Psychiatry Research: Neuroimaging 288 (2019) 12–20

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Progressive brain structural changes after the first year of treatment in first-episode treatment-naive patients with deficit or nondeficit schizophrenia

Wei Lei[a,b,c,d,1], Brian Kirkpatrick[e,1], Qiang Wang[a,b], Wei Deng[a,b], Mingli Li[a,b], Wanjun Guo[a,b], Sugai Liang[a,b], Yinfei Li[a,b], Chengcheng Zhang[a,b], Xiaojing Li[a,b], Pingping Zhang[a,b], Zhe Li[a,b], Bo Xiang[a,b,c], Jing Chen[c], Xun Hu[b,f], Nanyin Zhang[g], Tao Li[a,b,*]

[a] Mental Health Center and Psychiatric Laboratory, The State Key Laboratory of Biotherapy, West China Hospital of Sichuan University, Chengdu, China
[b] Huaxi Brain Research Center, West China Hospital of Sichuan University, Chengdu, China
[c] Department of Psychiatry, The Affiliated Hospital of Southwest Medical University, Luzhou, China
[d] Nuclear Medicine and Molecular Imaging Key Laboratory of Sichuan Province, Luzhou, China
[e] Department of Psychiatry & Behavioral Sciences, University of Nevada, Reno School of Medicine, Reno, NV, USA
[f] Huaxi Biobank, West China Hospital, Sichuan University, Chengdu City, Sichuan Province, China
[g] Department of Biomedical Engineering, The Huck Institutes of Life Sciences, The Pennsylvania State University, University Park, PA, USA

ARTICLE INFO

Keywords:
Deficit schizophrenia
Longitudinal study
Magnetic resonance imaging
Voxel-based morphometry
Grey matter volume
White matter volume
Negative symptoms

ABSTRACT

Progressive brain volume atrophy has been reported in patients with schizophrenia. However, whether this progress differs between patients with primary negative symptoms (deficit schizophrenia; DS) and those without such symptoms (nondeficit schizophrenia; NDS) is unknown. Here, we examined grey matter volume (GMV) and white matter volume (WMV) changes over 12 months in 34 first-episode treatment-naive patients with schizophrenia (14 DS and 20 NDS) and 32 healthy controls (HCs) using structural magnetic resonance imaging and voxel-based morphometry. At baseline, compared to HCs, patients with DS but not NDS had less WMV in bilateral posterior limb of the internal capsule (PLIC) and cerebellar tonsil ($P < 0.05$, FDR corrected) and smaller GMV in the cerebellar culmen ($P < 0.05$, FWE corrected). At follow-up, NDS group showed WMV reduction in bilateral PLIC ($P < 0.05$, FDR corrected), while DS group showed no progressive WMV changes. While both patient groups exhibited GMV reduction in the hippocampus and insular cortex, patients with NDS showed additional GMV loss in the frontal and cingulate cortex and a selective increase in GMV in the left thalamus ($P < 0.05$ FWE corrected). Our study revealed double dissociations in developmental brain volume changes in the first year after clinical contact for psychosis in DS versus NDS patients.

1. Introduction

Accumulating evidence suggests that patients with schizophrenia experience progressive structural brain changes during the course of the illness; that is, patients tend to have greater tissue loss than healthy controls (HCs) as they grow older (Fusar-Poli et al., 2013; Olabi et al., 2011). Existing evidence is mainly focused on volume changes in grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) provided by structural magnetic resonance imaging (MRI) studies. In 2011, Andreasen et al. reported the results of a longitudinal study that included 202 schizophrenia patients and 125 controls who were followed up for 18 years and found that excessive volume changes in patients were significant in wide spread regions and tissues: grey matter volume (GMV) reduction was found in the whole brain, frontal and temporal lobe, and thalamus; white matter volume (WMV) reduction was found in the whole brain and frontal and temporal lobe; and CSF volume was increased in the ventricles and temporal and occipital lobes (Andreasen et al., 2011). Two year later, Fusar-Poli reported a meta-analysis of 30 longitudinal studies including 1046 patients and 780 controls followed up for 72.4 weeks (median) that found excessive GMV reduction and increased CSF volume in patients, whereas healthy controls showed no change during this period (Fusar-Poli et al., 2013).

The clinical and genetic heterogeneity within schizophrenia is now widely accepted (Tandon et al., 2009; Tsuang et al., 2001). The concept

* Corresponding author at: Mental Health Center and Psychiatric Laboratory, The State Key Laboratory of Biotherapy, West China Hospital of Sichuan University. No. 28 South Dianxin Street, Wuhou District, Chengdu, Sichuan Province 610041, P R China.
E-mail address: xuntao26@hotmail.com (T. Li).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.pscychresns.2019.04.009
Received 11 September 2018; Received in revised form 27 April 2019; Accepted 28 April 2019
Available online 30 April 2019
0925-4927/ © 2019 Published by Elsevier B.V.

of deficit schizophrenia (DS) is regarded as one of the most promising attempts to reduce the heterogeneity within the spectrum (Kirkpatrick et al., 2017). DS represents a clinically homogeneous subgroup of schizophrenia patients with primary and sustained negative symptoms (Carpenter et al., 1988). The diagnosis of DS, separate from non-deficit schizophrenia (NDS), has been demonstrated as stable and enduring (Galderisi et al., 2013; Strauss et al., 2008). Compared with NDS, DS is characterized by more WM changes; more impaired social, global cognition and executive functions; worse premorbid functioning, and worse long-term prognosis (Kirkpatrick et al., 2017). Previous studies have shown that neurobiological underpinnings of DS are distinct from NDS at the illness onset (Lei et al., 2015a, 2015b). However, it is not clear whether patients with DS and NDS exhibit a different progression of brain structural changes during the course of illness. To address this issue, we performed a longitudinal voxel-based morphometry (VBM) study to trace structural brain changes during first 12 months after treatment in first-episode treatment-naive patients with DS or NDS.

2. Materials and methods

2.1. Subjects

A total of 40 treatment-naive patients with first-episode schizophrenia (18 with significant primary negative symptoms according to the criteria of the schedule for the deficit syndrome [Kirkpatrick et al., 1989] and 22 without) from the mental health center in West China Hospital were enrolled at baseline. Four patients were excluded because of excessive head movement during the MRI scan and 2 did not attend the follow-up test. Results from 34 patients (14 DS and 20 NDS; dropout rate = 15%) who finished both the MRI scan at baseline and 1-year follow-up scan were included in the subsequent analysis. The patients were assessed using the patient version of the structured clinical interview for the DSM-IV (SCID-P) (First et al., 2002) and fulfilled diagnostic criteria for schizophrenia based on the DSM-IV. Subjects with evidence of organic brain disorders (such as brain tumor or epilepsy), alcohol or drug abuse, severe physical illness, or comorbidity of any other main psychiatric disorders such as depression or bipolar disorder were excluded. The diagnoses of DS or NDS were reached using the schedule for the deficit syndrome (Kirkpatrick et al., 1989), 12 months after enrollment.

A total of 32 HCs were recruited from the same geographical area as patients. A research psychiatrist screened HCs using the nonpatient version of the SCID (Spitzer et al., 2002) to exclude subjects with any psychiatric disorder.

