Schizophrenia Research 173 (2016) 140–145

Contents lists available at ScienceDirect

Schizophrenia Research

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

Trajectories of subcortical volume change in schizophrenia: A 5-year follow-up

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ARTICLE INFO

Article history:
Received 3 July 2015
Received in revised form 15 September 2015
Accepted 18 September 2015
Available online 3 October 2015

Keywords:
Schizophrenia
Subcortical volumes
Longitudinal
MRI

ABSTRACT

Longitudinal structural MRI studies in schizophrenia patients show a consistent pattern of excessive brain tissue loss over time, which appears in different stages of the disease. So far, little is known on how age (or illness duration) is related to subcortical volume change across the course of illness in schizophrenia patients as compared with healthy individuals.

At baseline, 151 schizophrenia patients and 154 age and gender matched controls participated. Of these, 89 patients and 109 controls were rescanned after an interval of approximately five years. FreeSurfer was used for subcortical segmentations. Baseline volumes and volume changes were compared. Fits with different degrees of freedom were fitted to explain the effect of age on brain volume change per group. These fits were then compared between groups.

At baseline, patients had significantly smaller volumes of the thalamus, and hippocampus and significantly larger volumes of the caudate, putamen, and globus pallidum as compared with controls. Over time, similar trajectories but with a significant difference in offset were found for caudate, amygdala, and thalamus (in males only), indicating that annual volume loss was more pronounced in patients. Curvilinear fits were found in controls for putamen and hippocampus, while linear fits were found for patients.

Except for the accumbens and globus pallidum, subcortical volumes showed excessive loss over time in patients with schizophrenia. In the putamen and hippocampus, this loss may be explained by abnormal maturational processes during adulthood.

1. Introduction

Meta-analyses on controlled longitudinal structural MRI studies in schizophrenia patients show a consistent trend of excessive brain tissue loss over time in different stages of the disease (Vita et al., 2012; Hulshoff Pol and Kahn, 2008; Olabi et al., 2011). Despite this consistency, there are individual reports finding no differences in change in brain measures over time between patients and controls (e.g., (Schaufelberger et al., 2011)), suggesting that progressive brain abnormalities are specific for particular subgroups or are more pronounced during some stages of the disease than in others.

Here, we investigate differences in age-related change over a five-year interval in nucleus caudate, nucleus accumbens, putamen, globus pallidum, thalamus, amygdala, and hippocampus between a sample consisting of recent-onset and chronically ill schizophrenia patients and healthy individuals, ranging in age at first measurement between 16 and 64 years. This can provide information on how the maturational processes deviate from normal in schizophrenia patients and provide further insight into how the change in subcortical volumes depends on age or stage of the illness.

2. Experimental/materials and methods

2.1. Subjects

This is a five-year follow-up magnetic resonance imaging (MRI) study, including schizophrenia patients and healthy subjects (see (van Haren et al., 2008)). At baseline, 151 schizophrenia patients and 154 age and gender matched controls were included. Of these, 89 patients and 109 controls participated in the follow-up measurement after a mean interval of approximately five years. The study was approved by the Humans Ethics Committee of the University Medical Center Utrecht. After complete description of the study to the subjects, written informed consent was obtained. For demographic information of the subjects, see Table 1.

At both measurements, psychopathology was assessed using the Comprehensive Assessment of Symptoms and History (CASH

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http://dx.doi.org/10.1016/j.schres.2015.09.027
0920-9964/

Table 1
Demographic and clinical information for all patients and controls who participated at baseline, as well as for those who participated also at follow-up measurement.

