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Review article

Cerebellar structural and functional abnormalities in first-episode and drug-naive patients with schizophrenia: A meta-analysis

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ABSTRACT

Schizophrenia (SZ) is a mental disorder that involves cerebral and cerebellar abnormalities. The cerebellum plays an indispensable role in the pathophysiology of SZ. However, individual studies pertaining to the structural and resting-state functional cerebellar abnormalities in patients with SZ have been inconsistent. To make a relatively robust conclusion with little interference, such as different disease episode times and antipsychotic treatment, we conducted this meta-analysis as a first attempt to comprehensively analyze and combine studies of voxel-based morphometry (VBM), amplitude of low-frequency fluctuation (ALFF), and functional connectivity strength (FCS) in first-episode and drug-naive SZ patients, employing the Seed-based d Mapping (SDM) method. Thirteen VBM studies, eight ALFF studies, and three FCS studies involving 783 patients and 704 matched healthy controls were included. Our results showed the presence of structural and functional abnormalities within the cerebellar regions, including most superior/anterior cerebellum (lobule III-V or VI) and posterior/inferior cerebellum (lobule VIII) related to motor function, and posterior cerebellum (lobule VIIa, Crus I, and II) associated with cognition and emotion, and such anomalies might be related to illness duration and clinical symptom severity.

1. Introduction

Schizophrenia (SZ), characterized by disordered cognition, psychotic symptoms, and deficiency of specific cognitive functions, such as working memory, self-reflection (Parnas et al., 2005; Pinkham, 2014), as well as motor symptoms (e.g., catatonia, neurological soft signs (Bombin et al., 2005; Heinrichs and Buchanan, 1988), deficits in postural control, and motor learning) (Marvel et al., 2004; Marvel et al., 2007), is perhaps the most intriguing and tragic mental illness known to mankind. Brain structural and functional abnormalities have been implicated in the development of schizophrenia. These abnormalities may be found in brain regions including the dorsolateral prefrontal cortex (DLPFC) (Cui et al., 2016) within the working memory network, default mode network (DMN) (Guo et al., 2015a; Guo et al., 2015b; Wang et al., 2016a), and cerebello-thalamo-cortical circuit (CTCC) (Bernard and Mittal, 2014; Bernard et al., 2017b; Guo et al., 2015a).

In recent years, the involvement of the cerebellum in traditional motor networks and systems and higher cognitive and affective function (Dean et al., 2014; Moberget and Ivry, 2016) in individuals with SZ is of interest (Bernard et al., 2014; Bernard et al., 2017a; Shinn et al., 2015). A great deal of neuroimaging and neuropathological studies have linked cerebellar abnormalities with widespread neuropsychological deficits with schizophrenia with inconsistent findings. For instance, some researchers reported a decreased cerebellar gray matter volume (GMV) in patients with SZ (Jayakumar et al., 2005; Salgado-Pineda et al., 2003; Venkatasubramanian, 2010; Yue et al., 2016), whereas other studies had negative or even opposite results (Guo et al., 2018; Salgado-Pineda et al., 2003). The inconsistent findings are attributed to several factors. First, the sample size, demographic characteristics of subjects, and methods of analysis differ across studies. For example, the proportion of male to female may be a potential significant bias owing to sex differences in the cerebellar volume trajectories (Bernard et al., 2015; Lei et al., 2015). Moreover, most of the advanced analyses designed for structural brain imaging data were optimized for the cerebrum and not for the cerebellum (Moberget. et al., 2017). Second, medication and long illness duration, which may increase heterogeneity and limit the interpretability and generalizability of results, can confound results greatly. Some researchers (Guo et al., 2017b; Lui et al., 2010; Yue et al., 2016) have demonstrated that medication can normalize functional connectivity of

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the brain. In addition, researchers employ different study designs that concentrate on different cerebellar subregions, which relate to different cerebral cortices devoted to distinct functions (Guo et al., 2018). Finally, it is possible that the contributions of the cerebellum to the pathophysiology of schizophrenia may be reflected by the abnormalities of other cerebral regions because of the reciprocal links between cerebrum and cerebellum. Therefore, it is meaningful to systematically analyze the cerebellar abnormalities underpinning the neurobiology of schizophrenia.

Voxel-based morphometry (VBM), unlike traditional labor-intensive regions of interest (ROI) method that is vulnerable to selection bias, can provide an unbiased mean of identifying regions of structural brain abnormalities through magnetic resonance imaging (MRI) examination (Ashburner and Friston, 2000). Structural alterations in the superior temporal gyrus, cingulate gyrus, thalamus, middle frontal cortex, and cerebellum have been reported in patients with SZ (Andreasen et al., 2011; Gutierrez-Galve et al., 2015).

Resting-state functional MRI is an ideal method for investigating basic brain activity without external stimuli (Raichle and Mintun, 2006), and it can avoid heterogeneity during the design and conduct of the tasks (Wang et al., 2017b). In particular, determining the amplitude of low-frequency fluctuation (ALFF) is one of the approaches of resting-state MRI to quantify the intensity of low-frequency oscillations in spontaneous neural activity (Lu et al., 2007), and it can be used to explore specific impaired brain regions.

In addition, seed-based resting-state functional connectivity is commonly used to explore abnormal resting-state functional connectivity in SZ. Most of these studies (Bluhm et al., 2007; Mannell et al., 2010) are based on some putatively proposed ROIs within some priori brain networks relating to SZ, such as the DMN, affective network, ventral attention network, and thalamocortical network. On the one hand, these studies give accumulative support to the hypothesis that SZ is a disease of disconnection (Dong et al., 2018; Fitzsimmons et al., 2013; Fornito et al., 2012). On the other hand, it is challenging to integrate these diverse results and make a convincing conclusion on a whole brain basis. Hence, functional connectivity strength (FCS) analysis, a kind of graph theoretical analysis that presents characterization of the entire functional connectome and shows a striking spatial correlation with the regional cerebral blood flow, is preferable (Wang et al., 2017a).