All participants were Han Chinese and right handed. This study was carried out in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of West China Hospital, Sichuan University. After a complete description of the study to the subjects, written informed consent was obtained.

All patients, but not HCs, were followed up at 12-month intervals after enrollment in the present study. The severity of symptoms was evaluated by a trained psychiatrist using the positive and negative symptoms scale (PANSS) (Kay et al., 1987) at baseline and 12 months after.

2.2. Antipsychotic treatment

After the baseline MRI scan, patients with schizophrenia received antipsychotic medications according to the case-clinician's preference. The details of treatment were assessed from patients' or their guardians' reports and hospital records. The dosage of antipsychotic medication taken by each patient was recorded and converted to chlorpromazine-equivalent mean daily dosages (MDD) (Woods, 2003).

2.3. MRI data acquisition

All participants were scanned on a 3T scanner (EXCITE, General Electric, WI, USA) at baseline and at 12 months (follow-up scan performed only in patients) at the Department of Radiology at West China Hospital. T1-weighted images were acquired by three-dimensional spoiled gradient echo sequence as follows: repetition time 8.5 ms, echo time 3.93 ms, flip angle 12°, slice thickness 1 mm, single shot, field of view 240 × 240 mm^2, matrix 256 × 256. This sequence generated 156 contiguous axial slices with the in-plane resolution of 0.94 × 0.94 mm^2. The quality of the brain images was examined immediately after scanning.

2.4. Image preprocessing and longitudinal VBM analysis

T1-weighted images were realigned and then manually reoriented so that the anterior commissure was positioned at coordinate (0, 0, 0). Then the non-parametric, non-uniformity intensity normalization technique (N3) in MINC (Medical Image NetCDF) software package (https://en.wikibooks.org/wiki/MINC) was used to rectify the non-uniformity of a high-magnetic field signal in reoriented images.

The preprocessed images were then analyzed using SPM8 (Statistical Parametric Mapping version 8, http://www.fil.ion.ucl.ac.uk/spm) running on Matlab7.6 (MathWorks, Natick, MA, USA). We adopted the procedure developed by Asami et al. (2012) for the longitudinal VBM analysis, which provides more precise spatial alignment by using an individualized baseline-to-follow-up DARTEL-based template. Briefly, the analysis was conducted as follows: (1) The baseline image was coregistered to the follow-up scan image. (2) All images were then segmented into probability maps of GM, WM and CSF by the unified segmentation approach. (3) To evaluate the longitudinal morphometric changes of each subject, a subject-specific template was created by combining the GM (or WM) maps of the baseline and follow-up scans of each subject into average GM (or WM) maps using the DARTEL toolbox. The baseline and follow-up scan GM (or WM) maps were then spatially normalized onto the corresponding subject-specific template non-linearly, and were modulated by the determinant of the Jacobian of the transformation and resampled into 1-mm^3 isotropic voxels. (4) A population template was created by simultaneously non-linearly registering all subject-specific templates using DARTEL. The baseline and follow-up scan normalized maps of each subject were spatially nonlinearly normalized to the population template and then modulated. (5) The population template was registered automatically to the MNI space through an affine transformation. All individual GM (or WM) maps residing in the population template space were then co-registered to MNI using the same affine transformation. Finally, these GM (or WM) images were smoothed with a 6-mm full-width half-maximum Gaussian kernel and retained for subsequent statistical analysis.

2.5. Statistical analysis

Statistical analysis of demographic data was conducted using SPSS16.0 (SPSS Inc., Chicago, IL, USA). Where appropriate, parametric (analysis of variance or Student's *t*-test) and nonparametric (Mann-Whitney's *U* test) procedures were used to compare the differences in categorical and continuous data between groups. For categorical data, χ^2 tests were applied.

Voxel-wise comparisons of GMV (or WMV) were performed using SPM8. The procedure is as follows: First, differences in GMV and WMV at baseline among groups (DS, NDS, and HCs) were tested using analysis of covariance (ANCOVA) followed by post hoc two-sample *t*-tests, including gender, age and whole brain volume (WBV = total GMV + total WMV) as covariates. Second, the pattern of GMV and WMV longitudinal changes was explored in the DS and NDS group separately, using paired t-tests. To evaluate the effect size of the

progressive volume change in each group, we also calculated the percentage change (PC) of each group, using the formula: (follow-up – baseline)/baseline × 100%. For voxel-wise comparisons, an explicit WM (or GM) mask constructed using segmented and normalized (using DARTEL-based normalization) images from all participants was applied to ensure that only voxels within the WM (or GM) were analyzed. The threshold for WMV comparisons was set at voxel-level false discovery rate (FDR) corrected $P < 0.05$. For GMV contrasts, results that adopted a relatively strict threshold of $P < 0.05$ voxel-level family-wise error rate (FWE) corrected were reported. Results of GMV comparisons with the threshold of voxel-level FDR corrected $P < 0.05$ can be found in supplementary materials.

To identify possibly selective volume changes, the regions showing significant brain volume abnormalities in the DS and NDS group at any time points were defined as regions of interested (ROIs), and the WMV or GMV of ROIs were extracted and compared between groups using repeated-measure ANCOVA in SPSS16.0, with gender, age, baseline WBV and MDD as covariates. The statistic power of these comparisons was estimated using Gpower software, and post hoc type power analyses were used (Faul et al., 2007). To identify the clinical meaning of the brain volume changes, a series of partial correlations were carried out between the extracted volume (WMV or GMV) of ROIs and the PANSS subscale scores, with gender, age, and baseline WBV as covariates. The statistical threshold was set at $P < 0.05$ for ROI analyses.

3. Results

3.1. Demographic characteristics and clinical measures

The demographic characteristics of the subjects are shown in Table 1. No significant difference was found in age, gender or education years among the three groups. According to the clinical symptoms, patients with DS had more severe negative symptoms than patients with NDS at both time points. No significant difference among other symptom domains (including PANSS total scores, positive and general psychopathology subscale scores) or MDD were found between the DS and NDS group.

The longitudinal improvement of symptoms was accessed using the reduction rate of PANSS scores. DS and NDS groups showed similar reduction rates on PANSS total scores (59% vs. 56%), negative symptoms (8% vs. 7%), positive symptoms (46% vs. 42%), and general psychopathology (62% vs. 59%) ($P > 0.5$ in χ^2 tests). However, the symptomatic profile of the DS and NDS groups remained after 12 months. That is, the DS group still had more severe negative symptoms, but the two patient groups had analogous scores on other symptom dimensions.

3.2. MRI baseline comparisons

Compared with HCs, patients with DS presented significantly smaller WMV in the bilateral posterior limb of the internal capsule (PLIC) and a cluster in cerebellum tonsil (cerebelum_10_R in AAL atlas) (Fig. 1A, Table 2). Patients with NDS showed no significant WMV abnormality at baseline.

As for GMV, patients with DS showed smaller GMV in cerebellum culmen (cerebelum_6_R in AAL atlas) when compared with HCs (Fig. 2). Again, patients with NDS showed no significant GMV abnormality at baseline.

3.3. MRI longitudinal comparisons

Compared with baseline, patients with NDS exhibited WMV reductions in bilateral PLIC (PC = 4.32% and 3.20%, for left and right PLIC respectively), whereas patients with DS showed no progressive WMV change (PC = 0.94% and 0.28%, for left and right PLIC, respectively) during the 12-month follow-up period (Fig. 1B).

