patients remained on monotherapy throughout the study. Treatment compliance of the patients that adhered to treatment was considered good on the basis of clinical interviews, counting of pills and plasmatic levels of clozapine and risperidone.

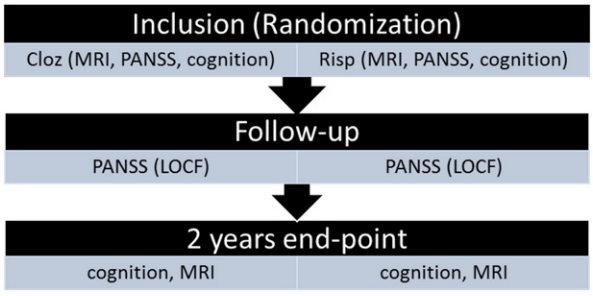

Fig. 1. Flowchart showing the basic design of the study. Inclusion criteria are described in the text. When patients dropped out before the 2 year end-point the clinical scores at the last observation carried forward (LOCF) were used as dependent variables for prediction. Structural and cognitive variables were reassessed after 2 years.

Mean cumulative doses were assessed in milligrams with the use of haloperidol equivalents (on the basis of 1:1 for risperidone and 40:1 for clozapine) according to the Netherlands Pharmacotherapeutic Compass guidelines (2002) Mean cumulative dose in haloperidol equivalents by the last-observation-carried-forward (LOCF) was 2154.52 (SD: 1717.66) mg.

For the assessment of side effects, we employed the Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale (Lingjaerde et al., 1987); we defined two scores derived from the UKU: "motor" (M) (sum of severity scores for dystonia, rigidity, hypokinesia, hyperkinesia, tremor, and akathisia) and "subjective" (SUB) (sum of severity scores for concentration, asthenia, somnolence, memory, excessive sleep, emotional indifference, and depression).

Patients would be excluded from the study for the following reasons: their condition did not evolve to a diagnosable schizophrenia disorder, withdrawal of consent, non-fulfillment of treatment to a minimum of four weeks, follow-up protocol violation, pregnancy, important adverse occurrences (defined according to the "Norms of Good Clinical Practice" of the Spanish Agency of Medicine and Sanitary Products (AEMPS)) or therapeutic failure (defined as an increase of 50% of the total PANSS scores with respect to baseline, with scores higher or equal to "Moderate" (=4) in the positive subscale items for more than two weeks) during follow-up. Clinical interviews and urinalyses were periodically used throughout the study in order to discard substance abuse.

2.1. Cognitive assessment

At baseline and after 2 years cognitive assessment was performed by following standard neuropsychological tests and variables: (1) total number of completed categories and (2) percentage of perseverative errors of the WCST as a measure of cognitive flexibility; (3) total hits for level 2 of the N-back task, as a measure of working memory capacity; (4) Rey Auditory–Verbal Learning Test delayed recall and (5) Rey–Osterrieth Complex Figure Test delayed recall – raw scores – as measures of verbal and visual memory; (6) Stroop Word/Color Test Interference raw score, as a measure of selective attention capacity and (7) WAIS-III Vocabulary subtest (using scaled scores) as a Global IQ predictor.

2.2. Imaging methods

2.2.1. Image acquisition

3D SPGR T1 MRI studies were acquired in 24 patients with schizophrenia and 12 controls using a General Electric GE (Waukesha, WI) 1.5 T MRI system and in 11 patients and 12 controls using a Phillips (Best, the Netherlands) Achieva 3 T system ($\chi^2 = 2.08$, df = 1, p = 0.163). All of the cases with both baseline MRI and follow-up MRI acquired these studies with the same system.

2.2.2. Image processing

All of the T1 images were B1 bias corrected in order to improve the spatial signal homogeneity. Cortical thickness measurements were carried out following the steps and recommendations described in Fischl and Dale (2000) and Han et al. (2006). The cortical thickness results were generated using the fully automated processing pipeline by the FreeSurfer toolkit (version 3.3, http://surfer.nmr.harvard.edu), which requires no manual intervention. However, segmentations were checked visually for inconsistencies by an expert and no editing was needed. Cortical thickness was assessed bilaterally in the following regions (chosen a priori due to previous reports of changes in cortical thickness in schizophrenia and/or treatment response): frontal (superior frontal, caudal middle frontal, rostral middle frontal, pars opercularis, pars triangularis, pars orbitalis, lateral orbital, medial

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