White matter and schizophrenia: a meta-analysis of voxel-based morphometry and diffusion tensor imaging studies

Abstract

Voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) are the most implemented methodologies to detect alterations of both gray and white matter (WM). However, the role of WM in mental disorders is still not well defined. We aimed at clarifying the role of WM disruption in schizophrenia and at identifying the most frequently involved brain networks. A systematic literature search was conducted to identify VBM and DTI studies focusing on WM alterations in patients with schizophrenia compared to control subjects. We selected studies reporting the coordinates of WM reductions and we performed the anatomical likelihood estimation (ALE). Moreover, we labelled the WM bundles with an anatomical atlas and compared VBM and DTI ALE-scores of each significant WM tract. A total of 59 studies were eligible for the meta-analysis. WM alterations were reported in 31 and 34 foci with VBM and DTI methods, respectively. The most occurred WM bundles in both VBM and DTI studies and largely involved in schizophrenia were long projection fibers, callosal and commissural fibers, part of motor descending fibers, and fronto-temporal-limbic pathways. The meta-analysis showed a widespread WM disruption in schizophrenia involving specific cerebral circuits instead of well-defined regions.

Keywords: Schizophrenia; White Matter; Meta-analysis; Voxel-Based Morphometry; Diffusion Tensor Imaging.

1. Introduction

For many years, schizophrenia has been conceptualized as an inter- intra-hemispheric disconnection syndrome characterized by disconnections in gray matter (GM) areas (Friston and Frith, 1995; McGuire and Frith, 1996; Friston, 1998). Friston and Frith (1995) suggested the "disconnection hypothesis" according to which functional abnormalities involve not only specific GM regions, but also impaired communications between such regions (i.e., prefrontal-temporal and temporal-limbic pathways). Subsequently, McGuire and Frith (1996) postulated the existence of a disrupted fronto-temporal-limbic connection by observing anatomical structural GM alterations. These studies suggested the presence of a widespread GM disruption instead of well-defined alterations underlying the involvement of white matter (WM) connections across different areas. Although GM alterations associated with schizophrenia were examined thoroughly (Honea, et al., 2005; Glahn et al., 2008; Olabi et al., 2011), the role of the WM in the illness pathogenesis is still unclear.

Recently, several meta-analytic studies investigated the role of WM irregularities. A meta-analysis of 15 diffusion tensor imaging (DTI) studies with patients affected by chronic schizophrenia, observed significant fractional anisotropy (FA) reductions in left frontal and left temporal WM regions, namely the genu and the splenium of corpus callosum, the cingulum bundle, the left anterior thalamic radiation, the left corticobulbar tract, the left inferior fronto-occipital fasciculus (IFOF), the fornix, and the left inferior longitudinal fasciculus (ILF) (Ellison-Wright and Bullmore, 2009). Moreover, Di, Chan, and Gong (2009), by conducting a meta-analytic procedure implemented on 17 voxel-based morphometry (VBM) studies, described WM alterations of chronic and first-episode schizophrenia (FES) patients and observed significant WM reductions in frontal regions and in the bilateral internal

capsule. Finally, a recent meta-analysis, examined WM alterations in patients with FES, showing significant WM reductions in the corpus callosum, the cingulum bundle, the left ILF, and the left IFOF (Yao et al., 2013). Taken together, these studies emphasize that alterations of WM tracts involving frontal, temporal, and limbic circuits play an important role in schizophrenia, thus reinforcing the disconnection hypothesis.

Despite the great relevance of these meta-analytic studies, some critical issues remain to be addressed. First, two studies (Di et al., 2009; Yao et al., 2013) focused only on patients with FES but they did not evaluate possible effects of illness progression or age-dependent factors that may have influenced WM anomalies. A recent review by Chiapponi and colleagues (2013a) highlighted a significant influence of illness progression in WM anomalies, so that impaired WM regions such as the corpus callosum, the uncinate fasciculus, and the regions of frontal and temporal WM continuously worsen over time. Their results indicated a possible association between illness progression and a faster decline of WM trajectories. In a more recent study about structural brain changes in schizophrenia over time, Cropley and colleagues (2017) found that patients with schizophrenia showed a significantly fast rate of WM deterioration correlated with age, indicating a confounding relationship between WM reductions and patients' age. Taken together, these studies support the hypothesis that WM alterations worsen over time concurrently with aging and progression of illness. A second critical issue is that the adoption of a single technique (i.e., VBM or DTI) may not allow to evaluate properly the total amount of WM alterations given that VBM and DTI methods detect different features of WM alterations (Ashburner and Friston, 2000; Le Bihan et al., 2001). Third, since 2013 several authors, who were not

included in previous meta-analytic studies, investigated WM alterations by using both VBM or DTI methodologies.