Compared with baseline, patients with DS exhibited significant GMV reduction in the bilateral hippocampus and left anterior insula cortex (Fig. 3A). Patients with NDS showed GMV atrophy in the right hippocampus, left and right anterior insula cortex, left anterior cingulate gyrus, bilateral middle cingulate gyrus and left medial frontal cortex, and increased GMV in the left thalamus (PC = –18.53% in NDS vs. –8.56% in DS) (Fig. 3B).

3.4. ROI-wise repeated-measure ANCOVA analyses

Every cluster identified in voxel-wise comparisons (Table 2) was defined as an ROI. Since the purpose of this analysis was to identify possibly selective volume changes and based on the results of voxel-wise comparisons, for regions that showed significant volume change in both patient groups (i.e. bilateral PLIC, right hippocampus and right anterior insula cortex), the clusters identified in NDS comparisons were selected. Repeated-measures ANCOVA using extracted WMV (or GMV) was performed in each ROI. We found significant group (DS vs. NDS) by time (baseline vs. follow-up) interactions in both PLIC clusters (Table 3), where NDS exhibited selective WMV reduction in both clusters. The group main effects were also significant in both PLIC clusters, with the NDS group having a larger WMV than DS group at

Table 1
Demographic and clinical summary of the patients and the healthy controls.

	NDS (n = 20)	DS (n = 14)	HC (n = 32)	$F/t/\chi^2$	P
Gender (female/male)	8/12	4/10	9/23	0.89	0.642
Age(years)	22.20 ± 6.65	21.79 ± 5.35	21.59 ± 4.65	0.08	0.927
Education years	12.80 ± 2.75	12.21 ± 2.08	13.22 ± 2.43	0.82	0.444
WBV	1.19 ± 0.11	1.18 ± 0.10	1.21 ± 0.08	0.53	0.592
Baseline					
Age of onset	21.80 ± 6.73	20.68 ± 5.37		0.52	0.610
PANSS-TS	86.30 ± 11.25	96.21 ± 17.27		−2.03	0.051
PANSS-PS	24.30 ± 7.12	20.93 ± 6.62		1.40	0.172
PANSS-NS	16.40 ± 4.76	26.86 ± 6.88		−5.25	0.001*
PANSS-GP	45.60 ± 7.13	48.43 ± 10.94		−0.92	0.367
12 *months follow-up*					
PANSS-TS	54.89 ± 22.25	57.14 ± 14.20		−0.39	0.743
PANSS-PS	11.89 ± 6.05	10.21 ± 3.93		0.78	0.372
PANSS-NS	12.42 ± 4.03	17.79 ± 4.66		−3.23	0.001*
PANSS-GP	28.26 ± 11.45	28.36 ± 8.30		−0.13	0.979
MDD	227.28 ± 117.16	275.18 ± 146.41		−1.06	0.298

Demographic data are shown as mean ± standard deviation; *$P < 0.05$; WBV, whole brain volume = total gray matter volume + total white matter volume; PANSS-TS, total score of the PANSS; PANSS-PS, positive symptom score of the PANSS; PANSS-NS, negative symptom score of the PANSS; PANSS-GP, general psychopathology score of the PANSS; MDD, mean daily dosage.

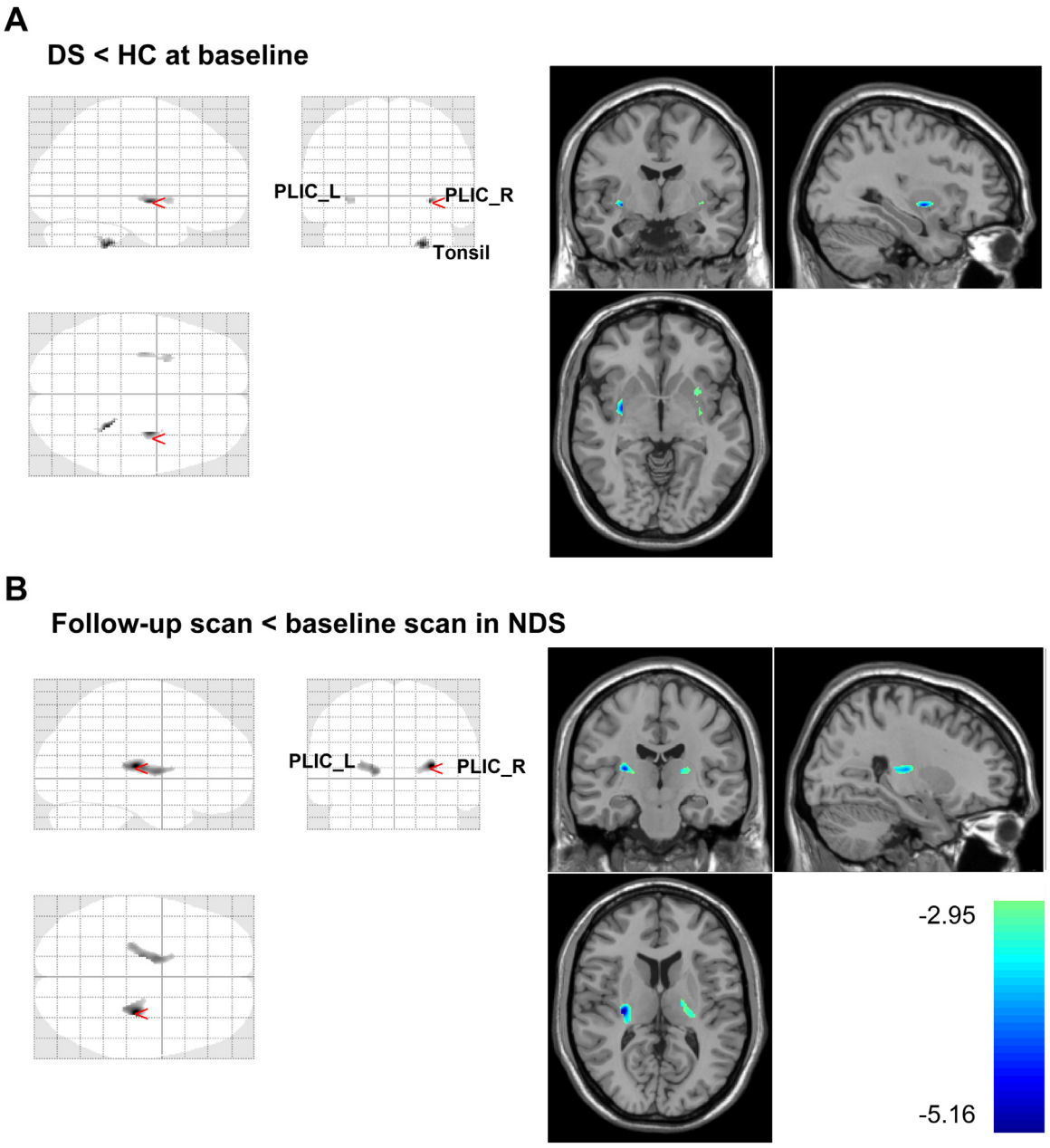

Fig. 1. WMV reductions in patients with DS and NDS. At baseline, compared with HCs, only DS patients presented significantly smaller WMV in cerebellum tonsil and bilateral PLIC (A). Selective progressive WMV reduction was found in NDS patients in bilateral PLIC (B). The results were threshold at $P < 0.05$, voxel-level FDR corrected. *Abbreviations: L, left; R, right; PLIC, posterior limb of internal capsule; Tonsil, cerebellum tonsil.*

both time points. Another significant interaction was found in the left thalamus, where the NDS group showed a selective GMV increase after 12 months; however, the group and time effect in this ROI was not significant.

