Schizophrenia Research xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

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

Longitudinal regional brain volume loss in schizophrenia: Relationship to antipsychotic medication and change in social function

Joyce Y. Guo [a,b], Sanna Huhtaniska [c,f], Jouko Miettunen [c,e,f], Erika Jääskeläinen [e,f], Vesa Kiviniemi [g], Juha Nikkinen [g], Jani Moilanen [c], Marianne Haapea [g], Pirjo Mäki [c,d,h,i,j,k,l], Peter B. Jones [a], Juha Veijola [c,d], Matti Isohanni [c,d], Graham K. Murray [a,b,*]

[a] Department of Psychiatry, Cambridge Biomedical Campus, University of Cambridge, Box 189 CB2 0QQ, United Kingdom
[b] Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge CB2 0SZ, United Kingdom
[c] Department of Psychiatry, Research Group for Clinical Neuroscience, University of Oulu, Oulu, Finland
[d] Department of Psychiatry, Oulu University Hospital, Oulu, Finland
[e] Institute of Health Sciences, University of Oulu, Oulu, Finland
[f] Medical Research Center Oulu, University of Oulu and Oulu University Hospital, Oulu, Finland
[g] Department of Diagnostic Radiology, Oulu University Hospital, Oulu, Finland
[h] Department of Psychiatry, Länsi-Pohja Healthcare District, Finland
[i] Department of Psychiatry, the Middle Ostrobothnia Central Hospital, Kiuru, Finland
[j] Mental Health Services, Joint Municipal Authority of Wellbeing in Raahe District, Finland
[k] Mental Health Services, Basic Health Care District of Kallio, Finland
[l] Visala Hospital, the Northern Ostrobothnia Hospital District, Finland

ARTICLE INFO

Article history:
Received 30 October 2014
Received in revised form 1 June 2015
Accepted 18 June 2015
Available online xxxx

Keywords:
Longitudinal MRI
Schizophrenia
Antipsychotic medication

ABSTRACT

Background: Progressive brain volume loss in schizophrenia has been reported in previous studies but its cause and regional distribution remains unclear. We investigated progressive regional brain reductions in schizophrenia and correlations with potential mediators.

Method: Participants were drawn from the Northern Finland Birth Cohort 1966. A total of 33 schizophrenia individuals and 71 controls were MRI scanned at baseline (mean age = 34.7, SD = 0.77) and at follow-up (mean age = 43.4, SD = 0.44). Regional brain change differences and associations with clinical mediators were examined using FSL voxelwise SIENA.

Results: Schizophrenia cases exhibited greater progressive brain reductions than controls, mainly in the frontal and temporal lobes. The degree of periventricular brain volume reductions were predicted by antipsychotic medication exposure at the fourth ventricular edge and by the number of days in hospital between the scans (a proxy measure of relapse duration) at the thalamic ventricular border. Decline in social and occupational functioning was associated with right supramarginal gyrus reduction.

Conclusion: Our findings are consistent with the possibility that antipsychotic medication exposure and time spent in relapse partially explain progressive brain reductions in schizophrenia. However, residual confounding could also account for the findings and caution must be applied before drawing causal inferences from associations demonstrated in observational studies of modest size. Less progressive brain volume loss in schizophrenia may indicate better preserved social and occupational functions.

1. Introduction

Since the earliest neuroimaging studies using pneumoencephalography, it has been postulated that there is progressive brain volume reduction in schizophrenia (e.g. Moore et al., 1935; Haug, 1962). However, it was only with the application of modern neuroimaging techniques and the introduction of control groups (Johnstone et al., 1976), and in particular by the advent of longitudinal controlled MRI studies (DeLisi et al., 1995; DeLisi et al, 1997), that progressive brain changes in schizophrenia were confirmed with greater certainty. Numerous MRI studies

Abbreviations: NFBC 1966, Northern Finland Birth Cohort 1966; SIENA, Structural Image Evaluation, Using Normalisation; FSL, FMRIB software library; FLIR, FMRIB's linear image registration tool; PBVC, Percentage brain volume change; FAST, FMRIB's automated segmentation tool; TFCE, Threshold-free cluster enhancement; PANSS, Positive and Negative Syndrome Scale; CGI, Clinical Global Impression; SOFAS, Social and Occupational Functioning Assessment Scale.