Finally, by an in-depth examination of the literature, we observed several heterogeneous findings in VBM and DTI studies. For example, some VBM studies agreed in finding WM reductions in frontal and temporal areas regardless of the stage of illness (e.g., Paillère-Martinot et al., 2001; Spalletta et a., 2003; Price et al., 2006; Witthaus et al., 2008; Kim and Jeong, 2015; Lyu et al., 2015), but it remains still unclear which WM tract is damaged in these regions. Indeed, some VBM studies reported differences between patients and healthy subjects in different regions, such as the internal capsule (Suzuki et al., 2002; Hulshoff Pol et al., 2004), the superior longitudinal fasciculus (SLF) (Antonova et al., 2005), the cingulum bundle (Wagner et al., 2013; Singh et al., 2015), the corpus callosum (Sigmundsson et al., 2001), the optic radiations (Ananth et al., 2002), and the cerebellum (Singh et al., 2014 and 2015), providing a great heterogeneity in findings of these studies. Moreover, several DTI studies reported different tracts involved in WM aberration and a clear convergence of the results of these studies is still missing. Several DTI studies showed different WM aberrations expressed as FA reductions in patients with schizophrenia compared to healthy subjects in different bundles, for example in the internal capsule (Buchsbaum et al., 2006; Kanaan et al., 2009; Nakamura et al., 2012) and in long projection fibers such as IFOF (Rotarska-Jagiela et al., 2009), inferior and superior longitudinal fasciculus (Buchsbaum et al., 2006; Seok et al., 2007; Shergill et al., 2007), and arcuate fasciculus (Hubl et al., 2004). This observed heterogeneity in published findings prompted us to try to find a clearer convergence between published studies. In addition, given that important findings have been published during the last

three years, further and definitive meta-analytic studies may clarify how aberrations of WM pathways are involved in schizophrenia.

To address the aforementioned issues, we conducted a systematic literature research to investigate the role of WM reductions in schizophrenia by using the coordinate-based anatomical likelihood estimation (ALE) analysis of VBM and DTI studies. ALE is a quantitative voxel-based meta-analysis method that gives anatomical information by selecting studies comparison (Laird et al., 2005; Eickhoff et al., 2009; Eickhoff et al., 2012; Eickhoff et al., 2016). In ALE analysis, a pool of coordinates is extract from a single neuroimaging study. In the neuroimaging studies of cerebral alterations, a triad of coordinates (x, y, z) given in a standard stereotactic space usually represent the highest point of alteration (increase or decrease) of a defined brain area, as the center of a cluster of voxels. This methodology is widely adopted in neuroimaging meta-analyses, in particular for structural brain data. The ALE output is an overview of previous selected studies, giving information about results concordance. The use of ALE analysis on WM studies of schizophrenia could be helpful to better understand which are the most altered WM tracts in this illness.

Overall, we aimed at summarizing previous studies results on WM reductions in patients with schizophrenia and clarifying the possible concordance between findings of different studies. We considered the following schizophrenic categories: FES, early-onset schizophrenia (EOS), late-onset schizophrenia (LOS), and chronic schizophrenia, to elucidate the relationship between WM pathways abnormalities and pathogenesis of schizophrenia spectrum disorders. An in-house developed MATLAB routine was employed for coordinate data analyzing and, subsequently, defining ALE maps of altered foci pooled from the selected studies. In addition, a series of meta-regression were computed to evaluate effects of age-dependent factors or illness

progression on WM anomalies in patients with schizophrenia. Moreover, we performed a direct comparison between VBM and DTI data to clarify potential differences in WM reductions as detected by those two techniques. On this basis, we may hypothesize the presence of WM tracts commonly detected that could be represent the most impaired WM bundles in schizophrenia.