A significant group main effect was found in the two cerebellum clusters. The NDS group had a larger WMV in cerebellum tonsil and larger GMV in the cerebellum culmen than the DS group at both time points. No significant effects were found in the other ROIs (including the left anterior cingulate cortex, bilateral hippocampus, anterior insula cortex, middle cingulate gyrus, and left medial frontal gyrus). See Table 3 for detailed results of repeated-measure ANCOVA analyses.

3.5. ROI correlation analyses

The correlation analyses in all patients showed that, at baseline, WMV in the right PLIC ($r = –0.36$, $P = 0.048$) and GMV in the cerebellum culmen ($r = –0.44$, $P = 0.013$) were inversely correlated with negative symptoms. The WMV in the left PLIC ($r = –0.27$, $P = 0.144$) and cerebellum tonsil ($r = –0.22$, $P = 0.233$) was also negatively correlated with negative symptoms, but the correlation coefficient did not reach the level of significance (Table S1). At the follow-up test, WMV in the cerebellum tonsil ($r = –0.39$, $P = 0.030$) and GMV in the cerebellum culmen ($r = –0.43$, $P = 0.016$) and left hippocampus ($r = –0.39$, $P = 0.030$) were inversely correlated with negative symptoms (Table S2).

4. Discussion

To our knowledge, this is the first study to use an optimized longitudinal VBM approach to compare and discriminate the patterns of progressive brain volume changes in patients with DS and NDS. We found that: at baseline, patients with DS but not NDS had less WMV in

Table 2
Significant volume differences from control subjects.

	Abnormal at baseline		Progressive change during follow-up	
	DS	NDS	DS	NDS
White matter volume comparisons				
Tonsil	135, 5.16, (27 −39 −41)	–	–	–
PLIC-L	38, 3.71, (−27 6 −3) 29, 3.95, (−34 −9 −3)	–	–	837, 3.89, (−17 −15 9)
PLIC-R	153, 4.65, (32 −5 −4)	–	–	657, 4.45, (29 −20 10)
Gray matter volume comparisons				
Culmen	52, 5.25, (11 −58 −23)	–	–	–
HIPP-L	–	–	468, 5.76, (−30 −31 −9)	–
HIPP-R	–	–	48, 5.70, (30 −6 27);	536, 6.24, (31 −19 −18)
AIC_L	–	–	–	321, 5.84, (−33 24 5)
AIC_R	–	–	55, 5.15, (30 28 −1)	104, 5.16,(33 19 11)
ACC-L	–	–	–	434, 5.64, (−10 19 30)
MCG-L	–	–	–	21, 5.09, (−1 −7 30)
MCG-R	–	–	–	65, 5.19,(13 −30 37)
MFG-L1	–	–	–	83, 5.11, (−17 59 −2)
MFG-L2	–	–	–	41, 5.13, (−43 2 37)
THA-L	–	–	–	90, −5.48, (−14 −15 10)

*The data were present as "cluster-size, peak z-value, MNI coordinate (x y z)", when there's more than one cluster in the same region the clusters were separate by semicolon. Abbreviations: L, left; R, right; Tonsil, cerebellum tonsil; PLIC, posterior limb of the internal capsule; Culmen, cerebellum culmen; HIPP, hippocampa gyrus; AIC, anterior insula cortex; ACC, anterior cingulate cortex; MCG, middle cingulate gyrus; MFG, medial frontal gyrus; THA, Thalamus.

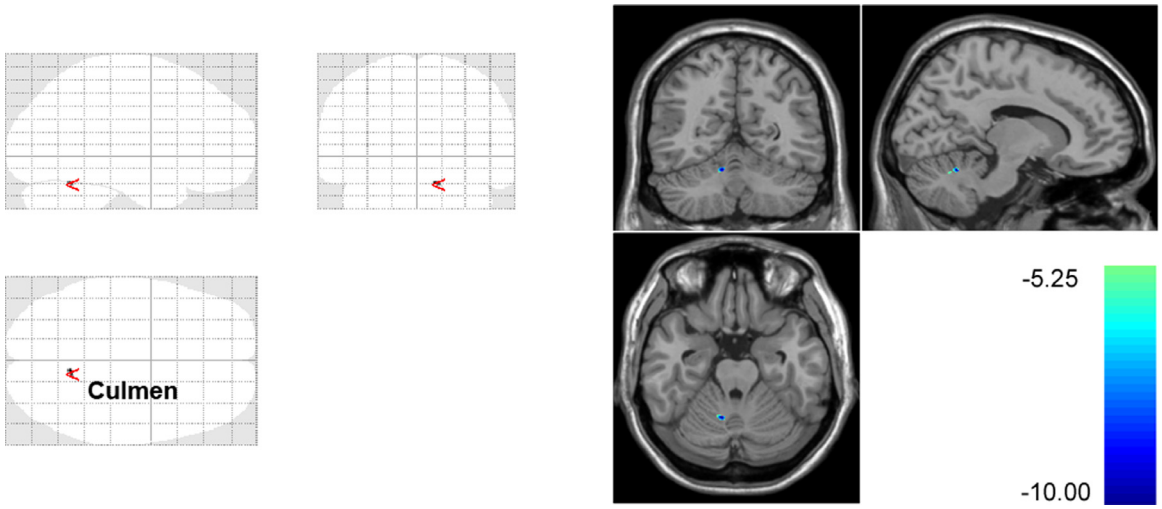

Fig. 2. Patients with DS showing less GMV in the cerebellum culmen than HCs at baseline ($P < 0.05$, voxel-level FWE corrected). *Abbreviations: Culmen, cerebellum culmen.*

the bilateral PLIC and cerebellar tonsil ($P < 0.05$ FDR corrected), and smaller GMV in the cerebellum culmen ($P < 0.05$ FWE corrected) compared with HCs. At 12-month follow-up, patients with NDS showed selective WMV reduction in the PLIC ($P < 0.05$ FDR corrected), but no progressive WMV change was found in the DS group. Both patient groups exhibited GMV reduction in regions such as the hippocampus and insular cortex ($P < 0.05$ FWE corrected). Patients with NDS showed additional GMV loss in the anterior and middle part of the cingulate cortex and a selective increase in GMV in the left thalamus ($P < 0.05$ FWE corrected). WMV in the PLIC and cerebellum tonsil and GMV in the cerebellum culmen were significantly smaller in patients with DS than in NDS patients at both time points ($P < 0.05$ in ROI-wise ANCOVA). GMV in the cerebellar culmen was inversely correlated with negative symptoms in all patients at both time points ($P < 0.05$).

