CNS Spectrums (2013), **18**, 315–321.
doi:10.1017/S1092852913000333

ORIGINAL RESEARCH

Is there an association between cortical thickness, age of onset, and duration of illness in schizophrenia?

Idaiane Batista Assunção Leme,[1]* Ary Gadelha,[2] João Ricardo Sato,[3] Vanessa Kiyomi Ota,[4] Jair de Jesus Mari,[5] Maria Isabel Melaragno,[6] Marilia de Arruda Cardoso Smith,[6] Sintia Iole Nogueira Belangero,[4] Rodrigo Affonseca Bressan,[2] and Andrea Parolin Jackowski[1]

[1] *Laboratório Interdisciplinar de Neurociências Clínicas (LiNC), Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil*
[2] *Laboratório Interdisciplinar de Neurociências Clínicas (LiNC) and Programa de Esquizofrenia (PROESQ), Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil*
[3] *Center of Mathematics, Computation and Cognition, Universidade Federal do ABC (UFABC), Santo André, Brazil*
[4] *Laboratório Interdisciplinar de Neurociências Clínicas (LiNC) and Morphology and Genetics Department, Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil*
[5] *Psychiatry Department, Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil*
[6] *Morphology and Genetics Department, Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil*

Objective. Several studies have shown cortical volume loss in frontotemporal regions in schizophrenia patients, and it is known that these reductions may be associated with disease symptoms and cognitive deficits. The aim of this study was to investigate possible cortical thickness correlations in frontotemporal regions in relation to age at onset and duration of illness.

Methods. One hundred forty-eight schizophrenia patients (97 males; age and SD 36.30 ± 10.06) and 87 (57 males; age and SD 36.48 ± 10.10) age-matched healthy subjects underwent a brain MRI scan. Cortical segmentation and surface statistical analysis were performed using the FreeSurfer software package. Results were corrected for multiple comparisons using the Monte Carlo method considering a cluster-corrected Type I Error of 5%.

Results. Compared to controls, schizophrenia patients presented significant cortical thinning in the frontotemporal, parietal, and occipital cortices. No correlation between prefrontal cortex thickness and duration of illness in patients with schizophrenia or between frontotemporal cortical thickness and age at onset was found. However, a significant interaction between age and diagnosis was observed on frontal cortical thickness with patients presenting a thinner cortex than expected for age.

Conclusion. Although there was no correlation between age of onset and duration of illness with brain volume, our findings suggest that there is an accelerated cortical loss in schizophrenia, thus reinforcing the progressive processes of the disease.

Received 23 January 2013; Accepted 10 April 2013; First published online 6 June 2013

Key words: Age, age at onset, cortical thickness, duration of illness, frontal lobe, schizophrenia.

Clinical Implications

- The quantification of cortical thickness expands our understanding of the neurobiological bases of schizophrenia, and therefore provides more robust data for understanding the pathophysiology of the disease.
- No significant correlations between frontotemporal cortical thickness and age of onset and duration of the disease were found.
- There is progressive cortical thinning associated with schizophrenia.
- There is a significant interaction between age and diagnosis, with patients presenting an accelerated cortical thinning in the frontal regions.

*Address for correspondence: Idaiane Batista Assunção Leme, Laboratório Interdisciplinar de Neurociências Clínicas (LiNC), Departamento de Psiquiatria, Universidade Federal de São Paulo, Rua Pedro de Toledo, 669 - 3° andar (fundos), Vila Clementino, São Paulo, SP CEP: 04039-032, Brazil.
(Email: idaiane@gmail.com)

We would like to thank Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brazil), Coordenadoria de Aperfeiçoamento de Pessoal de Ensino Superior (CAPES, Brazil), and Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP, Brazil; grant number n° 07/58736-1) for the financial support. We also thank the patients, their families, psychiatrists, psychologists, and nurses for their participation in this study.