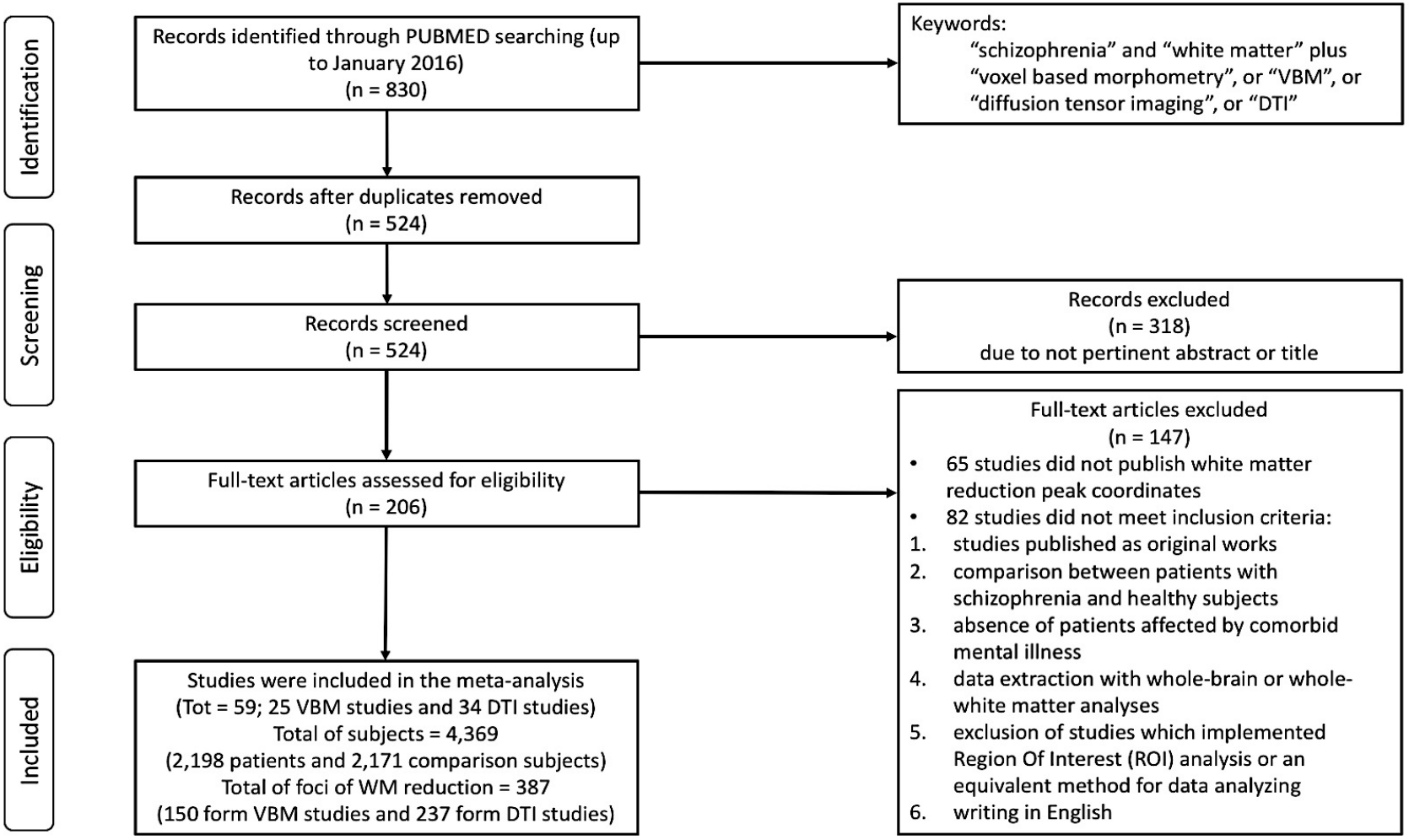
2. Methods

2.1. Study selection

We followed PRISMA statement in selecting papers and presenting the results (Moher et al., 2009). The electronic research literature database included PubMed from early 2000 to January 2016. Studies selection was supervised and approved by one neuroimaging expert (FC) and one clinical expert (AZ). Titles, abstracts and topics were searched using the following combined terms: “schizophrenia” and “white matter” plus “voxel-based morphometry”; “schizophrenia” and “white matter” plus “VBM”; “schizophrenia” and “white matter” plus “diffusion tensor imaging”; “schizophrenia” and “white matter” plus “DTI”. The search terms had to be present in abstract or title of the selected study. Articles were considered to be eligible according to the following criteria: 1) studies published as original works: we excluded meta-analytic results and we considered only original data of WM reductions; 2) publication of WM reduction peak coordinates in a standard stereotactic space: for VBM studies, we pooled coordinates of volumetric reductions, while for DTI studies we selected the coordinates representing foci of decreased FA; 3) comparison between patients with schizophrenia and healthy subjects; 4) absence of patients affected by comorbid mental illness in order to avoid a confounding effect of a concomitant mental illness; 5) data extraction with whole-brain or whole-white matter analyses; 6) exclusion of studies which implemented Region of Interest (ROI) analysis or an

equivalent method for data analysis, so that studies that might have neglected significant data because implemented a well-defined region analysis were excluded; 7) writing in English. Figure 1 shows the detailed flow-diagram of studies selection.

FIGURE 1. Flow-diagram of studies selection [a]



[a] WM, white matter. VBM, voxel-based morphometry. DTI, diffusion tensor imaging.

2.2. Anatomical Likelihood Estimation (ALE)

Before performing ALE analysis, we normalized the reported coordinates of each selected paper in a stereotactic standard space: we transformed the reported coordinates from MNI space to Talairach space by using the ICBM2Tal transform (Lancaster et al., 2007; Laird et al., 2010). Subsequently, we performed the ALE meta-analyses to estimate WM reductions across the selected articles by using the in-house MATLAB routine (MATLAB 2016a, The MathWorks, Inc., Natick, Massachusetts, United States), which implemented the ALE algorithm proposed by Laird et al. (2005) and further improved by Eickhoff et al. (2009), Eickhoff et al. (2012), and Eickhoff et al. (2016).

In the ALE analysis, the anatomical foci (represented by the x, y, z coordinate system) are treated not as a single point but as spatial probability distributions centered at the given coordinates (peak). Thus, each reported coordinate is considered as a central point of a 3D Gaussian probability distribution that models the spatial uncertainty associated with the foci and defined by a default full-width half maximum (FWHM). The FWHM is defined by the number of subjects in each experiments as reported in Eickhoff et al. (2009). The ALE method uses the sample size of each experiment to weight the size of the distribution around foci, assuming that a larger sample size should have less associated spatial uncertainty (Eickhoff et al., 2009; Eickhoff et al., 2012). In other words, larger studies are less sensitive to sampling errors and, thus, coordinates values should be closer to their true location, leading to a higher validity of meta-analytic results. For each selected study of structural neuroimaging, the ALE approach yield to a Modeled Anatomic (MA) map containing the voxels associated to the probability of observing alterations (in our analysis, we considered only WM reductions). If any alteration was not observed, the probability

value associated to the selected voxel is equal to 0 (Eickhoff et al., 2009; Eickhoff et al., 2012). In these maps, voxels union forms a cluster which size increases when more studies report foci near to each other. Thus, bigger clusters are more informative about the probability of observing alterations in the given foci because of the convergence of studies reporting the same coordinates (Eickhoff et al., 2012). Each MA map is combined in a single map to provide an estimation of the spatial convergence across the selected studies. The union of all the MA maps allows to calculate voxel-wise ALE scores that are tested against an empirical null hypothesis representing a random spatial association between experiments; this comparison distinguishes the "true" ALE scores from those obtained by random choice (Eickhoff et al., 2009; Eickhoff et al., 2012; Eickhoff et al., 2016).

The ALE analysis was performed on two separated groups of data, one for VBM studies and one for DTI studies, thus obtaining two ALE maps. The ALE maps were computed at an FDR-corrected threshold of $p < 0.05$ and a minimum cluster size of $K > 50$ mm^3.