This study identified a significant difference in patterns of progressive brain volume (especially WMV) change in DS and NDS patients. First, consistent with our previous studies (Lei et al., 2015a, 2015b), only patients with DS had significantly less GMV and WMV than HCs at baseline, whereas patients with NDS exhibited no brain volume abnormalities. Second, during the 12-month follow-up, patients with NDS showed selective WMV reduction in the bilateral PLIC and increased GMV in the left thalamus. Finally, we emphasize that while patients with NDS showed progressive WMV change in bilateral PLIC, patients with DS showed no WMV change during the 12 months follow-up period. A similar pattern was also found in GMV progressive changes: in addition to GMV reduction in the hippocampus and insula in both patients groups, the NDS group showed additional GMV atrophy in the cingulate cortex and middle frontal gyrus. These three lines of results provide significant evidence for different patterns of progressive brain volume change in patients with DS and NDS. Although patients with DS have a trend of higher baseline PANSS total scores (96.21 ± 17.27 vs. 86.30 ± 11.25, $P = 0.051$) than those with NDS, this difference was largely derived from negative symptoms (26.86 ± 6.88 vs. 16.40 ± 4.76, $P < 0.001$), rather than positive (20.93 ± 6.62 vs. 24.30 ± 7.12, $P = 0.172$) or general psychopathology symptoms (48.43 ± 10.94 vs. 45.60 ± 7.13, $P = 0.367$). This different trajectory of brain volume changes in DS and NDS thus could not be attributed to confounding by the severity of positive symptoms or general psychopathology symptoms. Differences in illness progress between DS and NDS patients have been reported. In a 5-year prospective study, Tek et al. found that during follow-up DS patients had a poorer quality of life, worse social and occupational functioning,

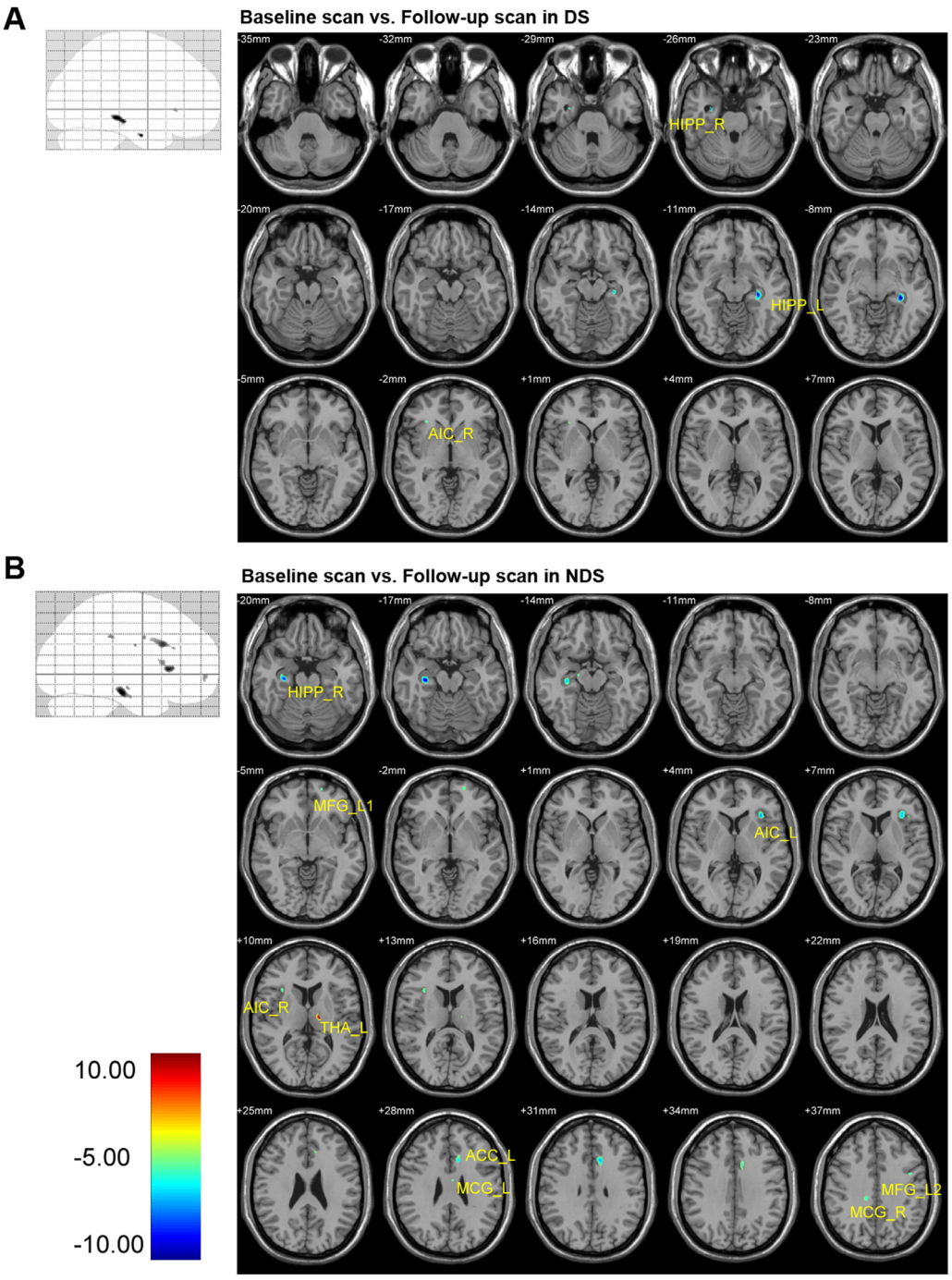

Fig. 3. GMV reductions in patients with DS and NDS during follow-up. Compared with baseline, DS patients exhibited GMV reduction in the bilateral hippocampus and left anterior insula cortex (A), while NDS patients showed GMV atrophy in the right hippocampus, left anterior insula cortex, left anterior cingulate cortex, bilateral medial frontal gyrus and bilateral middle cingulate gyrus (B). The results were threshold at $P < 0.05$, voxel-level FWE corrected. *Abbreviations: L, left; R, right; HIPP, hippocampus; AIC, anterior insula cortex; ACC, anterior cingulate cortex; MCG, middle cingulate gyrus; MFG, medial frontal gyrus.*

and more severe negative symptoms, but did not show more severe positive symptoms than NDS patients (Tek et al., 2001). In a study by Fenteon et al., 46 patients with DS and 141 with NDS were followed up and assessed at a mean of 19 years after admission; those with DS were highly stable and but had poor outcome and long term disability (Fenton and McGlashan, 1994). The findings of the present study are in line with those of the other studies, suggesting that DS is a homogeneity form of schizophrenia with a distinct pattern of progressive changes in brain volume as compared with NDS.

The reduced WMV in the bilateral PLIC in patients with DS at baseline is consistent with our previous study (Lei et al., 2015b) as well as two other studies of the DS/NDS difference (Chua et al., 2007; Price et al., 2010). The striatum has structural connections to the neocortex and midbrain dopamine neurons constitute the crucial part of the "reward system". These connections are at least partly made via the PLIC clusters found in this study, and they play an important role in motivation, pleasure experience and learning (Millan et al., 2014). The WMV atrophy in PLIC might thus relate to the negative symptoms in patients (Lei et al., 2015b). This concept is compatible with the correlation of WMV in bilateral PLIC with negative symptoms at baseline in the present study.