Introduction

Schizophrenia is a chronic and debilitating disease that causes significant disruption in daily activities and

social relationships, and may result in decreased quality of life.[1] Magnetic resonance imaging (MRI) studies have evaluated brain volume and, more recently, cortical thickness in schizophrenia patients.[2–4] There is evidence that patients with schizophrenia present neurostructural abnormalities, such as cortical volume loss in the frontotemporal regions.[3,4] These alterations seem to progress over time[5–11] and may be attributed to a plastic adaptation of the brain to the environment[12] or genetic factors,[13] or they may be related to exposure to antipsychotic drugs.[14,15] Cortical thickness has gained attention in recent years. Because the cerebral cortex makes up most of the brain, the extent of its thickness becomes of great interest for neurodegenerative diseases and in psychiatric disorders. The decrease in cortical thickness is usually regionally specific, and the progress of atrophy can reveal much about the evolution of the disease and the factors that cause disease.[16]

Significant thinning of the dorsolateral prefrontal cortex, medial prefrontal cortex, lateral temporal cortices, left entorhinal cortex, posterior cingulate cortex, precuneus, and lingual cortex, bilaterally have been clearly observed in schizophrenia patients in comparison to healthy controls.[17] A recent meta-analysis of longitudinal structural MRI studies has identified significant frontal, temporal, and parietal lobe gray and white matter volume reductions over time in patients with schizophrenia compared with healthy controls. These findings support the hypothesis that there are progressive reductions associated with schizophrenia,[11] possibly associated with the duration of illness in the brain structure. Premkumar *et al*[18], reported smaller prefrontal cortical grey matter volumes, but larger premotor cortical and putamen volumes in chronic patients, when compared to first episode patients and healthy controls, suggesting progressive brain changes in schizophrenia. However, another study failed to provide evidence for progressive cortical atrophy in short to medium durations of illness.[17] Age at onset of psychosis was also investigated in one study, and seems to be correlated with superior temporal gyrus volume—a region of the brain that is involved in the pathophysiology of schizophrenia.[19] Nevertheless, the relationship between age at onset and brain abnormalities has not been established.

In another longitudinal study, results of the comparison between patients with schizophrenia and healthy controls showed reduced cortical thickness in frontal-temporal areas in patients. This study also reported an association between cortical thinning and the use of antipsychotics, demonstrating cortical changes in patients with schizophrenia during the course of the disease.[20] Van Haren *et al*[21] revised the confounding effects of brain volume loss in schizophrenia, and showed that the use of cannabis and medication intake are important confounding factors on the interpretation of changes in brain volume. However, the volume changes in the brains of patients with schizophrenia appear to be related to the outcome of the disease, even after considering medication intake.[21]

Bose *et al*[22] conducted a study to evaluate the effect of age on brain volume in patients with schizophrenia. In this study, a reduction in the gray matter volume related to age was observed in patients with schizophrenia when compared to healthy controls. Also, an increased loss of white matter in schizophrenic patients was also observed, suggesting that at disease onset or during neurodevelopment, there is an initial reduction in gray matter, followed by a subsequent effect on the white matter.[12]

The aim of this study was to evaluate the effect of age of onset and duration of illness on cortical thickness in patients with schizophrenia in comparison to healthy controls.

Methods

Subjects

One hundred fifty-seven patients with schizophrenia were recruited from the Schizophrenia Program (PROESQ) at the Federal University of São Paulo (UNIFESP). The Structured Diagnostic Interview for *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. [DSM-IV (SCID)], applied by trained psychiatrists, was used to confirm the DSM-IV criteria for schizophrenia. Age at onset of illness was defined as onset of psychotic symptoms according to any available source. Duration of illness was defined as the difference in years between age at onset and age at investigation. Eighty-seven healthy controls without any psychiatric disorders and family history of psychotic illness, assessed through a modified version of SCID, were enrolled in this study. The groups were matched according to education, age, and gender (see Table 1 for details). No subjects had a history of neurological illness, substance abuse, or traumatic brain injury. All participants signed an informed consent approved by the Research Ethics Committee of UNIFESP.

MRI data acquisition

All subjects were submitted to a brain MRI scan at the Department of Diagnostic Radiology (UNIFESP) on a 1.5 T Siemens (Magnetom Sonata AG, Medical Solutions, Erlangen, Germany) with an 8-channel head coil Siemens (MAGNETON Sonata) scanner. A series of exploratory sagittal images (9 to 11 slices of 5 mm with 1 mm spacing) was performed in order to evaluate the image quality and positioning of the heads of the

https://doi.org/10.1017/S1092852913000333 Published online by Cambridge University Press

Table 1. *The socio-demographic and clinical characteristics of the sample*

	Patients with schizophrenia (97M/51F)		Healthy controls (57M/30F)	
Age (years: range; mean ± SD)	18–65	36.30 ± 10.06	18–65	36.48 ± 10.10
Age at onset (years: range; mean ± SD)	13–40	22.62 ± 5.94	N/A	N/A
Duration of illness (years: range; mean ± SD)	0.83–39	13.65 ± 8.35	N/A	N/A

SD: standard deviation; N/A: not applicable; M: male; F: female.