2.3. WM Labelling

We used the BVQXTools, a MATLAB toolbox (available from http://support.brainvoyager.com/available-tools/52-matlab-tools-bvxqtools.html), to transform the ALE maps in a compatible format for the analysis on BrainVoyager QX software (http://www.brainvoyager.com, version 2.3.5). Subsequently, we uploaded the transformed maps on BrainVoyager QX to visualize the WM tracts emerged from our meta-analysis on a standard Talairach template. We built a specific Volume of Interest (VOI) map, representing a 3D model of a WM mask that contains a list of coordinates (x, y, z) specifying the voxels belonging to the selected VOI. The WM mask is based on the WM atlas developed by Catani and Thiebaut de Schotten (2008),

so each WM tract represented in the VOI map is correctly named following the atlas. The transformed ALE maps and the 3D model of the WM mask could be both visualized at the same time, so that it was possible to evaluate where a cluster emerging from ALE map overlapped the WM mask. This procedure allowed to evaluate whether a significant cluster belonged to a specific WM tract, thus defining the name of the involved WM tract. Finally, we calculated the average ALE *p*-value expressed by the voxels of an entire WM bundle, so that each WM tract that emerged from the ALE analysis had an ALE score mediated by the total number of voxels of the same tract.

2.4. Conjunction analysis

We conducted a conjunction analysis to test the existence of overlapping clusters between VBM and DTI studies. VBM and DTI are two distinct methodologies for brain structural investigation and they detect different aspects of WM alteration. Thus, we hypothesized that VBM and DTI would produce different results on WM alterations. Indeed, if the conjunction analysis would have not found any overlapping clusters for the same WM tract, it would be possible that clusters identified by VBM or DTI were different for the same WM bundle. To test this hypothesis, the transformed ALE maps were uploaded to BrainVoyager QX to obtain volume maps from each ALE map. These anatomical-resolution volume maps (AR-VMP) were stored by BrainVoyager QX as files of volume maps containing statistical results in 3D format. By using specific functions, BrainVoyager QX produced two distinct VOI maps for VBM and DTI studies starting from the transformed ALE maps. A third VOI map representing the logical union of the two maps was created. This final map contains the overlapped clusters of the two ALE maps and, thus, it

represents the significant clusters outlined by ALE analysis of both VBM and DTI studies.

2.5. VBM-DTI comparison

Once obtained the WM labeled tab, we organized the WM bundle in 3 major cerebral circuits: (a) inter-hemispheric connections, including the anterior commissure, the corpus callosum and the fornix; (b) fronto-temporal-limbic pathways, including the arcuate fasciculus and its segmentations, the cingulum bundle, the uncinate fasciculus, the optic radiations, the internal capsule, and the long projection fibers as ILF, IFOF, and SLF; (c) cortico-cerebellar tracts, including the internal capsule, the cortico-spinal tracts, the cortico-ponto-cerebellum tracts, and the cerebellar penduculi. Subsequently, we reported the average ALE *p*-values obtained from ALE analysis of VBM and DTI studies on a double bar chart.

2.6. Meta-Regression

To examine potential effects of age, duration of illness, and gender, we conducted a series of meta-regressions with the Signed Differential Mapping (SDM) software (Radua and Mataix-Cols, 2009; Radua and Mataix-Cols, 2012; Radua et al., 2012), which implemented linear regressions, weighted by the square root of the sample size and intra-studies and between-studies variance (Radua and Mataix-Cols, 2009). The main output for each selected variable is a map of the regression slope, representing the amount of volumetric change (in VBM studies comparison) and FA change (in DTI studies comparison) associated with each variable. For each examined variable, SDM software returns a map containing significant clusters of WM changes, with associated peak coordinates, significant *p*-values, and *SDM-Z* scores. Positive *SDM-Z* scores represent positive correlations, while negative *SDM-Z* scores represent negative correlations. The voxel level threshold of regression was automatically given

at $p < 0.005$, while the extent threshold for cluster size was minimum 10 voxels. The variable "gender" was dichotomized to have value 1 (sample entirely composed by male patients) or value 0 (sample entirely composed by female patients) (Bora et al., 2011). We conducted separate meta-regressions for VBM and DTI studies. For a clearer view, we organized the significant clusters emerged from each regression in different maps using MRIcron (Rorden et al., 2007).

3. Results

3.1. Included studies and sample characteristics

The initial review process yielded 830 studies. Five hundred twenty-four records remained after duplicates removed, 318 of which were excluded due to not pertinent abstract or title. Among the remaining 206 studies, 65 studies were rejected due to the lack of peak coordinates of altered WM tracts voxels, and other 82 studies did not meet the inclusion criteria. Finally, a total of 59 articles published between 2000 and 2016 were included in our meta-analysis, 25 VBM studies and 34 DTI studies (Figure 1). Overall, our study included 2,198 patients with schizophrenia and 2,171 comparison subjects, and analyzed 150 foci of WM volume reductions (from VBM studies) and 237 foci of FA decrease (from DTI studies). Table 1 summarizes the demographic and clinical characteristics of the participants.