* Corresponding author at: Department of Psychiatry, University of Cambridge, Box 189 Cambridge Biomedical Campus, CB2 0QQ, United Kingdom. Tel.: +44 1223769499.
E-mail address: gm285@cam.ac.uk (G.K. Murray).

http://dx.doi.org/10.1016/j.schres.2015.06.016

since then have indicated that patients with schizophrenia have greater progressive volume reductions in the frontal, temporal or parietal lobes and/or progressive ventricular enlargement, compared to controls (e.g. Saijo et al., 2001; Ho et al., 2003; Nakamura et al, 2007; van Haren et al., 2007; DeLisi, 2008; van Haren et al., 2008; Andreasen et al., 2011; van Haren et al., 2011; Cobia et al., 2012). The meta-analysis by Kempton and colleagues (2010) pooled results from 13 studies examining ventricular change in a total of 473 patients and 348 controls, finding that patients show increased rates of ventricular enlargement over time compared to controls. The meta-analysis by Olabi and colleagues (2011) confirmed evidence of progressive volume loss in frontal, temporal and parietal regions, and of progressive ventricular enlargement, compared to controls. However, two other meta-analyses present differing results. One meta-analysis that focussed on gray matter changes confirmed chronic temporal lobe progressive change but suggested a nuanced picture with increased rates of widespread volume loss in the earlier stages of illness (Vita et al., 2012). A meta-analysis of progressive change in a restricted set of regions in early-onset psychosis (mean age of onset in the five included studies ranged between 13 and 16 years) suggested that the frontal lobe was the only region in which brain volume loss significantly differed between patients and controls (Fraguas et al., in press).

Given that there is significant progressive brain structural change during the course of schizophrenia, but not complete consensus even amongst meta-analyses on the regional nature of change, further studies are required to explore the detailed regional basis of structural changes. In order to evaluate the importance of morphological changes, it is critical to examine whether the progressive changes are associated with clinical and/or social function deterioration. Some groups have suggested that greater brain atrophy over time predicts poor clinical and social outcomes or greater brain reduction over time is correlated with less improvement of clinical and social outcomes and/or duration of time spent in hospital during the follow-up (e.g. DeLisi et al., 2004; Andreasen et al., 2011; Asami et al., 2012). However, the associations between regional brain structural change over time and clinical or social outcomes in schizophrenia have not been universally replicated and it remains uncertain which, if any, brain regions are more vital than others for long-term outcomes (van Haren et al., 2003; DeLisi, 2008; Olabi et al., 2011; Gutiérrez-Galve et al., 2015).

Cumulative evidence has revealed significant associations between cortical and subcortical brain structural change and antipsychotic medication exposure (e.g. Moncrieff and Leo, 2010; Ho et al., 2011; Ebdrup et al., 2013; Haijma et al., 2013; Torres et al., 2013). The systematic review by Fusar-Poli and colleagues (2013) reported that higher cumulative antipsychotic dose associated with more pronounced decrease in gray matter volume and increase in lateral ventricular size. In original studies, antipsychotic medication exposure has been associated with, for example, decreases in frontal, temporal and parietal gray matter (Ho et al., 2011), hippocampal volume (Ebdrup et al., 2011; Mamah et al., 2012) and thalamic volume (Khorram et al., 2006), and increases in the volume of the basal ganglia (Lang et al., 2004) and lateral ventricles (Crespo-Facorro et al., 2008). However, this topic is controversial; furthermore, whether typical and atypical antipsychotic medication have the same effects on regional brain structure change in patients with schizophrenia remains disputable (Ebdrup et al., 2013; Lieberman et al., 2005; McClure et al., 2006; Navari and Dazzan, 2009; Smieskova et al., 2009).