A systematically review of cerebellar volume alterations in SZ has been conducted (Moberget. et al., 2017) and the resting-state functional connectivity changes of large-scale brain networks (Dong et al., 2018) have also been reviewed, but a meta-analysis with focus on cerebellar structural alterations, as well as regional functional abnormalities in first-episode drug-naive patients with SZ that limits confounding factors, has never been done. Hence, in this meta-analysis, we provided an up-to-date quantitative summary of studies exploring cerebellar GMV and ALFF and FCS abnormalities in first-episode and drug-free patients with SZ, which can eliminate interferences by illness duration and antipsychotic treatment, using Seed-based *d* mapping (SDM), a statistical technique for meta-analyzing studies on differences in brain activity or structure (Radua and Mataix-Cols, 2012; Radua et al., 2014). Based on the abovementioned studies, we aimed to investigate whether SZ individuals exhibited GMV and functional alterations in the cerebellum and whether these changes had associations with clinical variables in order to reveal a more comprehensive and detailed portrait of cerebellar abnormalities in first-episode and treatment-naïve patients with SZ by combining results of different modalities, including both structure and function of the cerebellum.

2. Methods

2.1. Literature selection

A literature search was performed in September 2018 without restriction to regions, publication types, or languages. The primary sources were the electronic databases of the PubMed, Web of Science, and Cochrane Library, and no time span restriction. The following Medical Subject Heading (MeSH) keywords and their combinations were searched in the [Title/Abstract]: schizophrenia/SZ/SCZ and voxel-based morphometry/VBM/morphometry/voxel. Similarly, resting-state functional imaging studies were sought using [Title/Abstract]: schizophrenia/SZ/SCZ and ALFF/amplitude of low-frequency fluctuation/low-frequency fluctuation/LFF or functional connectivity strength/FCS. When multiple reports describing the same population appeared, the most recent or the complete report was selected.

2.2. Inclusion and exclusion criteria

All studies were included according to the following criteria: (1) using VBM or ALFF to analyze whole brain GM changes in SZ patients, (2) comparing patients with healthy controls (HC), and (3) only including first-episode and drug-naive SZ patients. Taking into account that the peak periods for the onset of SZ were late adolescence and early adulthood, most of the patients recruited in our study aged from 18 to 35 years old, only a few of them were over 45 years old or less than 15 years old (aged 13 to 55 years old). Exclusion criteria were as follows: (1) studies without peer review, (2) no HC, (3) using ROIs instead of whole-brain analysis or using different thresholds within different brain regions, (4) data could not be obtained from the published articles or after contacting the authors, (5) editorials, letters to the editor, review articles, case reports, and animal experimental studies.

2.3. Quality assessment and data extraction

To achieve a high standard of analysis, we adopted the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher et al., 2010) and assessed the quality of those included studies by using a checklist, which was based on some previous meta-analysis studies (Brambilla et al., 2003; Shepherd et al., 2012; Wang et al., 2017b), containing 11 main points relating to clinical and demographical characteristics of subjects, as well as important scanner parameters and methodology details (see the Supplementary Information).

Literature search, data extraction, and summarization were conducted independently by two authors (YD and YO). Any disagreement was resolved by the adjudicating senior authors (WG and JZ). The general characteristics of each study, including the first author, year of publication, sample size, sex of subjects, years of education, illness duration, medication use, tesla of MRI, image package, full width at half maximum (FWHM), and the threshold, were extracted as the basic data (Tables 1 and 2). Moreover, we obtained the peak coordinates and *t/z* values of statistically significant differences in regional cerebellar gray matter and localized connectivity between patients with SZ and healthy controls (Table 3).

2.4. Statistical analysis

Meta-analysis was performed using the SDM software (https://www.sdmproject.com/), which has been previously used in several neuropsychiatric disorders (Radua and Mataix-Cols, 2009; Radua et al., 2012). SDM software is a voxel-based meta-analytic approach, which adopts and combines various positive features from previous methods, such as activation likelihood estimation (ALE) or Multi-level Kernel Density Analysis (MKDA), and introduces a series of improvements and novel features. First, it represents both positive differences and negative differences in the same map, which avoids positive and negative findings in the same voxel as seen in previous methods, thus obtaining a signed differential map ("SDM"). Furthermore, the use of effect sizes (leading to effect-size SDM or "ES-SDM"), which allows a combination

Table 1
Demographic and clinical characteristics of subjects in 22 involved studies.