TABLE 1. Studies included in the meta-analysis [a]

Study			Schizophrenia sample						Healthy sample			Morphological changes foci	
	Year	First Author	Patients (N)	Gender (male/female) (N)	Average age (years)	Age at onset (years)	Stage of illness	Duration of Illness (years)	Control subjects (N)	Gender (male/female) (N)	Average Age (years)	WM decrease	FA reduction
VBM	2001	Paillère-Martinot, M. L.	20	20/0	29	19.1	EOS	10	20	20/0	26	6	
	2001	Sigmundsson, T.	27	26/1	34.9	-	-	13.9	27	25/2	32.2	1	
	2002	Ananth, H.	20	10/10	37.8	-	-	15.85	20	10/10	38.6	1	
	2002	Shapleske, J.	72	-	34.1	-	-	11.51	32	-	33.3	1	
	2002	Suzuki, M.	45	23/22	26.4	21.5	-	5.2	42	22/20	26.1	5	
	2003	Spalletta, G.	28	14/14	34.6	23.6	Chronic	11	28	14/14	34.4	8	
	2004	Hulshoff Pol, H. E.	159	112/47	35.6	21.1	-	12.3	158	106/52	37.7	4	
	2005	Antonova, E.	45	27/18	40.49	25.33	-	16.88	43	25/18	33.72	2	
	2005	Farrow, T.	25	18/7	20(m); 19(f)	-	FES	-	22	13/9	20(m); 21(f)	10	
	2006	Price, G.	16	12/4	29.9	26.3	FES	-	12	4/8	36	6	
	2007	Chua, S.	26*	12/17	32	-	FES	0.33	38**	18/22	33	2	
	2007	Pstore Bassitt, D.	50	38/12	31.7	20.5	-	11.4	30	21/9	31.2	1	
	2007	Whitford, T., exp_A	41	26/15	19.8	-	FES	0.69	47	33/14	19.3	6	
	2007	Whitford, T., exp_B	25	15/10	20	-	FES	2.57	26	15/11	20	6	
	2008	Witthaus, H.	23	16/7	26.4	-	FES	-	29	17/12	25.7	19	
	2008	Wolf, R.	28	20/8	33.1	-	-	5.82	14	9/5	30.9	1	
	2008	Yoshihara, Y.	18	9/9	15.8	-	EOS	1.2	18	9/9	15.8	2	
	2012	Watson, D.	25	19/6	28.8	-	FES	-	25	19/6	28.2	29	
	2013	Wagner, G.	34	23/11	35.9	-	-	-	36	25/11	32.4	4	
	2014	Singh, S.	14	8/6	34.06	23.9	-	9.6	14	7/7	32.63	2	
	2014	van Tol, M. J.	51	44/7	34.04	25.2	-	8.77	51	37/14	36.14	6	
	2014	Yao, L.	68	30/38	24.2	-	FES	0.72	68	31/37	24.7	3	
	2015	Kim, G.W.	20	12/8	30	-	-	-	20	12/8	30.9	4	
	2015	Lei, W., exp_A	33	22/11	22.33	20.41	FES	-	41	24/17	23.49	3	
	2015	Lyu, H.	51	34/17	22.29	-	FES	0.93	59	38/21	23.2	2	

	Study		Schizophrenia sample						Healthy sample			Morphological changes foci	
	Year	First Author	Patients (N)	Gender (male/female) (N)	Average age (years)	Age at onset (years)	Stage of illness	Duration of Illness (years)	Control subjects (N)	Gender (male/female) (N)	Average Age (years)	WM decrease	FA reduction
	2015	Singh, S.	14	11/3	31.5	23.7	-	10.03	14	10/4	27.21	16	
DTI	2003	Burns, J.	30	15/15	36.4	-	-	-	30	15/15	35.7		3
	2005	Kumra, S.	26	14/12	15.2	12	EOS	2	34	20/14	15.4		1
	2005	Szeszko, P.	10	6/4	26.9	-	FES	-	13	7/6	28.9		3
	2006	Buchsbaum, M. S.	63	44/19	41.7	23.5	-	18.2	55	32/23	42.4		19
	2006	Hao, Y.	21	12/9	23.71	-	FES	0.86	21	10/11	25.05		17
	2007	Ashtari, M.	23	13/10	15.8	13.5	EOS	2.4	21	11/10	15.3		4
	2007	Mori, T.	42	26/16	40	23.3	Chronic	16.8	42	26/16	39.2		10
	2007	Schlosser, R.	18	14/4	29.6	-	-	-	18	12/6	29		3
	2007	Seok, J. H.	30	15/15	29.5	-	-	7.5	22	11/11	30.3		5
	2007	Shergill, S.	33	30/3	32	-	-	7	40	35/5	34		3
	2008	Cheung, V.	25	11/14	28.5	-	FES	0.5	26	13/13	28.2		7
	2008	Kyriakopoulos, M.	19	12/7	17.09	-	EOS	-	20	12/8	16.33		3
	2008	Szeszko, P.	33	21/12	25.1	20.5	EOS	4.25	30	18/12	25.9		4
	2009	Bai, Y. M., exp_A	20	5/15	40.5	29.5	-	10.6	20	5/15	41.2		6
	2009	Bai, Y. M., exp_B	20	5/15	41.5	25.8	-	15	20	5/15	41.2		9
	2009	Jeong, B. S.	10	10/0	39.6	19.9	Chronic	19	10	10/0	44.1		6
	2009	Kanaan, R.	76	66/10	30.9	-	-	4	76	65/11	30.5		10
	2009	Kyriakopoulos, M., exp_A	17	13/4	16.62	14.8	FES	-	17	10/7	16.4		2
	2009	Kyriakopoulos, M., exp_B	17	13/4	23.71	22.01	FES	-	17	13/4	23.85		5
	2009	Rotarska-Jagiela, A.	24	12/12	39	26.21	-	12.58	24	12/12	39.21		14
	2010	Herbsman, T.	13	-	37.4	-	-	-	16	-	41.4		4
	2010	Tang, J.	38	20/18	16.3	15.5	FES EOS	0.76	38	20/18	16.5		1
	2011	Cui, L.	25	16/9	25.8	-	Paranoid	3.9	30	18/12	23.9		1
	2011	Wang, Q.	68	32/36	24.23	-	FES	0.75	100	52/48	25.58		3
	2012	Guo, W.	20	9/11	24	-	FES	0.55	26	14/12	23.62		3
	2012	Miyata, J.	26	16/10	34.5	23.2	-	11.3	32	16/16	39		2