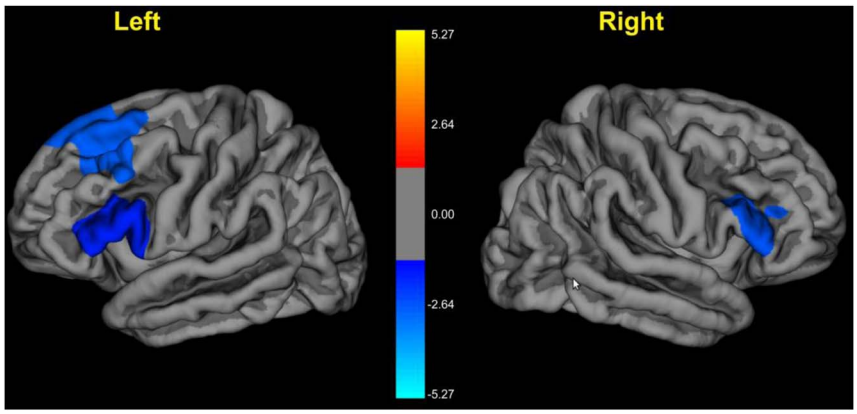

Figure 1. Statistical maps showing age-related differences in cortical thickness between patients with schizophrenia and healthy control subjects. The colourbar represents the z-statistics value of the cluster.

subjects. T1 images were acquired sequentially using a pulse sequence (SPGR) with the following parameters: TR = 2000 ms, TE = 3.42 ms, matrix size = 256 × 256, FOV = 245 mm, flip angle = 15°, NEX = 1, 1.0-mm slice thickness with no gaps, yielding 192 slices). Nine images were excluded because of poor-quality MRI data (due to movement).

Image processing

Cortical surface modeling and volumetric estimation of brain regions (based on T1 images) were performed by using the Freesurfer image analysis package (http://surfer.nmr.mgh.harvard.edu/). In summary, this automated processing includes (implemented in recon-all pipeline): imaging intensity normalization, removal of nonbrain tissues, segmentation of the gray/white matter and subcortical volumetric structures, tessellation of the gray/white matter boundary, topology correction, spherical surface-based intersubject registration based on the cortical surface curvature (ie, sulcus and gyri), and automated parcellation of brain regions. Further technical details of these procedures are described in prior publications.[23–25] A postprocessing visual inspection for quality was conducted, and all processed images were considered in further analysis.

Statistical analysis

The Query Design Estimate Contrast (QDEC) interface of FreeSurfer was used to carry out a general linear model (GLM) analysis at each vertex of the cortical surface. Cortical thickness was considered as the dependent variable; group (patients vs healthy controls), age, and their interaction were explanatory variables, and intracranial volume was a nuisance variable. Results were corrected for multiple comparisons at the cluster level using the Monte Carlo approach for p-cluster < 0.05 (z-vertex > 1.3).

Findings

Overall, the cortex was significantly thinner in patients with schizophrenia compared to healthy controls, mainly in the temporal and prefrontal cortical regions, and also parietal and occipital cortices.