study	Number(female)		Age(y)		Education(y)		Illness duration(months)	PANSS PS	PANSS NS	PANSS GS	PANSS TS	Mean episode	Drug status	Quality score(total:11)
	SZ	HC	SZ	HC	SZ	HC								
VBM														
Salgado-Pineda et al., 2003	13(0)	13(0)	23.76	23.36	NA	NA	NA	41.61	24.38	41.92	107.91	FE	Drug-naive	9
Lui et al., 2009	68(38)	68(37)	24.2	24.7	11.8	13	8.6	26.6	20.6	51.8	107.4	FE	Drug-naive	11
Yue et al., 2016	20(10)	24(10)	24.45	24.79	11.95	13.17	22.92	21.25	19.10	48.60	88.95	FE	Drug-naive	11
Venkatasubramanian et al., 2010	30(9)	27(8)	30.1	27.4	12	13	41.7	22	23	39	84	FE	Drug-naive	11
Jayakumar et al., 2005	18(9)	18(9)	24.9	25.7	10.9	12.5	10.3	19	23	36	79	FE	Drug-naive	10
Filippi et al., 2014	43(19)	17(11)	29.3	30.7	11.0	15.2	7.9	28.2	23.0	49.6	100.8	FE	Drug-naive	9.5
Chua et al., 2007	23(NA)	38(NA)	32	33	10	13	4	NA	NA	NA	72	FE	Drug-naive	9.5
Berge et al., 2011	21(9)	20(12)	24.81	25.30	NA	NA	NA	26.19	17.48	40.33	84.43	FE	Drug-naive	11
Guo et al., 2018	49(19)	50(27)	22.69	23.48	10.94	11.46	22.45	22.27	22.82	46.22	91.31	FE	Drug-naive	11
Bonilha et al., 2008	14(3)	13(2)	40	35	NA	NA	NA	24	21	44	96	FE	Drug-naive	9.5
Zhao et al., 2018	58(31)	39(20)	20.4	22.2	NA	NA	NA	23.6	21.4	41.0	86.0	FE	Drug-naive	10.5
Zhang et al., 2017	26(13)	26(13)	16.87	16.81	10.35	11.19	3.61	25.12	20.46	47.85	93.42	FE	Drug-naive	11
Job et al., 2002	34(11)	36(19)	21.35	21.17	NA	NA	NA	NA	NA	NA	NA	FE	Drug-naive	9.5
ALFF														
Li et al., 2017	83(35)	42(18)	23.09	23.29	11.9	12.57	19.99	23.76	21.98	45.00	92.8	FE	Drug-naive	11
Cui et al., 2016	32(14)	19(9)	21.88	23.79	13.56	14.74	8.36	24.52	24.13	48.50	97.16	FE	Drug-naive	10.5
Guo et al., 2018	49(19)	50(27)	22.69	23.48	10.94	11.46	22.45	22.27	22.82	46.22	91.31	FE	Drug-naive	11
Wang et al., 2016	23(15)	29(17)	18.78	19.45	NA	NA	3.20	NA	NA	NA	NA	FE	Drug-naive	10.5
Liu et al., 2010	34(21)	34(21)	24.6	25.0	12.1	13.4	7.8	26.9	19.1	49.9	104.2	FE	Drug-naive	11
Zhao et al., 2018	58(31)	39(20)	20.4	22.2	NA	NA	NA	23.6	21.4	41.0	86.0	FE	Drug-naive	10.5
Huang et al., 2010	66(36)	66(36)	24.2	24.5	11.5	12.7	8.8	26.4	20.7	51.3	107.2	FE	Drug-naive	11
Zheng et al., 2016	35(15)	30(17)	15.50	15.43	8.7	8.5	6.6	20.42	20.91	33.28	74.62	FE	Drug-naive	11
FCS														
Guo et al., 2017b	17(9)	24(13)	33.12	30.67	14.41	13.83	12.03	23.00	20.24	44.82	88.06	FE	Drug-naive	10.5
Guo et al., 2017	28(10)	40(20)	22.93	23.28	10.54	11.53	24.14	22.68	21.18	44.25	88.11	FE	Drug-naive	11
Wang et al., 2017a	48(27)	31(17)	15.79	15.42	8.88	8.44	5.35	21.50	17.92	34.25	75.10	FE	Drug-naive	11

Abbreviations: ALFF, amplitude of low-frequency fluctuation; FE, first-episode; GS, General score; HC, healthy control; NA, not available; NS, Negative score; PANSS, Positive and Negative Symptom Scale; PS, Positive score; SZ, schizophrenia; TS, total score; VBM, voxel-based morphometry.

Table 2
Technique details of VBM, ALFF, and FCS studies on SZ in meta-analysis.

study	MRI scanner	Software	Smoothing(FWHM)	*P* - value	Correction method
VBM					
Salgado-Pineda et al., 2003	1.5T	SPM99	8 mm	<0.001(uncorrected)	MCC
Lui et al., 2009	3.0T	SPM2	8 mm	<0.05(corrected)	GRF
Yue et al., 2016	3.0T	SPM8	8 mm	<0.001(uncorrected)	MCC
Venkatasubramanian et al., 2010	1.5T	SPM2	12 mm	<0.05(corrected)	FDR
Jayakumar et al., 2005	1.5T	SPM2	8 mm	<0.05(corrected)	FDR
Filippi et al., 2014	1.5T	SPM8	8 mm	<0.001(uncorrected)	MCC
Chua et al., 2007	1.5T	BAMM2.5	4.4 mm	<1(corrected)	MCC
Berge et al., 2011	NA	SPM5	8 mm	<0.0001(uncorrected)	MCC
Guo et al.,2018	3.0T	SPM8	4 mm	<0.05(corrected)	GRF
Bonilha et al.,2008	3.0T	SPM5	10 mm	<0.05(corrected)	FDR
Zhang et al.,2017	3.0T	SPM8	4 mm	<0.05(corrected)	FWE
Zhao et al., 2018	3.0T	DPARSF	6 mm	<0.001(uncorrected)	MCC
Job et al.,2002	1.0T	SPM99	8 mm	<0.05(corrected)	MCC
ALFF					
Li et al.,2017	3.0T	DPARSF	6 mm	<0.05(corrected)	MCC
Cui et al.,2016	3.0T	DPARSF	4 mm	<0.01(corrected)	ASC
Guo et al.,2018	3.0T	DPARSF	4 mm	<0.05(corrected)	GRF
Wang et al.,2016	3.0T	DPARSF	6 mm	<0.05(corrected)	MCC
Lui et al.,2010	3.0T	SPM2	8 mm	<0.05(corrected)	FWE
Zhao et al., 2018	3.0T	DPARSF	6 mm	<0.001(uncorrected)	MCC
Huang et al., 2010	3.0T	SPM2	8 mm	<0.001(corrected)	MCC
Zheng et al., 2016	3.0T	DPARSF	6 mm	<0.05(corrected)	ASC
FCS					
Guo et al., 2017b	3.0T	DPARSF	4 mm	<0.001(corrected)	GRF
Guo et al., 2017	3.0T	DPARSF	8 mm	<0.05(corrected)	GRF
Wang et al., 2017a	3.0T	DPARSF	8 mm	<0.05(corrected)	GRF