In this study, patients with NDS exhibited selective WMV reduction

Table 3
Results of ROI-wise repeated-measure ANCOVA.

	Volume	Effects	*F*	*P*	Power	f
PLIC_L	WMV	Group	7.03	0.014*	0.934	0.531
		Time	0.29	0.597	0.092	0.105
		Interaction	4.65	0.041*	0.685	0.432
PLIC_R	WMV	Group	4.31	0.047*	0.619	0.400
		Time	0.35	0.560	0.099	0.115
		Interaction	5.57	0.026*	0.728	0.454
Tonsil	WMV	Group	5.88	0.022*	0.734	0.457
		Time	1.37	0.252	0.241	0.222
		Interaction	1.25	0.274	0.224	0.212
Culmen	GMV	Group	10.64	0.003*	0.936	0.616
		Time	0.44	0.513	0.107	0.123
		Interaction	0.05	0.829	0.057	0.045
ACC_L	GMV	Group	0.49	0.488	0.115	0.132
		Time	0.02	0.884	0.054	0.032
		Interaction	0.29	0.597	0.088	0.101
AIC_L	GMV	Group	3.34	0.078	0.495	0.344
		Time	0.313	0.581	0.092	0.105
		Interaction	1.31	0.263	0.233	0.217
AIC_R	GMV	Group	0.00	0.999	0.050	0.010
		Time	0.52	0.476	0.119	0.135
		Interaction	0.03	0.860	0.054	0.032
HIPP_L	GMV	Group	0.80	0.380	0.160	0.180
		Time	0.19	0.666	0.076	0.084
		Interaction	0.97	0.333	0.186	0.188
HIPP_R	GMV	Group	0.00	0.967	0.050	0.010
		Time	0.00	0.987	0.050	0.010
		Interaction	2.35	0.137	0.372	0.289
MCG_L	GMV	Group	1.72	0.201	0.289	0.248
		Time	1.11	0.301	0.050	0.010
		Interaction	2.15	0.153	0.203	0.199
MCG_R	GMV	Group	0.01	0.943	0.050	0.010
		Time	0.93	0.343	0.177	0.182
		Interaction	0.97	0.758	0.061	0.055
MFG_L1	GMV	Group	4.10	0.053	0.582	0.383
		Time	1.12	0.299	0.203	0.199
		Interaction	1.01	0.324	0.190	0.190
MFG_L2	GMV	Group	0.03	0.855	0.054	0.032
		Time	0.15	0.704	0.069	0.071
		Interaction	0.01	0.933	0.050	0.010
THA_L	GMV	Group	0.07	0.801	0.057	0.045
		Time	2.52	0.124	0.394	0.299
		Interaction	4.36	0.046*	0.608	0.395

* $P < 0.05$; f, the effect size value; Group, the group main effect; Time, the time main effect; Interaction, the group by time interaction effect. *Abbreviations: L, left; R, right; PLIC, posterior limb of the internal capsule; Tonsil, cerebellum tonsil; Culmen, cerebellum culmen; ACC, anterior cingulate cortex; AIC, anterior insula cortex; HIPP, hippocampa gyrus; MCG, middle cingulate gyrus; MFG, medial frontal gyrus; THA, Thalamus.*

in bilateral PLIC regions. This result suggests that the WMV change in PLIC could commonly emerge in both DS and NDS, and the early detection of PLIC WMV atrophy in patients with DS could thus be due to the relatively higher genetic effect, as suggested in our previous study, in which relatives of DS patients also exhibited WMV deficit in these regions (Lei et al., 2015b). Moreover, the PLIC was associated with negative symptoms at baseline but not in the follow-up scan, suggesting that the PLIC may contribute to different symptom dimensions in DS and NDS. The excessive PLIC volume reduction during follow-up in patients with NDS might have slightly biased this correlation toward symptoms other than negative ones. Further studies are needed to confirm the exact role of the PLIC in the pathology of DS and NDS.

This study identified a stable DS/NDS difference in WMV in cerebellum tonsil, and GMV in cerebellum culmen. GMV in cerebellum culmen was correlated with negative symptoms at both time points. A smaller GMV of the cerebellum culmen in patients with DS has also been reported in our previous study of first-episode patients (Lei et al., 2015a) and two studies of chronic patients with DS and NDS (Cascella et al., 2010; Ozdemir et al., 2012), suggesting that the cerebellum culmen may play a significant role in the differentiation of DS from NDS. Structural and functional abnormalities of the cerebellum have traditionally been linked to the neurocognitive impairment in schizophrenia (Andreasen and Pierson, 2008). However, studies suggest that abnormal cerebellar vermal-fastigial function can also contribute to impaired attention and affect as well as social dysfunction (such as apathy) (Schmahmann et al., 2008). This putative psychopathology related to the cerebellar region is thus largely consistent with some of the negative symptoms of schizophrenia, such as flat affect, and social withdrawal. These results suggest that less GMV in DS could relate to the excessive negative symptoms of these patients.

We found a selectively increased GMV in the left thalamus of patients with NDS during the first year of illness. Studies of GMV change in schizophrenia have suggested that this region might be sensitive to medication treatment (Byne et al., 2008). Significant thalamus volume expansion in patients treated with both typical (Khorram et al., 2006) and atypical antipsychotics has been reported (Dazzan et al., 2005; Strungas et al., 2003), suggesting a possible link between volume expansion and clinical response.

In this study, both the DS and NDS groups had progressive GMV reduction in the hippocampus and insula. GMV reduction in the hippocampus has been observed in previous longitudinal studies on schizophrenia (Andreasen et al., 2011; Steen et al., 2006). For instance, in a recent longitudinal study by van Haren et al., while hippocampal volume change in HCs remained stable until the age of approximately 40 years, patients showed a linear stable pattern of volume loss with increasing age irrespective of their current age (van Haren et al., 2016). The GMV reduction in the hippocampus found in DS and NDS patients in this study thus may reflect the common pathology of progressive GMV loss in schizophrenia. Progressive GMV atrophy of the insula cortex is also one of the most consistent findings in neuroanatomical studies of schizophrenia (Asami et al., 2012; Takahashi et al., 2009). According to previous studies, less GMV in the insula is associated with negative symptoms in patients (Lei et al., 2015a; Takahashi et al., 2009). Together, this evidence suggests that GMV loss in the insula could be associated with negative symptoms that occur during the course of illness.

Besides the hippocampus and insula, patients with NDS also had excessive GMV reduction in the bilateral frontal and cingulate cortex. The GMV reduction in the frontal and cingulate regions was suggested to be the prominent structural change in schizophrenia according to a review by Pantelis et al. (2003). Our results are partly in line with the work of Pantelis et al., suggesting that GMV loss in the frontal and cingulate cortex would mainly appear in patients with NDS.