There was a significant negative correlation between duration of illness and the bilateral prefrontal (superior, inferior, and rostral middle gyri) and the left medial orbitofrontal cortical thickness. Since significant correlations were found between duration of illness and cortical thickness in patients with schizophrenia, regression analyses were performed to further evaluate the

https://doi.org/10.1017/S1092852913000333 Published online by Cambridge University Press

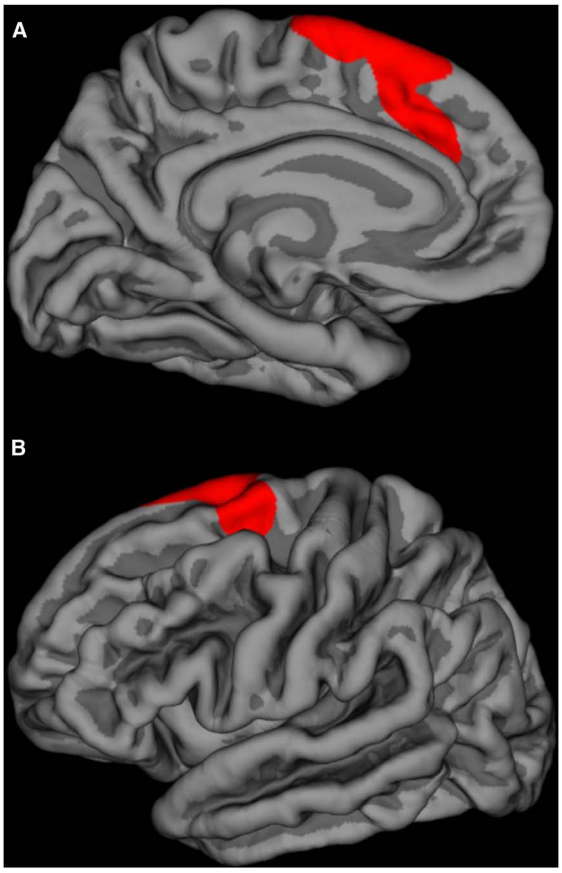

Figure 2. Cortical thickness maps showing interaction effects between the between age and group (schizophrenia patients vs healthy control) at the left superior frontal gyrus (in orange).

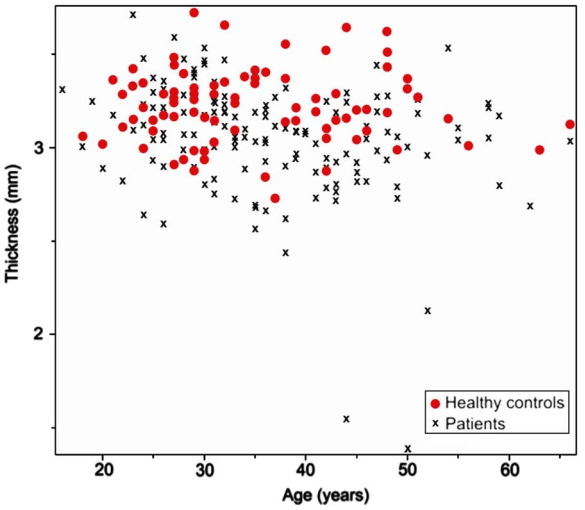

Figure 3. Scatter-plots of age and cortical thickness (local maxima of interaction effect) for the two groups.

relationship between age and duration of illness. In this model, only age remained significant.

A significant age effect on cortical thickness was observed in the bilateral middle frontal, rostral middle frontal, and left superior frontal cortices (Figure 1).

A significant age by group interaction was observed for cortical thickness, with patients with schizophrenia having a thinner left superior frontal cortex with increasing age to a greater degree than did the controls (Figure 2).

No significant correlations between cortical thickness and age of onset were observed.

Discussion

Our main findings indicate that there is a pattern of loss of cortical thickness in the frontal region that is more pronounced in patients with schizophrenia than in healthy controls (Figure 3). In addition, there is a correlation between age in schizophrenia and thinning of the cortex in the frontal regions of patients. Significant differences were reported in the bilateral middle frontal, rostral middle frontal, and left superior frontal cortices. Furthermore, the results of our regression analysis demonstrated that age contributed more to the variation of cortical thickness than the duration of illness.

Changes in cortical thickness are of great interest because they may suggest different neurobiological processes. Cortical thickness is able to reflect the dendritic arborization or changing myelination at the gray/white matter interface.[26–29] The geometric differences are predominantly linked to the development of neuronal connections and cortical patterns of connectivity, and are thus markers of brain development.[30,31]

A previous study that evaluated the correlation between age and cortical thickness in patients with schizophrenia and healthy controls showed a similar pattern of loss of cortical thickness among schizophrenic patients, suggesting that the reduction in cortical thickness may not be progressive throughout the course of the disease, but a pathological process occurring in a limited time related to disease onset.[32] These results are inconsistent with our findings.