Abbreviations: ALFF, amplitude of low-frequency fluctuation; ASC, AlphaSime correction; FDR, false discovery rate; FWE, family-wise error correction; GRF, Gaussian random field; MCC, multiple comparison correction; VBM, voxel-based morphometry.

of reported peak coordinates with statistical parametric maps, results in more exhaustive and accurate meta-analyses. In addition, it employs anisotropic kernels during the recreation of effect size maps in order to account for the anisotropy in the spatial covariance (Xiao et al., 2017). Finally, it should be mentioned that the same threshold throughout the whole brain was used within each included study to avoid bias. The statistical significance of the analyses is checked by standard randomization tests (Monte Carlo randomizations) and the default parameters of the SDM software were used (the main threshold was set at uncorrected $p < 0.00500$, peak height threshold $z > 1.000$, and cluster extent ≥ 10 voxels). A false discovery rate (FDR) was used to correct for multiple comparisons at the $p < 0.05$ level.

SDM provides several different statistical analyses in order to complement the main outcome with sensitivity and heterogeneity analyses. For instance, Jackknife analysis consists in repeating a test as many times as studies have been included by exclusion of one different study each time. The idea is that if a significant brain region remains significant in all or most of the combinations of studies it can be concluded that this finding is highly replicable. Meta-regression, a kind of linear model analyses, can examine the impact of moderator variables on study effect size using regression-based techniques. We conducted a meta-regression analysis of voxel values across the studies to examine the associations between cerebellar changes and clinical features (PANSS and disease duration of the corresponding patients' samples). In addition, we used Egger's test (Egger et al., 1997), a linear regression approach designed to measure funnel plot asymmetry (or symmetry) on the natural logarithm scale of the odds ratio, to detect publication and related biases quantitatively instead of informal visual examination.

3. Results

3.1. Basic information of eligible studies

Thirteen data sets of VBM studies (Berge et al., 2011; Bonilha et al., 2008; Chua et al., 2007; Filippi et al., 2014; Guo et al., 2018; Jayakumar et al., 2005; Job et al., 2002; Lui et al., 2009; Salgado-Pineda et al., 2003; Venkatasubramanian, 2010; Yue et al., 2016; Zhang et al., 2017; Zhao et al., 2018), including 417 first-episode drug-naive patients with SZ (about 171 females; mean age 24.77 years), matched with 389 HC (about 168 females; mean age 25.08 years); eight data sets of ALFF studies (Cui et al., 2016; Guo et al., 2018; Huang et al., 2010; Li et al., 2017; Lui et al., 2010; Wang et al., 2016b; Zhao et al., 2018; Zheng et al., 2016), including 380 first-episode drug-naive patients with SZ (186 females; mean age 21.67 years), matched with 309 HC (165females; mean age 22.34 years); and three data sets of FCS studies (Guo et al., 2017a; Guo et al., 2017b; Wang et al., 2017a), including 93 first-episode drug-naïve patients with SZ (46 females; mean age 21.11 years), matched with 95 controls (50 females; mean age 22.58 years), fulfilled the predefined inclusion criteria and were included in the final analysis. The majority of the recruited patients were first-episode and drug naive prior to MRI scanning. Only twenty-eight of the included patients in the study of Lei et al. (2015) were minimally treated with low dose (25 to 75 mg of chlorpromazine daily dose equivalent) of risperidone or olanzapine before scanning. The flow diagram of Fig. 1 showed the process of identifying these studies. In particular, three of these VBM studies used the same group of samples, and thus, we selected the most recent one. Two of these studies reported VBM and ALFF results simultaneously; as a consequence, a total of twenty three peer-reviewed and published original studies were included. The mean quality score of these studies was 10.5 (total score was 11, see the Supplementary Information), indicating that these were of high quality. In these studies, there was no significant difference in age, sex, and framewise displacement values. The clinical and demographic characteristics of included studies were shown in Table 1. Table 2 summarizes technique details and the significance level of group comparisons in each study.

3.2. VBM meta-analysis of cerebellar gray matter

As shown in Table 3, a group comparison of first episode drug-naive schizophrenia patients with healthy controls showed decreased GM in the cerebellar lobule IV/V,VII, and left cerebellar lobule IV/V and left

Table 3
Regions showing statistically significant differences in GM and cerebellum activity between patients with SZ and healthy controls.