4.1. Limitations

There are several limitations in this study. First, the follow-up time was relatively short. Our results cannot be generalized to other illness stages (e.g., chronic stage). Nevertheless, according to recent meta-analyses, patients have the most severe progressive brain change in the early stages of the illness (Andreasen et al., 2011). Second, the small sample size could limit our power to detect more subtle differences between groups. Third, we did not repeat the MRI scan for HCs at the follow-up stage, and this leaves the possibility that our results could be confounded by age. However, our main finding is the different trajectory for brain volume changes between DS and NDS, and these results are still valid even without a follow-up scan of HCs. Moreover, the age of all participants in this study was less than 40 years (age range 16–40 years). According to a previous study of brain volume development in healthy adults, the WMV follows a nonlinear inverted “U-shaped” relationship with age, slightly increasing during early adulthood and then reaching a peak in the fourth decade (Giorgio et al., 2010). In our results, however, patients exhibited an opposite trajectory than healthy adults during the same period. Finally, although we had the advantage of using first-episode treatment-naïve patients at baseline to avoid the effects of medications and chronicity, the possible confounding effect of

medications remains after 12 months of treatment with various antipsychotics and other medications (e.g. antidepressants). We were unable to subgroup patients according to the class of antipsychotics due to the small sample size.

4.2. Conclusions

Compared with NDS, patients with DS appear to have excessive brain volume atrophy before illness onset in the PLIC and cerebellum, and these structural deficits were associated with negative symptoms at illness onset. Moreover, in contrast to the significant progressive volume reduction shown in patients with NDS, patients with DS exhibited moderate GMV reduction and no WMV reduction during the first year of illness. This double dissociation is intriguing because it is consistent with the hypothesis that has been mentioned by many researchers, including Kraepelin: that is, the existence of a subgroup of schizophrenia patients who have significant structural and functional brain abnormalities (and thus poor premorbid and cognitive function) before the onset of illness, who show nonprogressive brain changes during the illness course (DeQuardo et al., 1994). Also, it fits the previous findings of worse cognitive and premorbid function in first-episode patients with DS than those with NDS (Galderisi and Maj, 2009; Kirkpatrick and Galderisi, 2008). In summary, our study revealed double dissociations in developmental brain volume changes in the first year after clinical contact for psychosis in DS versus NDS patients, suggesting that deficit syndrome could significantly modulate the trajectory of brain changes during the illness course of schizophrenia.

Acknowledgments

The authors thank the patients and clinical team on this project. This work was supported by the National Nature Science Foundation of China Key Project (T.L., grants 81630030 and 81130024); National Key Technology R & D Program of the Ministry of Science and Technology of China (T.L., grant 2016YFC0904300); National Natural Science Foundation of China/Research Grants Council of Hong Kong Joint Research Scheme (T.L., grant 81461168029); 1.3.5 Project for disciplines of excellence, West China Hospital of Sichuan University (T.L., grants ZY2016103and ZY2016203); Natural Science Foundation Of China (W.L., grant 81701322; W.D., grant 8157051859); Humanity and Social Science Youth foundation of Ministry of Education of China (W.L., grant 17YJC190009); Sichuan Science & Technology Department (Q.W., grant 2015JY0173); and Joint Research Fund for Overseas Chinese, Hong Kong and Macao Young Scholars (N.Y.Z., grant 81528008).

Contributors

Wei Lei and Tao Li designed the study and contributed to imaging analysis, interpretation of results and writing the draft of the manuscript. Brian Kirkpatrick contributed to manuscript writing and editing. Qiang Wang and Wei Deng contributed to the design of the study, study implementation and manuscript editing. Mingli Li, Wanjun Guo, Sugai Liang, Yinfei Li, Chengcheng Zhang, Xiaojing Li, Pingping Zhang, Zhe Li, Bo Xiang, and Jing Chen contributed to subject recruitment and study implementation. Xun Hu and Nanyin Zhang contributed data analysis and manuscript writing and editing. All authors contributed to and have approved the final manuscript.

Conflicts of interest

Dr. Kirkpatrick receives licensing royalties from ProPhase LLC for the use of the Brief Negative Symptom Scale (BNSS) by for-profit groups; these fees are donated to the Brain and Behavior Research Foundation. He has also received honoraria and travel support from ProPhase LLC for training pharmaceutical company raters on the BNSS; consulting fees and travel support from Genentech/Roche, Minerva Neurosciences, and ProPhase LLC; consulting fees from anonymized pharmaceutical companies through Decision Resources, Inc., from an investment capital company through Guideposts, and from Sterne Kessler Goldstein & Fox for consulting on a legal issue. He also receives fees from Walsh Medical Media for editorial services, and received fees for editorial services from Physicians Postgraduate Press, Inc. All other authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.04.009.

References

Andreasen, N.C., Nopoulos, P., Magnotta, V., Pierson, R., Ziebell, S., Ho, B.C., 2011. Progressive brain change in schizophrenia: a prospective longitudinal study of first-episode schizophrenia. Biol. Psychiatry. 70, 672–679.
Andreasen, N.C., Pierson, R., 2008. The role of the cerebellum in schizophrenia. Biol. Psychiatry. 64, 81–88. http://doi.org/10.1016/j.biopsych.2008.01.003.
Asami, T., Bouix, S., Whitford, T.J., Shenton, M.E., Salisbury, D.F., McCarley, R.W., 2012. Longitudinal loss of gray matter volume in patients with first-episode schizophrenia: DARTEL automated analysis and ROI validation. NeuroImage 59, 986–996. http://doi.org/10.1016/j.neuroimage.2011.08.066.
Byne, W., Hazlett, E.A., Buchsbaum, M.S., Kemether, E., 2008. The thalamus and schizophrenia: current status of research. Acta Neuropathol 117, 347–368. http://doi.org/10.1007/s00401-008-0404-0.
Carpenter, W.T., Heinrichs, D.W., Wagman, A.M., 1988. Deficit and nondeficit forms of schizophrenia: the concept. Am. J. Psychiatry. 145, 578–583. http://doi.org/10.1176/ajp.145.5.578.
Cascella, N.G., Fieldstone, S.C., Rao, V.A., Pearlson, G.D., Sawa, A., Schretlen, D.J., 2010. Gray-matter abnormalities in deficit schizophrenia. Schizophr. Res. 120, 63–70. http://doi.org/10.1016/j.schres.2010.03.039.
Chua, S.E., Cheung, C., Cheung, V., Tsang, J.T.K., Chen, E.Y.H., Wong, J.C.H., et al., 2007. Cerebral grey, white matter and CSF in never-medicated, first-episode schizophrenia. Schizophr. Res. 89, 12–21. http://doi.org/10.1016/j.schres.2006.09.009.
Dazzan, P., Morgan, K.D., Orr, K., Hutchinson, G., Chitnis, X., Suckling, J., et al., 2005. Different effects of typical and atypical antipsychotics on grey matter in first episode psychosis: the ÆSOP study. Neuropsychopharmacology 30, 765–774. http://doi.org/10.1038/sj.npp.1300603.
DeQuardo, J.R., Tandon, R., Goldman, R., Meador-Woodruff, J.H., McGrath-Giroux, M., Brunberg, J.A., et al., 1994. Ventricular enlargement, neuropsychological status, and premorbid function in schizophrenia. Biol. Psychiatry. 35, 517–524.
Faul, F., Erdfelder, E., Lang, A.-G., Buchner, A., 2007. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav. Res. Methods 39, 175–191. http://doi.org/10.3758/BF03193146.
Fenton, W.S., McGlashan, T.H., 1994. Antecedents, symptom progression, and long-term outcome of the deficit syndrome in schizophrenia. Am. J. Psychiatry. 151, 351–356. http://doi.org/10.1176/ajp.151.3.351.
First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 2002. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P). Biometrics Research. New York State Psychiatric Institute, New York, NY.
Fusar-Poli, P., Smieskova, R., Kempton, M., Ho, B., Andreasen, N., Borgwardt, S., 2013. Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. Neurosci. Biobehav. Rev. 37, 1680–1691.
Galderisi, S., Bucci, P., Mucci, A., Kirkpatrick, B., Pini, S., Rossi, A., Vita, A., Maj, M., 2013. Categorical and dimensional approaches to negative symptoms of schizophrenia: focus on long-term stability and functional outcome. Schizophr. Res. 147, 157–162. http://doi.org/10.1016/j.schres.2013.03.020.
Galderisi, S., Maj, M., 2009. Deficit schizophrenia: an overview of clinical, biological and treatment aspects. Eur. Psychiatry. 24, 493–500. http://dx.doi.org/10.1016/j.eurpsy.2009.03.001.
Giorgio, A., Santelli, L., Tomassini, V., Bosnell, R., Smith, S., De Stefano, N., et al., 2010. Age-related changes in grey and white matter structure throughout adulthood. NeuroImage 51, 943–951.
Kay, S.R., Flszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.
Khorram, B., Lang, D.J., Kopala, L.C., Vandorpe, R.A., Rui, Q., Goghari, V.M., et al., 2006. Reduced thalamic volume in patients with chronic schizophrenia after switching from typical antipsychotic medications to olanzapine. Am. J. Psychiatry. 163, 2005–2007. http://doi.org/10.1176/ajp.2006.163.11.2005.
Kirkpatrick, B., Buchanan, R.W., McKenny, P.D., Alphs, L.D., Carpenter, W.T., 1989. The Schedule for the Deficit Syndrome: an instrument for research in schizophrenia. Psychiatry Res 30, 119–123.
Kirkpatrick, B., Galderisi, S., 2008. Deficit schizophrenia: an update. World Psychiatry 7, 143–147.
Kirkpatrick, B., Mucci, A., Galderisi, S., 2017. Primary, enduring negative symptoms: an update on research. Schizophr. Bull. 43, 730–736. http://doi.org/10.1093/schbul/sbx064.
Lei, W., Deng, W., Li, M., He, Z., Han, Y., Huang, C., et al., 2015a. Gray matter volume