Study		Schizophrenia sample						Healthy sample			Morphological changes foci	
Year	First Author	Patients (N)	Gender (male/female) (N)	Average age (years)	Age at onset (years)	Stage of illness	Duration of Illness (years)	Control subjects (N)	Gender (male/female) (N)	Average Age (years)	WM decrease	FA reduction
2012	Nakamura, K.	58	38/20	27.6	23.3	-	4.27	58	38/20	26.4		8
2012	Sugranyes, G.	22	14/8	17.2	14.7	EOS	-	19	11/8	16.5		14
2013	Chen, L.	20	5/15	46.9	-	LOS	2.9	17	4/13	47.4		2
2013	Chiapponi, C.	69	47/22	38.45	-	-	-	69	47/22	38.09		5
2013	Wang, Q., exp_A	35	16/19	23.84	23.39	FES	-	22	14/8	22.41		2
2013	Wang, Q., exp_B	35	16/19	23.84	23.39	FES	-	22	14/8	22.41		3
2014	Ellison-Wright, I.	21	17/4	34.2	-	Chronic	-	21	14/7	31.5		11
2014	Liu, X.	17	7/10	38.47	22.88	Chronic	15.41	17	6/11	34.12		1
2015	Lei, W., exp_B	33	22/11	22.33	20.41	FES	-	41	24/17	23.49		3
2015	Lei, W., exp_C	42	25/17	23.38	22.73	FES	-	41	24/17	23.49		4
2015	Reid, M. A.	29	20/9	33.8	-	-	13.4	20	14/6	37.1		21
2015	Situ, W.	50	50/0	31.1	-	-	6.21	50	50/0	29.14		8
2015	Spalletta, G., exp_A	21	19/2	33.8	22.4	-	11.4	21	19/2	33.7		3
2015	Spalletta, G., exp_B	21	19/2	34.1	22.6	-	11.5	21	19/2	33.7		4

[a] Average age, Age at onset and Duration of Illness are expressed as means. In “WM decrease” and “FA decrease” columns, values are referred to the number of foci of WM reduction found by the examined study. EOS, Early-Onset Schizophrenia. FES, First-Episode Schizophrenia. LOS, Late-Onset Schizophrenia. N, number of subjects. m, male. f, female. -, no data available.

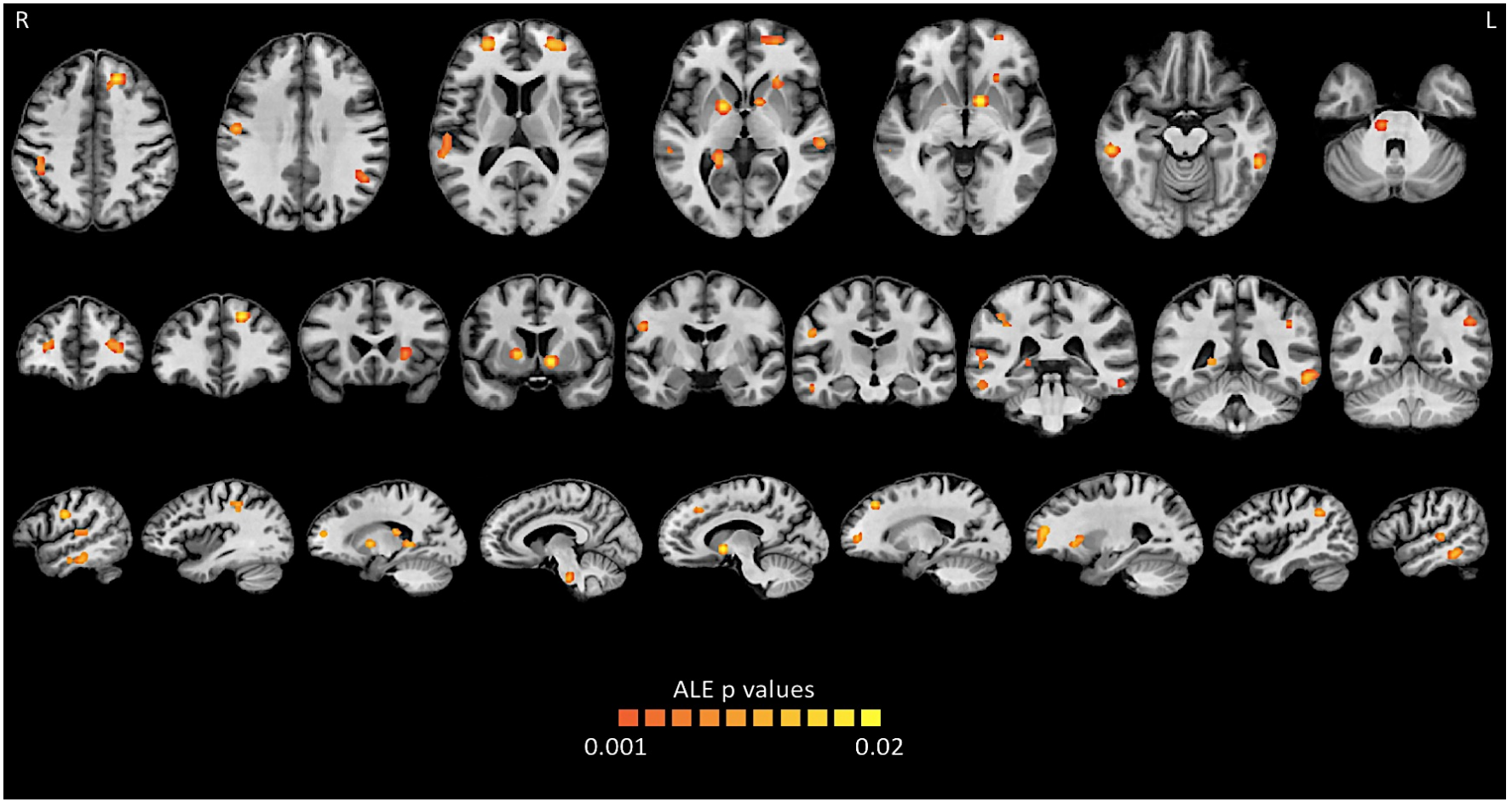
[*] The initial number of included patients was reduced from 29 to 26 because of the presence of massive brain damages in 3 patients [see Chua et al., 2007]