Region	MNI coordinates			SDM-*Z* score	*P* value	Number of voxels	Cluster breakdowns	Jackknife	Heterogeneity
	x	*y*	*z*						
GM									
Decreased GM									
Cerebellum, vermic lobule IV/V	−4	−56	−22	−1.179	0.000510931	88	Cerebellum, vermic lobule IV / V; Left cerebellum, hemispheric lobule IV / V, BA 18; Cerebellum, vermic lobule VI; Left cerebellum, hemispheric lobule VI; Left cerebellum, crus I; Cerebellum, vermic lobule VIII; Cerebellum, vermic lobule VII	13/13	No
Left cerebellum, hemispheric lobule IV/V, BA 18	−6	−52	−20	−1.167	0.000567675	142			
Cerebellum, vermic lobule VII	4	−68	−30	−0.887	0.004108012	18			
Left cerebellum, crus I	−40	−54	−36	−1.034	0.001207650	393	Left cerebellum, crus I, BA 37; Left cerebellum, crus II; Left cerebellum, hemispheric lobule VI; Left cerebellum, hemispheric lobule VIIb	10/13(Bonilha et al.,2008; Chua et al., 2007; Filippi et al., 2014)	No
Increased GM									
None									
Brain activity									
ALFF									
Decreased ALFF									
Right cerebellum, hemispheric lobule VIII	22	−−62	−58	−1.190	0.000366390	537	Right cerebellum, hemispheric lobule VIII; Right cerebellum, hemispheric lobule VIIb	8/9(Li et al., 2017)	No
Left cerebellum, hemispheric lobule IX	−12	−58	−42	−1.189	0.000397384	78	Middle cerebellar peduncles; Left cerebellum, hemispheric lobule IX; Left cerebellum, hemispheric lobule VIII	8/9(Li et al., 2017)	No
Right cerebellum, crus I	48	−58	−32	−1.127	0.002353311	107	Right cerebellum, crus I, BA 37; Right inferior temporal gyrus	9/9	No
Increased ALFF									
None									
Functional connectivity strength									
Decreased FCS									
Left fusiform gyrus, BA 30	−20	−44	−16	−1.525	0.000185788	743	Left cerebellum, hemispheric lobule IV / V, BA 30; Left fusiform gyrus; Left inferior temporal gyrus; Left lingual gyrus	1/3(Guo et al., 2017b; Guo et al., 2017)	No
Left cerebellum, hemispheric lobule IV / V	−22	−34	−24	−1.273	0.000428319	272			No
Increased FCS									
Left cerebellum, crus II	−16	−78	−34	1.179	0.000015497	348	Left cerebellum, crus I; Left cerebellum, crus II; Left cerebellum, hemispheric lobule VI, BA 18	2/3(Wang et al., 2017a)	No
Left cerebellum, crus I	−8	−70	−28	1.179	0.000061929	129			No

Abbreviations: ALFF, amplitude of low-frequency fluctuation; BA, Brodmann area; FCS, functional connectivity strength; GM, grey matter; MNI, Montreal Neurological Institute Space; SDM, Seed-based d Mapping.

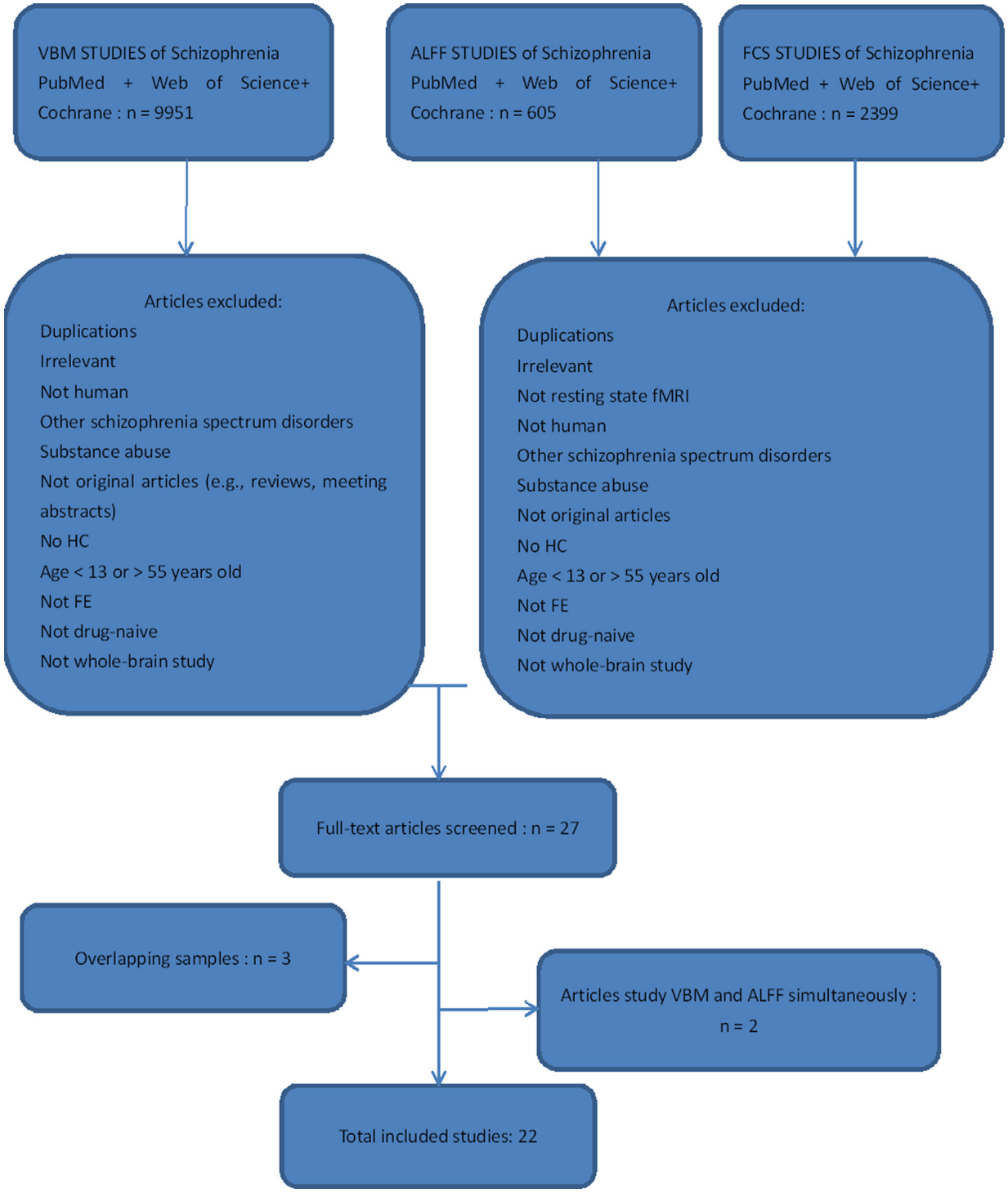

Fig. 1. A flow chart of selection process. Abbreviations: ALFF, amplitude of low-frequency fluctuation; FCS, functional connectivity strength; FE, first episode; HC, healthy control; VBM, voxel-based morphometry.

cerebellar Crus I. No significantly increased GM was found in the cerebellum in the patients (See Fig. 2 and Fig. 3).

