Psychiatry Research: Neuroimaging 232 (2015) 130–133

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Brief report

Family load impacts orbitofrontal volume in first-episode schizophrenia

Berend Malchow [a,*], Alkomiet Hasan [a], Kristina Meyer [b], Thomas Schneider-Axmann [a], Katrin E. Radenbach [b], Oliver Gruber [b], Wolfgang Reith [c], Andrew M. McIntosh [d], Andrea Schmitt [a,e], Peter Falkai [a], Thomas Wobrock [b,f]

[a] Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University, Nußbaumstraße 7, 80336 Munich, Germany
[b] Department of Psychiatry and Psychotherapy, Georg-August-University Goettingen, von-Siebold-Straße 5, 37075 Göttingen, Germany
[c] Department of Neuroradiology, Saarland University Hospital, Kirrberger Straße, 66421 Homburg, Germany
[d] Division of Psychiatry, The University of Edinburgh, Royal Edinburgh Hospital, Edinburgh EH10 5HF, United Kingdom
[e] Laboratory of Neuroscience (LIM27), Institute of Psychiatry, University of Sao Paulo, Rua Dr. Ovidio Pires de Campos 785, 05453-010 São Paulo, SP, Brazil
[f] Centre of Mental Health, County Hospitals Darmstadt-Dieburg, Krankenhausstraße 7, 64823 Groß-Umstadt, Germany

ARTICLE INFO

Article history:
Received 26 May 2014
Received in revised form
24 November 2014
Accepted 18 February 2015
Available online 9 March 2015

Keywords:
Orbitofrontal cortex
First episode schizophrenia
Genetic load
Magnetic resonance imaging

ABSTRACT

In schizophrenia, reduced orbitofrontal cortex (OFC) volume is inconsistently reported. To investigate the impact of genetic load on OFC volume, manual MRI-tracing in 23 first-episode schizophrenia patients (FE-SZ) and 23 controls was performed. FE-SZ with genetic load showed a decrease in OFC volume compared to FE-SZ without load and controls.

1. Introduction

Meta-analyses of structural imaging studies bespeak subtle, highly heritable structural brain abnormalities in schizophrenia patients (Wright et al., 2000; Baare et al., 2001; Cannon et al., 2002; Steen et al., 2006). Schizophrenia patients from multiply affected families showed greater impairment in neuropsychological performance than patients with no positive family history of schizophrenia (Sautter et al., 1997). In a magnetic resonance imaging (MRI) study, patients with no family history displayed bilaterally reduced volumes of the temporal lobes, whereas for those with several schizophrenia family members ventricular enlargement has been reported as a marker for genetic liability (McDonald et al., 2002). In a diffusion tensor imaging (DTI) study, patients with a negative family history showed larger deficits in fractional anisotropy (FA) compared with patients with a positive family history (Wang et al., 2011). Increased genetic load likewise was found to be associated with reduced hippocampal volume in schizophrenia (Van Erp et al., 2002).

Brain alterations are present at the onset of disorder (Steen et al., 2006; Vita et al., 2006; Borgwardt et al., 2008; Wood et al., 2008; Witthaus et al., 2009) and seem to progress during the course of the disease compared with findings in healthy controls (Mane et al., 2009). Among other brain regions, inconsistent reductions in volume and cortical thickness of the orbitofrontal cortex (OFC) have been described in antipsychotic-naïve as well as first episode (FE-SZ) patients as well as in chronic schizophrenia patients (Shenton et al., 2001; Antonova et al., 2004; Venkatasubramanian et al., 2008; Schobel et al., 2009; Schultz et al., 2010; Takayanagi et al., 2010). As part of the prefrontal cortex, the OFC with its broad connectivity is critically involved in sensory integration, learning processes and decision-making (Kringelbach, 2005). Following the neurodevelopmental hypothesis of schizophrenia, genetic load may contribute to the reported volume reductions (Schneider-Axmann et al., 2006).

The aim of our study was to for the first time examine the influence of family load on OFC volume in a well-characterised sample of FE-SZ patients with limited exposure to antipsychotic medication. Given the impact of genetic load on the risk to develop schizophrenia, we hypothesised patients with a positive family history of schizophrenia would show the most pronounced volume alterations.