A recent study on the effects of aging on cortical thickness in healthy subjects demonstrated that cortical regions are not affected equally by aging, suggesting that the frontal regions are susceptible to atrophy.[33] Another important finding of this study is that the standard loss of cortical thickness varies with age: In old–old age, the greatest loss in primary sensory/motor cortices and regions of low postnatal surface area expansion were found. This result supports our main findings that demonstrate a loss of cortical thickness related to age in the frontal region in patients with schizophrenia, which does not follow the pattern of normal aging.

https://doi.org/10.1017/S1092852913000333 Published online by Cambridge University Press

Some studies have evaluated the effect of duration of illness in schizophrenia, and the results are somehow controversial. Velakoulis *et al*[34] assessed disease duration and volume of gray matter, and reported volume reduction in the mean right temporal regions, anterior hippocampus, uncus, and parahippocampal gyrus, whereas Premkumar *et al*[18] reported a reduction in prefrontal cortex, parietal-occipital cortex gray matter, thalamus, and putamen volume. In another study, Premkumar *et al*[35] reported reduced volume in the right middle frontal, the left fusiform gyrus, and the prefrontal cortex. The cortical thickness of patients with schizophrenia was evaluated by another study,[3] which reported a significant negative correlation of cortical thickness with duration of illness in the inferior frontal cortex, the dorsolateral prefrontal cortex, and the anterior cingulate gyrus, while Schultz *et al*[17] and Nesvåg *et al* found no correlation.[4] Thus, our findings of duration of illness as it did not relate to cortical thickness are in agreement with previous studies.[4,17]

Our results also demonstrated widespread cortical thinning in patients with schizophrenia compared to healthy controls, which corresponds nicely to the findings of previous studies showing the involvement of the frontal and temporal regions, among others, in schizophrenia.[2–4]

Concerning the age at onset analysis, we found no correlation, whereas Matsumoto *et al*,[19] in a smaller sample (40 patients with early-onset schizophrenia), reported a positive correlation between volume and age at onset time. Nevertheless, the previous study investigated an early-onset schizophrenia sample, which could be a more severe form of the disease associated with a greater genetic predisposition,[36] and, hence, differing from our approach. Another important factor is the results of that study did not undergo repair statistics, which increases the probability of finding a random association.[16]

Neuropsychological studies have demonstrated the role of the frontotemporal regions in the physiopathology of schizophrenia. The frontal lobe features in the structure of the prefrontal cortex make up a large portion of the total cortex. They establish connections with other brain structures such as anatomic, motor, sensory, and limbic areas, possibly serving as a "central executive." The frontal lobe also contains the orbitofrontal cortex, which, according to some studies, plays a role in affective and motivational behavior. Furthermore it has been shown that abnormalities in these regions lead to affective and cognitive symptoms of schizophrenia.[37,38]

One of the main characteristics of this study that increase its validity is the large number of participants, with a sample that was properly paired and very homogeneous. The results underwent a conservative correction, using a threshold of $p = 0.05$, therefore controlling for false-positive results. A possible bias of this study is that the sample was selected from a referral center for the treatment of schizophrenia, which can make the sample unrepresentative of the community. Moreover, we have to consider the small sample of healthy controls, which could be a bias for the patients versus controls analysis. Also, an effect of medication intake and cannabis use should also be considered, as they could exert a confounding effect.[6] Another confounding effect is that, in this study, patients and controls were matched on level of education. Education has a significant effect on neuroanatomy, and its effect can be confounded with illness characteristics.

The cross-sectional nature of this study is a limitation on detecting effects of age on brain morphology, because it complicates the interpretation of the data. Moreover, the association between exposure and disease refers only to the time of data collection.

Therefore, more longitudinal studies are needed to evaluate a possible progression that is caused by schizophrenia.

Conclusion

Our findings suggest that cortical thinning observed in patients with schizophrenia is related to age, suggesting a possible progressive role of this disorder or an effect of long-term treatment with antipsychotics.