According to the whole-brain Jackknife sensitivity analysis, the findings of decreased GM in the cerebellar lobule IV/V, VII and left cerebellar lobule IV/V were highly replicable, which were preserved throughout all data sets. The left cerebellar Crus I remained significant in all but 3 combinations.

In heterogeneity analysis, these cerebellar regions with altered GMV did not reveal significant statistical heterogeneity between studies ($p > 0.005$).

According to Egger test, there was no significant publication bias detected in the VBM meta-analysis, with $p = 0.367$ in the cerebellar lobule IV/V, $p = 0.548$ in the cerebellar lobule VII, and $p = 0.323$ and 0.152 in the left cerebellar lobule IV/V and left cerebellar Crus I, respectively.

In the meta-regression analysis, patients with maximum PANSS positive scores showed altered GM without restricting to one direction in some regions compared to patients with minimum positive scores. Both decreased ($p = 0.0001$, SDM-Z = -1.916) and increased ($p = 0.00002$, SDM-Z = 2.594) GM were found surviving corrections

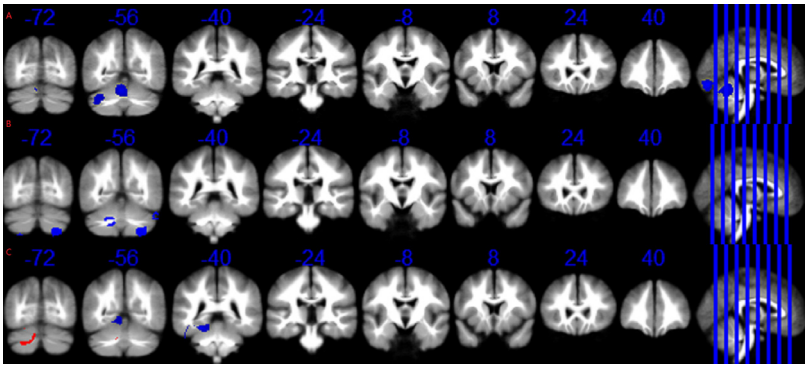

Fig. 2. Meta-analytic results of VBM (A), ALFF (B), and FCS (C) studies involved in patients with schizophrenia vs healthy controls. Abbreviations: ALFF, amplitude of low-frequency fluctuation; FCS, functional connectivity strength; VBM, voxel-based morphometry.

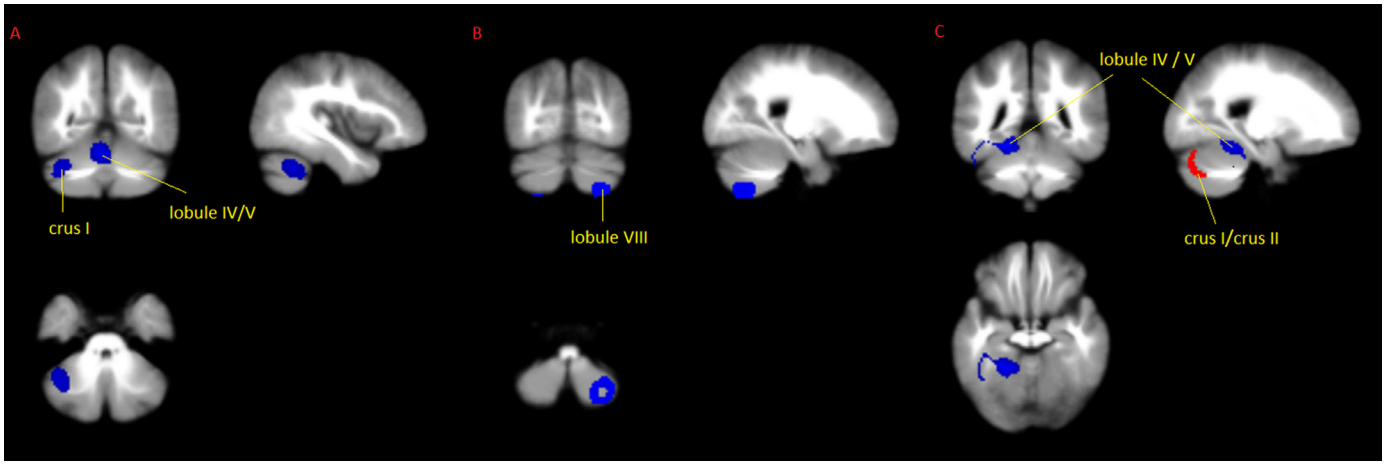

Fig. 3. Relative to healthy controls, patients with schizophrenia had significantly (A) decreased graymatter volume in the cerebellar lobule IV/V, left cerebellar lobule IV/V and left cerebellar Crus I; (B) reduced ALFF value in the right cerebellar lobule VIII; (C) reduced FCS in the left cerebellar lobule IV / V extending to the left fusiform gyrus, and enhanced FCS in the left cerebellar Crus Iand Crus II. Abbreviations: ALFF, amplitude of low-frequency fluctuation; FCS, functional connectivity strength; VBM, voxel-based morphometry.

for multiple comparisons in the left cerebellar lobule IV / V. Similarly, compared with patients with minimum PANSS negative scores, patients with maximum negative scores presented decreased (p = 0.001, SDM-Z = -0.822) or increased (p = 0.00004, SDM-Z = 1.081) GM in the left cerebellar lobule IV / V, and decreased GM in the left cerebellar lobule VI (p = 0.002, SDM-Z = −0.757) and left cerebellar Crus I (p = 0.002, SDM-Z = −0.763). Meta-regression of these included VBM studies demonstrated no significant differences either between patients with maximum illness duration and patients with minimum illness duration or between patients with maximum PANSS general or total scores and patients with minimum ones.