* Corresponding author. Tel.: +49 89 4400 55505; fax: +49 89 4400 55530.
E-mail address: Berend.Malchow@med.uni-muenchen.de (B. Malchow).

http://dx.doi.org/10.1016/j.pscychresns.2015.02.006
0925-4927/

2. Methods

2.1. Participants

Participants comprised 23 first episode schizophrenia patients (FE-SZ) who were recruited at the Department of Psychiatry and Psychotherapy, Saarland University, Homburg/Saar, Germany, and 23 healthy controls (HC) matched for age, sex, and handedness. Descriptive data are presented as mean ± standard deviation in Supplementary Table 1. In the patient sample, the average duration of untreated psychosis was 46.3 (±62.7) weeks, and the average duration of untreated illness was 184.8 (±168.8) weeks. At hospital admission, subscores on the Positive and Negative Syndrome Scale (PANSS) were 22.1 (±7.2) for positive, 20.0 (±6.6) for negative, and 44.9 (±10.9) for general psychopathology symptoms, and the PANSS total score was 87.0 (±20.2). Scores on Clinical Global Impressions (CGI, mean = 5.6 ± 0.7) and the Global Assessment of Functioning (GAF, mean = 33.3 ± 13.3) indicate marked impairment on admission. All patients received treatment with second generation antipsychotics at the utmost 6 weeks before scanning. The daily chlorpromazine-equivalent (CPZ) dose at scanning was 382.6 (±428.2), and the total cumulative CPZ-equivalent dose was 9240.9 (±17,775). Five patients had a family history of schizophrenia in a first or second degree relative (see Supplementary Table 1). Written informed consent was obtained from all subjects. The study was approved by the local ethics committee of Saarland University and performed in accordance with the declaration of Helsinki. FE-SZ diagnosis was confirmed by using the German version of the Structural Clinical Interview for DSM-IV (Wittchen et al., 1997). Patients with any other axis-I disorder and medical and neurological diseases were excluded. The HC subjects exhibited no past or present psychiatric, neurological or medical disorder and had no positive family history for psychiatric disorders.

2.2. MRI acquisition and volumetric measurement

MRI scanning was performed with a 1.5 T Magnetom Sonata (Siemens). Three-dimensional T1-weighted MR images were acquired (MPRAGE IR/GR sequence, TE = 4 ms, TR = 1900 ms, TI = 700 ms, flip angle = 15°, FOV 176 × 256 × 256 mm) with a voxel size of 1 mm^3. After the segmentation of grey and white matter and cerebrospinal fluid by means of the Statistical Parametrical Mapping Program (SPM99), the total grey matter was calculated automatically with MATLAB. Manual area measurements were obtained using the software MRIcro (Chris Rorden, http://www.mccauslandcenter.sc.edu/mricro/index.html). The left and right OFC volumes were traced in the coronal plane determined in accordance with the literature (Crespo-Facorro et al., 1999) (for details, see Supplementary material, Suppl. Fig. 1).

On 10 randomly selected images, OFC volumes were measured twice at different time points by the same investigator and two independent raters to calculate intraclass correlation coefficients (intrarater reliability: ICC = 0.992; interrater reliabilty: ICC = 0.986).

2.3. Statistical analysis

Statistical analyses were carried out with SPSS 22 for Windows, significance level was $\alpha = 0.05$. All tests were two-tailed. Dependent variables were right and left relative OFC volumes and total grey matter volume; diagnostic group was the independent variable (FE-SZ with or without family history of schizophrenia, HC). Intervening variables were age, sex, education, hand preference, duration of psychosis (DUP), PANSS score, CGI score, GAF score, Mini-Mental State Examination score, daily CPZ-equivalent dose and the total cumulative CPZ-equivalent dose. Eventual significant deviations of dependent variables from normal distribution were calculated with the Kolmogorov–Smirnov test. Two-way analysis of variance (ANOVA) adjusted for diagnostic group was used to determine potential significant influences on the dependent variables of sex or hand preference. Bivariate product-moment correlations were calculated separately for HC and FE-SZ participants to analyze whether age and duration of education had an influence on the dependent variables. Analysis of covariance (ANCOVA) with independent factors diagnosis and sex and covariates age and duration of education was performed to review possible significant diagnosis differences for total grey matter volume. Multivariate analysis of covariance (MANCOVA) with factor diagnosis, adjusted for age, education and sex was applied to determine whether there were differences between FE-SZ and HC participants for right and left relative OFC volume. Among the group of FE-SZ patients, those with positive family history of schizophrenia and those without a family history were compared on OFC volume differences with MANCOVA (factor genetic load, adjusted for age, education and sex). For this exploratory study, no Bonferroni adjustment of the type I error probability was applied.