[**] The initial number of included control subjects was reduced from 40 to 38 because of a failure in the procedure of imaging data acquisition [see Chua et al., 2007]

3.2. ALE meta-analysis

The ALE meta-analysis of VBM studies showed WM reductions in the anterior commissure, the corpus callosum, , the fornix, the internal capsule, the right anterior segment of arcuate fasciculus (AF), the left cortico-ponto-cerebellum tract, the right superior cerebellar penduculus, the bilateral AF, the bilateral cingulum, the bilateral cortico-spinal tract, the bilateral IFOF, the bilateral ILF, the bilateral inferior cerebellar penduculus, the bilateral optic radiation, the bilateral posterior segment of AF, the bilateral first part of superior longitudinal fasciculus (SLF1), the bilateral central part of SLF (SLF2), the bilateral final part of SFL (SLF3), and the bilateral uncinate fasciculus (UF) (see Figure 2 and Table 2).

FIGURE 2. WM volume decrease identified by ALE meta-analysis of VBM studies [a]



[a] In first row, axial view of human brain with main clusters of WM alterations found by ALE meta-analysis of VBM studies. The second row shows the coronal view, while the third row shows the axial view. We used a Talairach template to represent the clusters found by the meta-analysis. Left and right sides of the brain are flipped. The WM bundles involved are listed in Table 2, with peak coordinates and average ALE *p*-values. The images are visualized using BrainVoyager QX software.

TABLE 2. WM tracts found in ALE meta-analysis with ALE *p*-values and coordinates of alteration peaks [a]

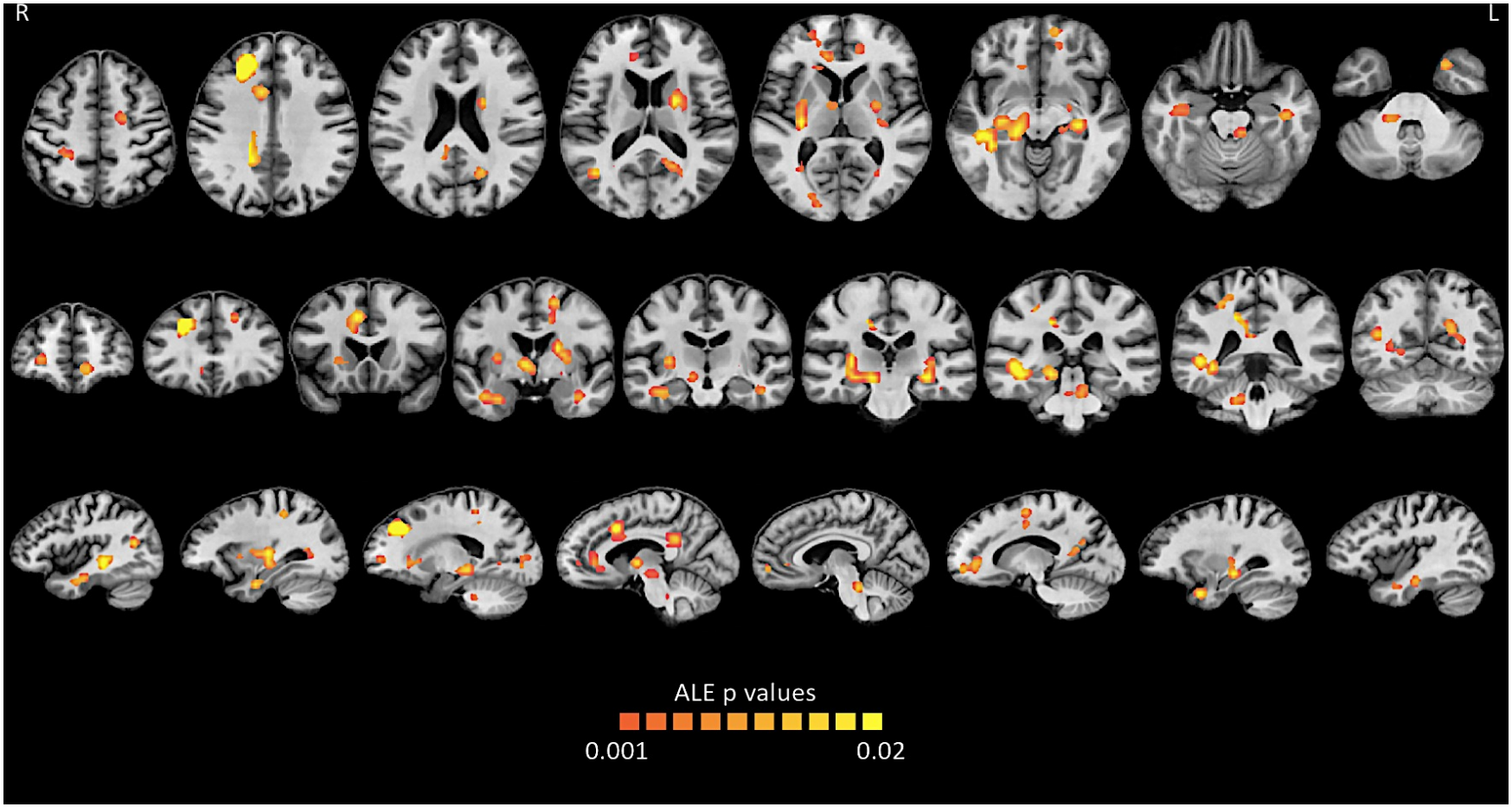
		DTI				VBM			
			Peak coordinates				Peak coordinates		
Tract Name	N° of voxels	Average ALE *p*-values	x	y	z	Average ALE *p*-values	x	y	z
AF L	24480	0.000112	-34	-40	-1	0.000124	-46	-49	35
AF R	23307	0.000258	44	-38	-1	0.000181	49	-10	29
Anterior Commissure	16636	0.000904	-25	8	-25	0.001020	-10	5	-1
Anterior Segment of AF L	5391	0.000036	-51	-7	15	0.000000			
Anterior Segment of AF R	8780	0.000000				0.000378	50	-10	29
Cingulum L	42476	0.000566	-19	-43	39	0.000082	-4	-4	27
Cingulum R	38840	0.001913	18	35	32	0.000166	20	-37	5
Corpus Callosum	114544	0.000655	17	35	35	0.000165	17	-28	17
Cortico Ponto Cerebellum tract L	2176	0.000226	16	-37	-32	0.000154	-22	-24	8
Cortico Ponto Cerebellum tract R	766	0.000206	25	-17	5	0.000000			
Cortico Spinal tract L	29175	0.000409	-19	-1	17	0.000133	-22	-28	8
Cortico Spinal tract R	23730	0.000592	29	-19	5	0.000258	17	2	5
Fornix	26318	0.000924	-29	10	-27	0.000455	17	-28	17
IFOF L	22154	0.000725	-31	-22	-7	0.000092	-28	-1	0
IFOF R	23185	0.001700	41	-31	-7	0.000002	18	26	5
ILF L	20131	0.000900	-34	-40	-1	0.000002	-23	-7	-7
ILF R	16338	0.002284	41	-31	-7	0.000110	40	-1	0