	Baseline only			Longitudinal		
	Patients N = 151	Controls N = 154	p	Patients N = 89	Controls N = 109	p
Sex (m/f)	107/44	104/50	0.53	63/26	76/33	0.87
Age (yr) at T0	34.53 (12.19)	37.48 (13.90)	**0.05**	31.54 (10.63)	37.49 (13.83)	**0.001**
[range]	[16.88–67.53]	[16.75–65.79]		[16.88–56.25]	[16.75–64.87]	
Handedness (right/left/ambidexter)	129/19/3	129/23/2	0.76	77/10/2	91/16/2	0.77
Level of education (yr)[a]	10.79 (2.96)	12.08 (2.98)	<**0.001**	11.09 (2.98)	12.10 (2.86)	**0.02**
Parental level of education (yr)	11.77 (3.58)	11.89 (3.39)	0.77	11.94 (3.50)	11.96 (3.36)	0.97
Follow-up duration (yr) [range]				4.79 (0.52) [3.48–6.21]	4.95 (0.30) [4.15–5.69]	**0.005**
Age of first psychotic symptoms (yr) [range]	20.93 (5.36) [9.00–36.00]			21.22 (5.48) [9.00–36.00]		
Duration of illness (yr) at T0 [range]	13.70 (12.17) [0.40–51.53]			10.32 (9.95) [0.40–36.25]		
First episode/chronically ill at T0 (N)	64/87			44/45		
Global Assessment of Functioning T5 [range]				52.49 (17.49) [11.00–90.00]		
Camberwell Assessment of Needs T5 [range]				0.38 (0.30) [0.00–1.33]		
PANSS positive T0	16.86 (5.49)			16.71 (5.63)		
PANSS negative T0	18.51 (5.66)			17.53 (5.13)		
PANSS general T0	36.23 (9.40)			35.70 (8.24)		
PANSS positive T5				13.69 (5.31)		
PANSS negative T5				13.31 (6.17)		
PANSS general T5				26.88 (8.45)		
Cumulative medication intake per year scan-interval (HEQ/yr)				N = 82 2479 (1185)		
Only typicals (HEQ/yr)				N = 9 1764 (1296)		
Only atypicals, exl. clozapine (HEQ/yr)				N = 13 1719 (1040)		
Only clozapine (HEQ/yr)				N = 13 3236 (1065)		
Atypicals, incl clozapine (HEQ/yr)				N = 9 2749 (828)		
Switchers between typical and atypical (incl clozapine) (HEQ/yr)				N = 38 2585 (1134)		
No medication				N = 1		
Cumulative dose unknown				N = 6		

m, male; f, female; yr., year; T0, baseline measurement; T5, follow-up measurement; N, number; HEQ, haloperidol equivalents.
At baseline measurement data were not available for some patients (PANSS: N = 25).
At follow-up measurement data were not available for some patients (CAN: N = 1 patient, PANSS at baseline: N = 14, PANSS at follow-up: N = 3).

(Andreasen et al., 1992)). Diagnostic consensus was achieved in the presence of a psychiatrist. All patients met DSM-IV criteria for schizophrenia or schizophreniform disorder at time of first measurement; those with schizophreniform disorder met the criteria for a diagnosis of schizophrenia after one year of illness.

For more clinical information see Supplementary material — eMethod 1.

2.2. Brain imaging

Acquisition parameters and processing procedures have been described before (van Haren et al. 2003). Magnetic resonance images were acquired on a 1.5 Tesla Philips NT scanner. Subcortical reconstruction and volumetric segmentation was performed with the Freesurfer image analysis suite, which is documented and freely available for download online http://surfer.nmr.mgh.harvard.edu/). See Supplementary Material (eMethod 2) for details on acquisition protocol and image processing.

2.3. Statistical analysis

Subcortical volumes of the left and right hemispheres were added, so total volume of a structure was used for the analyses. To investigate age-related group differences in subcortical volume change between baseline and follow-up uncorrected volume change and corrected volume change, i.e., volume change relative to intracranial volume, were calculated for each subject. Uncorrected annual volume change was calculated by subtracting the volume at first measurement (T0) from the volume at second measurement (T5), dividing it by the scan-interval in years (as this was significantly different between the groups, see Table 1). Corrected annual volume change was calculated by dividing the volume change by intracranial volume at T0, before dividing it by the scan-interval.

2.3.1. Group differences in subcortical brain volumes

First, multiple linear regression analyses were performed with baseline volumes or annual change of the thalamus, globus pallidum, putamen, nucleus caudate, hippocampus, amygdala or nucleus accumbens as dependent variable. Group (0 = control, 1 = patient) was added as independent variable, while age, gender, and intracranial volume at baseline were added as covariates. These analyses were Bonferroni corrected for the seven structures, leading to a two-tailed alpha value of 0.007 (0.05/7 structures). A p-value of <0.05 is considered trend level significant.

2.3.2. Age-related trajectory of subcortical volume change

Regression analysis in the form of a locally-weighted running-line smoother (Cleveland and Devlin, 1988; Hastie and Tibshirani, 1990) was used to obtain the dependence of volume changes on age (see also Van Haren et al., 2008). Software for these analyses was developed in house. We took a two-step approach. First, *within groups*, fits with different degrees of freedom (df) were calculated to find the one that described the data best (df = 0, horizontal line at 0; df = 1, horizontal line, different from 0 (offset); df = 2, straight line with slope; df = 3, curved ("parabolic") fit; df = 4, more pronounced curves allowed). Whether fits with more degrees of freedom were significantly better than fits with fewer degrees of freedom was tested using F-tests. Extra degrees of freedom were added to describe different fits for males and females (i.e., is there an offset difference and/or a difference in shape). When no significant effect was found for gender, it was not entered into further analyses. In case gender did have a significant contribution as a covariate, fits for both males and females are presented (per group).