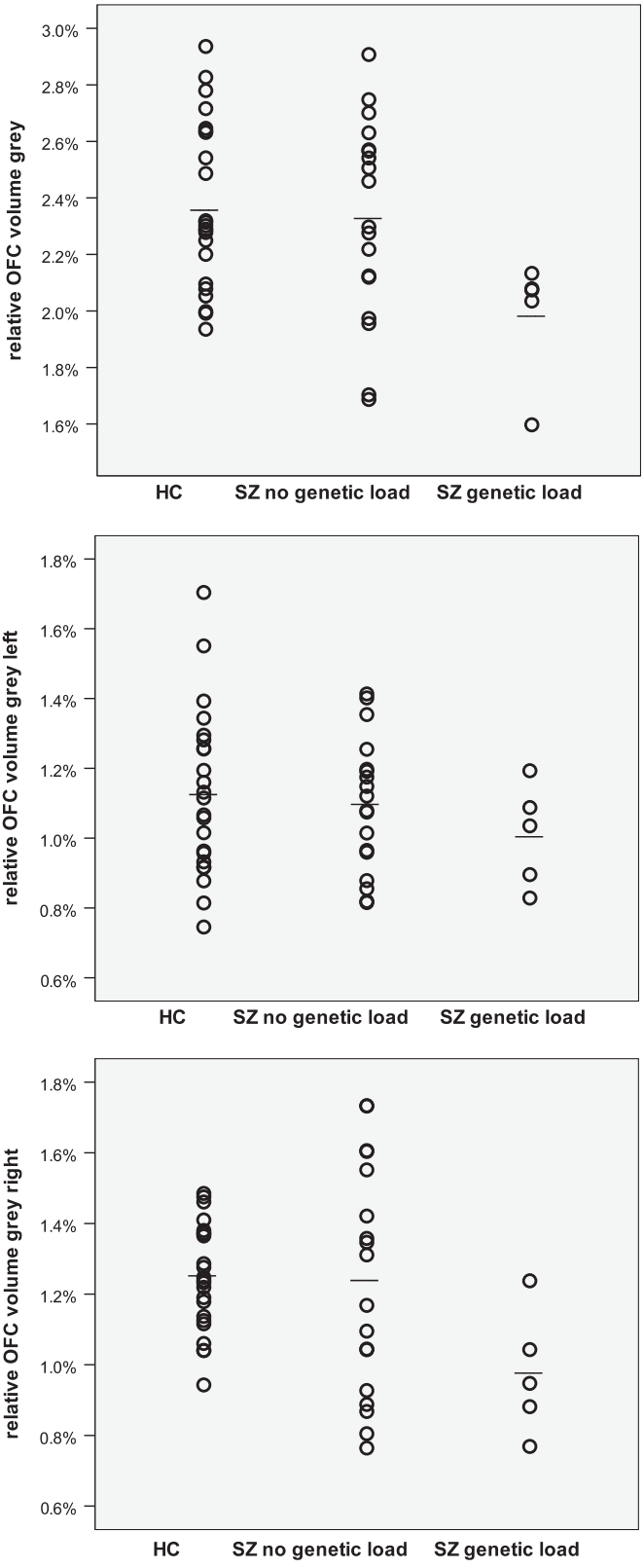

Fig. 1. Scatterplots of relative OFC grey matter volumes (total, left and right hemisphere) in first episode schizophrenia patients (FE-SZ) with (SZ genetic load) and without (SZ no genetic load) a positive family history and healthy controls (HC).

3. Results

Compared with values in the HC group, no significant volumetric differences in the OFC were detected in the FE-SZ group. A comparison of FE-SZ patients with positive family history and those without showed a significant volume decrease of 15% ($F = 7.8$, d.f. = 1, 17, $p = 0.013$) in OFC grey matter volume and