3.3. ALFF and FCS meta-analysis of cerebellar functional activity

The meta-analysis of the ALFF studies in patients with SZ showed significantly reduced ALFF in the right cerebellar lobule VIII, left cerebellar lobule IX, and right cerebellar Crus I. Also, significantly reduced FCS was demonstrated in the left cerebellar lobule IV / V, extending to the left fusiform gyrus. No significantly increased ALFF was found in the cerebellum in the patients. On the contrary, enhanced FCS in the left cerebellar Crus II and left cerebellar Crus I were found in the patients compared with healthy controls (See Fig. 2 and Fig. 3).

According to the whole-brain Jackknife sensitivity analysis, the findings of reduced ALFF in the patients in the right cerebellar lobule VIII and left cerebellar lobule IX remained significant in all but 1 combination. The right cerebellar Crus I was highly replicable, which was preserved throughout all data sets. The results of reduced FCS in the left cerebellar lobule IV / V remained significant in all but 2 combinations, and enhanced FCS in the left cerebellar Crus II and Crus I in all but 1 combination.

In heterogeneity analysis, these cerebellar regions with changed resting state regional brain activity, including ALFF and FCS values, did not reveal significant statistical heterogeneity between studies (p > 0.005).

According to Egger test, there was no significant publication bias detected either in the ALFF meta-analysis, with p = 0.387 in the right cerebellar lobule VIII, p = 0.434 in the left cerebellar lobule IX, and p = 0.612 in the right cerebellar Crus I, or in the FCS meta-analysis, with p = 0.976 in the left cerebellar lobule IV / V and p = 0.591 in the left cerebellar Crus II and Crus I.

In the meta-regression analysis, patients with maximum illness duration showed decreased ALFF in the right cerebellar Crus I (p = 0.0002, SDM-Z = −2.09) compared to patients with minimal illness duration. Likewise, compared with patients with minimum PANSS negative scores, patients with maximum negative scores presented attenuated ALFF in the right cerebellar Crus I (p = 0.00008, SDM-Z = −1.180) and right cerebellar lobule VIIb (p = 0.004, SDM-Z = −0.505). Meta-regression of these involved ALFF studies demonstrated no significant differences between patients with maximum PANSS positive, general or total scores and patients with minimum ones.

In the meta-regression analysis of FCS studies, reduced FCS in the left cerebellar lobule VI was found significantly between patients with maximum illness duration or PANSS scores and patients with minimum

ones.

4. Discussion

In this meta-analysis of thirteen VBM studies, nine ALFF studies, and three FCS studies, including 783 first-episode drug-naive patients with SZ compared with 704 HC, we provided a relatively comprehensive picture of cerebellum in SZ by using a relatively novel technique, SDM, which combines coordinate meta-analytic methods and standard meta-analytic methods. Our main findings showed that first-episode drug-naive patients with SZ had cerebellar abnormalities, including a significantly decreased GM volume in the left cerebellar lobule IV/V and Crus I, and cerebellar lobule IV/V and VII, along with reduced ALFF in the right cerebellar lobule VIII, left cerebellar lobule IX, and right cerebellar Crus I, as well as attenuated FC strength in the left cerebellar lobule IV/V, and enhanced FCS in the left cerebellar Crus I and Crus II, which may contribute to the neuropathology of SZ. Moreover, significant differences were observed in cerebellar lobule IV/V, VI and Crus I among SZ subjects with different illness durations and PANSS scores, indicating that these clinical features have associations with the anomalies in specific cerebellar regions. Because of our restrictions on the episode time and medication condition, which were beneficial to avoid some potential biases, these results suggested that the differences in the cerebellum were due to disease rather than the side effects of medication usage.

Some post-mortem investigations have already provided direct evidence to indicate cerebellar morphological alterations in patients with SZ. For instance, reduced gyrification and decreased neuronal integrity in the cerebellar vermis were found by some researchers (Deicken et al., 2001; Schmitt et al., 2011). In addition, a decrease in Purkinje cell density was observed in SZ patients (Maloku et al., 2010). In line with our findings, in the study of Greenstein et al., patients with SZ had smaller anterior cerebellar volume and vermis volume compared with controls (Greenstein et al., 2011). Similarly, another study (Dean et al., 2014), focusing on adults with ultra-high risk (UHR) for psychosis who had greater probability of developing psychosis due to the emergence of some attenuated psychotic symptoms and a progressive declining function demonstrated that the anterior cerebellum and Crus I differed between this group of patients and healthy controls.