Disclosures

Idaiane Batista Assunção Leme, Vanessa Kiyomi Ota, João Ricardo Sato, Maria Isabel Melaragno, Sintia Iole Nogueira Belangero, Marilia de Arruda Cardoso Smith, and Andrea Parolin Jackowski do not have anything to disclose. Ary Gadelha: speaker's honoraria, Janssen. Jair de Jesus Mari: speaker's honoraria, Eli-Lilly. Rodrigo Affonseca Bressan: research grants, Roche and Eli-Lilly; speaker's honoraria, Eli-Lilly.

References

1. Jung WH, Kim JS, Jang JH, *et al*. Cortical thickness reduction in individuals at ultra-high-risk for psychosis. *Schizophr Bull*. 2011; **37**(4): 839–849.
2. Honea R, Crow T, Passingham D, Mackay CE. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. *Am J Psychiatry*. 2005; **162**(12): 2233–2245.
3. Kuperberg GR, Broome MR, McGuire PK, *et al*. Regionally localized thinning of the cerebral cortex in schizophrenia. *Arch Gen Psychiatry*. 2003; **60**(9): 878–888.
4. Nesvåg R, Lawyer G, Varnäs K, *et al*. Regional thinning of the cerebral cortex in schizophrenia: effects of

https://doi.org/10.1017/S1092852913000333 Published online by Cambridge University Press