alterations in first-episode drug-naïve patients with deficit and nondeficit schizophrenia. Psychiatry Res. Neuroimaging 234, 219–226.
Lei, W., Li, N., Deng, W., Li, M., Huang, C., Ma, X., et al., 2015b. White matter alterations in first episode treatment-naive patients with deficit schizophrenia: a combined VBM and DTI study. Sci. Rep. 5, 1–11. http://doi.org/10.1038/srep12994.
Millan, M.J., Fone, K., Steckler, T., Horan, W.P., 2014. Negative symptoms of schizophrenia: clinical characteristics, pathophysiological substrates, experimental models and prospects for improved treatment. Eur. Neuropsychopharmacol. 24, 645–692. http://doi.org/10.1016/j.euroneuro.2014.03.008.
Olabi, B., Ellison-Wright, I., McIntosh, A.M., Wood, S.J., Bullmore, E., Lawrie, S.M., 2011. Are there progressive brain changes in schizophrenia? A meta-analysis of structural magnetic resonance imaging studies. Biol. Psychiatry 70, 88–96.
Ozdemir, H.I., Eker, M.C., Zengin, B., Yilmaz, D.A., Isman Haznedaroglu, D., Cinar, C., et al., 2012. . Gray matter changes in patients with deficit schizophrenia and nondeficit schizophrenia. Turk Psikiyatri Derg 23, 237–246.
Pantelis, C., Yucel, M., Wood, S.J., McGorry, P.D., Velakoulis, D., 2003. Early and late neurodevelopmental disturbances in schizophrenia and their functional consequences. Aust. N. Z. J. Psychiatry. 37, 399–406.
Price, G., Cercignani, M., Chu, E.M., Barnes, T.R.E., Barker, G.J., Joyce, E.M., et al., 2010. Brain pathology in first-episode psychosis: magnetization transfer imaging provides additional information to MRI measurements of volume loss. NeuroImage 49, 185–192. https://doi.org/10.1016/j.neuroimage.2009.07.037.
Schmahmann, J.D., Smith, E.E., Eichler, F.S., Filley, C.M., 2008. Cerebral white matter: neuroanatomy, clinical neurology, and neurobehavioral correlates. Ann. N.Y. Acad. Sci. 1142, 266–309. http://doi.org/10.1196/annals.1444.017.
Spitzer, R.L., Gibbon, M., Williams, J., 2002. Structured clinical interview for DSM-IV-TR axis I disorders, research version, non-patient edition (SCID-I/NP). Biometrics Research. New York State Psychiatric Institute, New York, NY.
Steen, R.G., Mull, C., McClure, R., Hamer, R.M., Lieberman, J.A., 2006. Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. Br. J. Psychiatry. 188, 510–518. http://doi.org/10.1192/bjp.188.6.510.
Strauss, G.P., Harrow, M., Grossman, L.S., Rosen, C., 2008. Periods of recovery in deficit syndrome schizophrenia: a 20-year multi–follow-up Longitudinal Study. Schizophr. Bull. 36, 788–799. http://doi.org/10.1093/schbul/sbn167.
Strungas, S., Christensen, J.D., Holcomb, J.M., Garver, D.L., 2003. State-related thalamic changes during antipsychotic treatment in schizophrenia: preliminary observations. Psychiatry Res. Neuroimaging 124, 121–124. http://doi.org/10.1016/S0925-4927(03)00092-1.
Takahashi, T., Wood, S.J., Soulsby, B., McGorry, P.D., Tanino, R., Suzuki, M., et al., 2009. . Follow-up MRI study of the insular cortex in first-episode psychosis and chronic schizophrenia. Schizophr. Res. 108, 49–56. http://doi.org/10.1016/j.schres.2008.12.029.
Tandon, R., Nasrallah, H.A., Keshavan, M.S., 2009. Schizophrenia,"just the facts" 4. Clinical features and conceptualization. Schizophr. Res. 110, 1–23.
Tek, C., Kirkpatrick, B., Buchanan, R.W., 2001. A five-year followup study of deficit and nondeficit schizophrenia. Schizophr. Res. 49, 253–260.
Tsuang, M.T., Stone, W.S., Faraone, S.V., 2001. Genes, environment and schizophrenia. Br. J. Psychiatry. 178, s18–s24.
van Haren, N.E.M., Schnack, H.G., Koevoets, M.G.J.C., Cahn, W., Hulshoff Pol, H.E., Kahn, R.S., 2016. Trajectories of subcortical volume change in schizophrenia: a 5-year follow-up. Schizophr. Res. 173, 140–145. http://dx.doi.org/10.1016/j.schres.2015.09.027.
Woods, S.W., 2003. Chlorpromazine equivalent doses for the newer atypical antipsychotics. J. Clin. Psychiatry. 64, 663–667.