Notably, we documented prominent alterations in lobule IV/V, VI, VII, VIII, and Crus I, not only in the VBM, ALFF and FCS meta-analysis, but also in meta-regression analysis between patient group with maximum illness duration or PANSS scores and those with minimal illness duration or PANSS scores. Therefore, we hypothesized that the changes in both structural and functional aspects might reflect a common pathophysiology of cerebellum in SZ. The involved cerebellar regions showed coordinated changes, and the ALFF and FC strength abnormalities might be mediated by underlying structural abnormalities. According to some researchers, the cerebellum can be preliminarily divided into two zones: one is the superior lobule of the cerebellar hemispheres (Lobule V, VI, and VIII), named primary sensorimotor zone, which has functional connectivity with motor, premotor, somatosensory, visual, and auditory cortex; another one is the supramodel zone, including the lobule VIIa, Crus I, and Crus II (the posterior cerebellum), which has a strong functional connectivity with the prefrontal and posterior-parietal cerebral-cortical regions (Bernard et al., 2012; Habas, 2010; Kelly and Strick, 2003; O'Reilly et al., 2010; Ramnani, 2006). Our findings, such as decreased GMV and reduced ALFF in the lobule IV/V, VIII, and Crus I, may indicate impaired motor and cognition functions in SZ. It is very likely for patients with schizophrenia exhibiting movement abnormalities (Bachmann et al., 2014; Bernard et al., 2014; Tosato and Dazzan, 2005) as well as cognitive and affective dysfunction (Adamaszek et al., 2017; Andreasen et al., 1998; Buckner, 2013; Moberget et al., 2014), both of which, according to a growing number of studies, are partly modulated by the cerebellum. The former involves a variety of domains, such as catatonia, neurological soft signs, and extrapyramidal signs, and the latter includes working memory, attention, and affect regulation. Edwards et al. revealed that SZ patients who showed impaired eye-blink conditioning had a smaller volume of the anterior cerebellum than that of controls though cerebellar volume and conditioning performance had no significant correlation (Edwards et al., 2008). Dean and colleagues found that compared with HC, UHR individuals had smaller volumes in specific areas of the cerebellum (Crus I) by employing pursuit rotor task, a gold standard task of procedural learning, to examine motor and cognitive function (Dean et al., 2014). When it comes to regional activity in the cerebellum, decreased ALFF in the right lobule IV/V, VIII and Crus I, as well as reduced FCS in left lobule IV/V extending to fusiform gyrus which may be due to the more traditional normalization and smoothing methods that result in bleeding of signal between the cerebellum and ventral visual areas (Diedrichsen, 2006; Diedrichsen et al., 2009). Enhanced FCS in the left Crus I / II indicated altered functional activity in these regions, which may affect connectivity with other brain regions. A group of studies (Friston, 1999; Guo et al., 2015a; Stephan et al., 2009) have reported abnormal FCs between the cerebellum and cerebrum, which are concordance with our expectation. For example, researchers found that the right Crus I exhibited abnormal cerebellar FC with cerebral networks, including the dorsal attention network (DAN), default-mode network (DMN), and ventral attention network (VAN) (Guo et al., 2018). In UHR populations with deficits in postural control, they showed decreased cerebello-cortical connectivity involved Crus II and lobule VIIb, which were associated with the prefrontal and parietal cortical regions (Bernard and Mittal, 2014). Similarly, other scientists found that patients with SZ exhibited decreased resting-state functional connectivity density (rsFCD) in the right louble VI, increased rsFC with the prefrontal cortex and subcortical nuclei, and decreased rsFC with the visual cortex and sensorimotor cortex (Zhou. et al., 2017). Interestingly, studies in healthy individuals suggest that the cerebellum widely connects with the cerebral cortex through multiple distinct circuits. Lobule V and VIII are associated with the motor cortex, whereas Crus I and II connect with the dorsolateral prefrontal cortex (DLPFC) and medial prefrontal cortex (MPFC), which is an important part of the executive control network (ECN) and DMN, respectively (Krienen and Buckner, 2009). To summarize, all abovementioned results of different studies are consistent with our findings and support our hypothesis. It is worth noting that we found discordant change of brain activity between the left and right cerebellum, to be specific, the alterations of ALFF were more significant in the right cerebellum, whereas the FCS changes were more prominent in the left cerebellum. Further studies are needed to exam our hypothesis that these changes were hemisphere-specific.

The present meta-analysis has the following limitations. First, all the studies involved, as well as the meta-analysis approach, relied on the whole brain methods, and thus, subtle changes of some subregions of the cerebellum would be omitted. Converging evidence indicates that distinct subregions make up a functional topography within the cerebellum and are a part of distinct motor and non-motor cortical circuits (Bernard and Mittal, 2014). In the future, it is important to assess the cerebellum by using some regional approaches because functional architecture of the cerebellum seems to differ in SZ and is differentially impacted on disease state. Second, we included a relatively wide age range in our samples, which might confound the results due to regional effects of aging in volumetric patterns of the cerebellum. Bernard et al. (2015) found that the more posterior part of the neocerebellum followed a quadratic “inverse-U” pattern in healthy individuals, whereas the vermis and the anterior cerebellum followed logarithmic patterns. Additionally, Luft and colleagues (1999) indicated that total cerebellar volume remained relatively stable until age 50, after which the volumes were negatively correlated with age, especially the vermis. Third, publications containing ALFF and FCS data of the cerebellum in first-episode drug-naive patients were extremely limited, and thus, the inadequate sample size weakened the efficacy of our

meta-analysis. Although the alterations of GMV, ALFF, and FCS of the cerebellum in patients with SZ were significant in this meta-analysis and favored a downward trend, the question of whether structural and functional abnormalities of the cerebellum overlapped in SZ was unclear. We need more studies and data sets that pertain to cerebellum in patients with SZ to further support our findings. Finally, different acquisition parameters and the lack of detailed and consistent demographic and clinical information across all involved studies, are also some of the weaknesses of the study.

Despite these limitations, we found through this meta-analysis that first-episode and drug-naive patients with SZ had cerebellar abnormalities. We found decreased cerebellar GMV and reduced ALFF and FCS relating to motor and cognitive zone of the cerebellum, which indicated that cerebellar abnormalities existed in the early stage of SZ and might contribute to its neurobiology. Our findings provide further support to the theory that the cerebellum is primarily involved in the control of movement, higher cognitive and affective function, which are regarded to be widely impaired in patients with SZ.

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Author contributions

Drs. Guo W., Chen J. and Zhao J. designed the study. Ding Y., Ou Y. and Pan P. searched for studies. Ding Y., Shan X. and Liu F. analyzed these included data. Ding Y. wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2018.11.009.

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