PREFRONTAL CORTICAL THICKNESS RELATED TO NEGATIVE SYMPTOMS IN ANTIPSYCHOTIC-NAÏVE, FIRST-EPISODE PSYCHOTIC PATIENTS

Guinart D[1,2], Bergé D[1,2,3,4], Mané A[1,2,3,4], Galindo L[1,2], Vilaroya O[2,4], Perez-Sola V[1,2,3,4]

1. Institut de Neuropsiquiatria i Addicions; Parc de Salut Mar, Barcelona. 2. Institut Hospital del Mar d'Investigacions Mèdiques; Parc de Salut Mar, Barcelona. 3. Centro de Investigación Biomédica en Red de Salud Mental (Cibersam); G21. 4. Universitat Autònoma de Barcelona

INTRODUCTION

Schizophrenia is a severe mental disorder with a devastating effect on patients and their families, but the etiology and the underlying pathophysiology of this terrible disease remain still unknown. However, recent advances in neuroimage quality and resolution, together with the use of sophisticated algorithms for data processing, have made it possible to reconstruct and estimate the subjects' cortical surface with high precision, allowing the identification and characterization of multiple structural elements of the gray matter (1). Using such novel techniques, a significant cortical thinning has been repeatedly observed in adult-onset first-episode schizophrenia patients compared to healthy controls, mostly in medial and inferior prefrontal areas, specially cingulate, dorsolateral prefrontal and orbitofrontal cortices (2,3). However, it is yet unclear whether all these replicated alterations are related to any particular clinical feature.

METHODS

In a longitudinal design, high-resolution T1-weighted images were acquired from 23 antipsychotic-naïve, first-episode psychotic patients and 26 age-matched healthy comparison subjects. Cortical thickness measurement and cortical parcellation according to the Desikan template (Figure 1) were performed with the Freesurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). Clinical features were measured with the negative subscale of the Positive and Negative Syndrome Scale (PANSS) (5) at basal point and after a 2-month follow-up period and regressed on cortical thickness from our a priori selected regions of interest in prefrontal cortex. Age and gender among groups were compared using t-tests and chi-square tests. All statistical analyses were performed using R software (6).

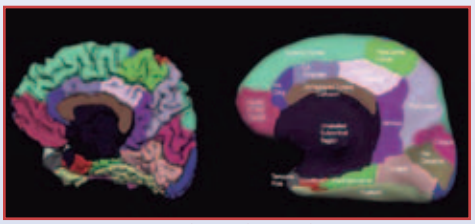

Figure 1. Medial view of pial (left) and inflated (right) cortical representations of the regions of interest in Desikan template (4).

RESULTS

No differences were found regarding age or gender when comparing patients and controls (Table 1, Table 2)

Table 1. Group differences on age.

Variable	Levels	n	mean	s
	Controls	23	29,3	3,4
	Patients	26	26,9	5,5
p=0.07	all	49	28,2	4,6

n: Number S: Standar desviation

Table 2. Gender distribution among groups.

Variable	Levels	n controls	% controls	n patients	% patiens	n all	% all
	F	12	46,1	13	13	56,5	51
	M	14	53,9	10	10	43,5	49
p=0.66	all	26	100	23	23	100	100

F: Female M: Male n:number %:percentage

We found a significant cortical thinning in the left medial orbitofrontal cortex (patients-controls = 2,50-2,72mm = -0,22mm; p = 0,00), as well as a significant volume and surface area reduction in this cortical area in patients compared to healthy age- and gender-matched controls. We also found a significant thinning of the right lateral orbitofrontal cortex in pacients compared to controls (patients-controls = 2,44-2,61mm = -0,21mm; p = 0,01), as shown in Table 3. All other prefrontal regions showed no significant differences in cortical thickness, volume or surface area.

Table 3. Statistically significant prefrontal alterations in cortical thickness in antipsychotic-naïve, first-episode psychotic patients compared to healthy controls.

Region	Cortical Thickness (patients), mean (mm)	Cortical thickness (controls), mean (mm)	Difference (mm)	P value
Medial orbitofrontal (left)	2,5	2,72	-0,22	0,00
Lateral orbitofrontal (right)	2,44	2,61	-0,21	0,01

Regarding clinical performance, no correlation was found at baseline between left medial orbitofrontal nor right lateral ortitofrontal cortical thickness and scores of the negative subscale of the PANSS. However, at the 2-month evaluation clinical performances were significantly associated to the left medial orbitofrontal cortical thickness values at baseline (p=0,017).

DISCUSSION

The main findings of this study were on the one side the thinning of the left medial orbitofrontal and right lateral orbitofrontal cortices in antipsychotic-naïve, first-episode psychotic patients compared to healthy controls and on the other hand the association between left medial orbitofrontal cortical thickness and clinical features, measured by the negative subscale of the PANSS, at a 2-month follow-up evaluation. Firstly, our findings regarding prefrontal cortical thickness alterations, which are already present at disease onset, are in line with previous literature[2,3] and support the idea that some subtle alterations in prefrontal cortices may be present at disease onset. This is a specially relevant finding in antipsychotic-naïve patients, as antipsychotic exposure may result in neuroanatomical changes, even within the first weeks of treatment[7]. Interestingly, we did not find a relation between cortical thickness alterations and clinical performance at baseline but we did find a correlation with clinical symptoms at the 2-month evaluation. This could imply the existance of compensatory mechanisms that may take place in the initial phases of the disease, but this shall be confirmed in further evaluations. Nevertheless, the clinical relevance of cortical thickness in first-episode psychosis remains unexplained.

CONCLUSION

Cortical thickness alterations in prefontal cortex appear to be present at disease onset and this alterations may relate to clinical outcome. However, our findings must be considered just as exploratory, given the small sample size of our study and the relatively short follow-up period. Larger longitudinal studies may help characterize , replicate and consolidate these findings to shed some light on the pathogenesis of this devastating condition.

BIBLIOGRAPHY

1. Fischl B, Dale A. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci U S A 2000; 97(20):11050–11055.
2. Venkatasubramanian G, Jayakumar PN et al. Automated MRI parcellation study of regional volume and thickness of prefrontal cortex (PFC) in antipsychoticnaïve schizophrenia. Acta Psychiatr Scand 2008; 117:420-431.
3. Schultz CC, Koch K, Wagner G et al. Reduced cortical thickness in first-episode schizophrenia.Schizophrenia Research 2010; 116: 204-209.
4. Desikan, R.S., Segonne, F., Fischl, B.,et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage; 2006 (31) 968-980.
5. Kay SR, Fiszbein A and Opler LA; The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia, Schizophr Bull (1987) 13 (2): 261-276.
6. R Development Core Team (2008). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL)(http://www.R-project.org).
7. Goghari VM, Smith GN, Honer WG et al. Effects of eight weeks of atypical antipsychotic treatment on middle frontal thickness in drug-naïve first-episode psychosis patients. Schizophr. Res. 2013; 149:149-155.