diagnosis, age and antipsychotic medication. *Schizophr Res*. 2008; **98**(1–3): 16–28.
5. Wright IC, Rabe-Hesketh S, Woodruff PW, *et al*. Meta-analysis of regional brain volumes in schizophrenia. *Am J Psychiatry*. 2000; **157**(1): 16–25.
6. Lieberman J, Chakos M, Wu H, *et al*. Longitudinal study of brain morphology in first episode schizophrenia. *Biol Psychiatry*. 2001; **49**(6): 487–499.
7. DeLisi LE, Sakuma M, Maurizio AM, *et al*. Cerebral ventricular change over the first 10 years after the onset of schizophrenia. *Psychiatry Res*. 2004; **130**(1): 57–70.
8. Vita A, De Peri L, Silenzi C, *et al*. Brain morphology in first-episode schizophrenia: a meta-analysis of quantitative magnetic resonance imaging studies. *Schizophr Res*. 2006; **82**(1): 75–88.
9. Crespo-Facorro B, Roiz-Santianez R, Perez-Iglesias R, *et al*. Specific brain structural abnormalities in first-episode schizophrenia: a comparative study with patients with schizophreniform disorder, non-schizophrenic non-affective psychoses and healthy volunteers. *Schizophr Res*. 2009; **115**(2–3): 191–201.
10. Crespo-Facorro B, Roiz-Santianez R, Perez-Iglesias R, *et al*. Global and regional cortical thinning in first-episode psychosis patients: relationships with clinical and cognitive features. *Psychol Med*. 2011; **41**(7): 1449–1460.
11. Olabi B, Ellison-Wright I, McIntosh AM, *et al*. Are there progressive brain changes in schizophrenia? A meta-analysis of structural magnetic resonance imaging studies. *Biol Psychiatry*. 2011; **70**(1): 88–96.
12. Weinberger DR, McClure RK. Neurotoxicity, neuroplasticity, and magnetic resonance imaging morphometry: what is happening in the schizophrenic brain? *Arch Gen Psychiatry*. 2002; **59**(6): 553–558.
13. Kähler AK, Rimol LM, Brown AA, *et al*. Effect of DISC1 SNPs on brain structure in healthy controls and patients with a history of psychosis. *Am J Med Genet B Neuropsychiatr Genet*. 2012; **159B**(6): 722–730.
14. Dorph-Petersen KA, Pierri JN, Perel JM, *et al*. The influence of chronic exposure to antipsychotic medications on brain size before and after tissue fixation: a comparison of haloperidol and olanzapine in macaque monkeys. *Neuropsychopharmacology*. 2005; **30**(9): 1649–1661.
15. Roiz-Santiáñez R, Tordesillas-Gutiérrez D, Ortíz-García de la Foz V, *et al*. Effect of antipsychotic drugs on cortical thickness: a randomized controlled one-year follow-up study of haloperidol, risperidone and olanzapine. *Schizophr Res*. In press. DOI: 10.1016/j.schres.2012.07.014.
16. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A*. 2000; **97**(20): 11050–11055.
17. Schultz CC, Koch K, Wagner G, *et al*. Complex pattern of cortical thinning in schizophrenia: results from an automated surface based analysis of cortical thickness. *Psychiatry Res*. 2010; **182**(2): 134–140.
18. Premkumar P, Kumari V, Corr PJ, *et al*. Frontal lobe volumes in schizophrenia: effects of stage and duration of illness. *J Psychiatr Res*. 2006; **40**(7): 627–637.
19. Matsumoto H, Simmons A, Williams S, *et al*. Superior temporal gyrus abnormalities in early-onset schizophrenia: similarities and differences with adult-onset schizophrenia. *Am J Psychiatry*. 2001; **158**(8): 1299–1304.
20. van Haren NE, Schnack HG, Cahn W, *et al*. Changes in cortical thickness during the course of illness in schizophrenia. *Arch Gen Psychiatry*. 2011; **68**(9): 871–880.
21. van Haren NE, Cahn W, Hulshoff Pol HE, Kahn RS. Confounders of excessive brain volume loss in schizophrenia. *Neurosci Biobehav Rev*. In press. DOI: 10.1016/j.neubiorev.2012.09.006.
22. Bose SK, Mackinnon T, Mehta MA, *et al*. The effect of ageing on grey and white matter reductions in schizophrenia. *Schizophr Res*. 2009; **112**(1–3): 7–13.
23. Fischl B, Salat DH, Busa E, *et al*. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*. 2002; **33**(3): 341–355.
24. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. II: inflation, flattening, and a surface-based coordinate system. *Neuroimage*. 1999; **9**(2): 195–207.
25. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A*. 2000; **97**(20): 11050–11055.
26. Panizzon MS, Fennema-Notestine C, Eyler LT, *et al*. Distinct genetic influences on cortical surface area and cortical thickness. *Cereb Cortex*. 2009; **19**(11): 2728–2735.
27. Ecker C, Marquand A, Mourão-Miranda J, *et al*. Describing the brain in autism in five dimensions: magnetic resonance imagingassisted diagnosis of autism spectrum disorder using a multiparameter classification approach. *J Neurosci*. 2010; **30**(32): 10612–10623.
28. Huttenlocher PR. Morphometric study of human cerebral cortexdevelopment. *Neuropsychologia*. 1990; **28**(6): 517–527.
29. Sowell ER, Thompson PM, Leonard CM, *et al*. Longitudinal mapping of cortical thickness and brain growth in normal children. *J Neurosci*. 2004; **24**(38): 8223–8231.
30. Rakic P. Defects of neuronal migration and the pathogenesis of cortical malformations. *Prog Brain Res*. 1988; **73**: 15–37.
31. Armstrong E, Schleicher A, Omran H, Curtis M, Zilles K. The ontogeny of human gyrification. *Cereb Cortex*. 1995; **5**(1): 56–63.
32. Kubota M, Miyata J, Yohida H, *et al*. Age-related cortical thinning in schizophrenia. *Schizophr Res*. 2011; **125**(1): 21–29.
33. McGinnis SM, Brickhouse M, Pascual B, Dickerson BC. Age-related changes in the thickness of cortical zones in humans. *Brain Topogr*. 2011; **24**(1): 279–291.
34. Velakoulis D, Wood SJ, Smith DJ, *et al*. Increased duration of illness is associated with reduced volume in right medial temporal/anterior cingulate grey matter in

patients with chronic schizophrenia. *Schizophr Res*. 2002; **57**(1): 43–49.
35. Premkumar P, Fannon D, Kuipers E, *et al*. Association between a longer duration of illness, age and lower frontal lobe grey matter volume in schizophrenia. *Behav Brain Res*. 2008; **193**(1): 132–139.
36. Kumra S, Schulz SC. Editorial: research progress in early-onset schizophrenia. *Schizophr Bull*. 2008; **34**(1): 15–17.
37. Berberian AA, Trevisan BT, Moriyama TS, *et al*. Working memory assessment in schizophrenia and its correlation with executive functions ability. *Rev Bras Psiquiatr*. 2009; **31**(3): 219–226.
38. Goldman-Rakic PS, Selemon LD. Functional and anatomical aspects of prefrontal pathology in schizophrenia. *Schizophr Bull*. 1997; **23**(3): 437–458.