We recently reported that antipsychotic medication exposure predicted loss of total brain volume in schizophrenia over time (Veijola et al, 2014) even after controlling for symptom severity, alcohol use and weight gain; however, our recent study, like the majority of other papers on this topic, looked only at summary brain volume indices rather than a fine-grained (voxel or vertex based) level of resolution. Indeed, only a small number of voxel-based or vertex-based previous studies have examined progressive morphological change in schizophrenia at all, and only one long-term study has examined associations between medication morphological change and medication exposure at this level of resolution (van Haren et al., 2011); moreover, as that study focussed only on the cortex it could not address any association between medication exposure and ventricular change. In this study, therefore, we employed voxelwise analyses to examine progressive brain changes in schizophrenia compared to controls, and the relationship between progressive changes and symptoms, level of function and antipsychotic medication exposure.

2. Method

2.1. Participants

As described previously (Veijola et al, 2014), 33 patients with DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders Third Edition Revised) schizophrenia and 71 controls, selected from a general population-based birth cohort study, the Northern Finland Birth Cohort 1966 (NFBC 1966 www.oulu.fi/nfbc), took part. Structured clinical interview for DSM-III-R (SCID) and full case records were obtained and scrutinized in order to validate the diagnoses using DSM-III-R criteria (Isohanni et al., 1997; Moilanen et al., 2003). Table 1 shows the demographic characteristics of the final 104 participants in the current study. The mean age of patients with schizophrenia was 34.1 years at baseline and 43.2 years at follow-up. The mean age of controls was 35.0 years at baseline and 43.5 years at follow-up (Table 1). There was no significant age difference between diagnostic groups. The patients who took part in the study are representative of the entire population of schizophrenia patients born in 1966 in Northern Finland in terms of age, sex and educational level (Veijola et al, 2014). The average interscan interval significantly (t (102) = 4.08, $p < .000$) differed between patients with schizophrenia (mean = 9.10 years, SD = 0.59) and controls (mean = 8.54 years, SD = 0.66), hence interscan interval, sex and handedness were used as covariates in the group comparison statistical analyses. Permission to gather data was obtained from the Ministry of Social and Health affairs, and the study design was approved by the Ethical Committee of the Ostrobothnian Hospital District, Oulu, Finland.

2.2. Clinical assessments

Clinical symptoms and social functioning in patients with schizophrenia at baseline and follow-up were examined using three clinical assessments: the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression (CGI) and the Social and Occupational Functioning Assessment Scale (SOFAS) (Haapea et al., 2007; Veijola et al., 2014). The change score of clinical assessments were calculated by subtracting the scores of clinical assessments at follow-up from the scores of clinical assessments at baseline. We also recorded time in hospital during the interscan interval as a measure of illness severity in patients with schizophrenia, reasoning that hospitalization time was a proxy measure of relapse duration, which has been associated with volume loss in schizophrenia (Andreasen et al., 2011).

2.3. Antipsychotic medication exposure

Current and earlier use of antipsychotic medication was ascertained by interview for all participants at both assessments, and individual

Table 1
Demographic data.

	Schizophrenia			Controls		
	Mean	SD	N	Mean	SD	N
Age at time point one (years)	34.12	0.63	33	34.97	0.67	71
Age at time point two (years)	43.21	0.43		43.52	0.41	
Follow-up time (years)	9.10	0.59		8.54	0.66	
Gender (men/women)	19/14			43/28		
Handedness (right/left)	31/2			66/5		

Please cite this article as: Guo, J.Y., et al., Longitudinal regional brain volume loss in schizophrenia: Relationship to antipsychotic medication and change in social function, Schizophr. Res. (2015), http://dx.doi.org/10.1016/j.schres.2015.06.016