		DTI				VBM			
			Peak coordinates				Peak coordinates		
Tract Name	N° of voxels	Average ALE *p*-values	x	y	z	Average ALE *p*-values	x	y	z
Inferior Cerebellar Pedunculus L	5648	0.000235	-7	-33	-22	0.000003	-2	-51	-16
Inferior Cerebellar Pedunculus R	5302	0.000502	14	-38	-31	0.000226	11	-25	-31
Internal Capsule	63671	0.000525	-19	-1	17	0.000181	10	-25	-31
Long Segment of AF L	7639	0.000218	-34	-40	-1	0.000000			
Optic Radiation L	7923	0.000797	-34	-40	-1	0.000004	-22	-24	5
Optic Radiation R	5982	0.002349	29	-19	5	0.000161	40	-55	1
Posterior Segment of AF L	11088	0.000313	-34	-40	-1	0.000001	-51	-42	-7
Posterior Segment of AF R	12107	0.001262	41	-34	-4	0.000091	56	-34	11
SLF1 L	109025	0.000169	-19	-43	39	0.000163	-16	35	41
SLF1 R	98037	0.001150	20	35	35	0.000103	22	50	14
SLF2 L	112229	0.000059	-20	-4	53	0.000140	-26	50	14
SLF2 R	117581	0.000437	20	35	35	0.000068	25	51	14
SLF3 L	72219	0.000115	-49	-37	14	0.000149	-43	-46	35
SLF3 R	119900	0.000078	23	27	31	0.000160	50	-10	29
Superior Cerebellar Pedunculus L	8012	0.000772	-7	-31	-22	0.000000			
Superior Cerebellar Pedunculus R	8113	0.000741	13	-24	-7	0.000253	8	-25	-11
UF L	12282	0.000883	-25	9	-21	0.000203	-21	23	2
UF R	13022	0.000888	16	27	2	0.000037	17	4	1

[a] Data were obtained with BrainVoyager QX software. A WM mask, based on WM atlas developed by Catani and Thiebaut de Schotten (2008), was applied in order to obtain structural data as N° of total voxel of each tract and coordinate of alteration peaks. Coordinates are expressed in Talairach space. L, left. R, right

The ALE meta-analysis of DTI studies showed WM reductions in the anterior commissure, the corpus callosum, the fornix, the internal capsule, the left anterior segment of AF, the left long segment of AF, the bilateral AF, the bilateral cingulum, the bilateral cortico-ponto-cerebellum tract, the bilateral cortico-spinal tract, the bilateral IFOF, the bilateral ILF, the bilateral inferior cerebellar penduculus, the bilateral optic radiation, the bilateral posterior segment of AF, the bilateral SLF1, the bilateral SFL2, the bilateral SLF3, the bilateral superior cerebellar penduculus, and the bilateral uncinate fasciculus (see Figure 3 and Table 2).

FIGURE 3. WM FA decrease identified by ALE meta-analysis of DTI studies [a]



[a] In first row, axial view of human brain with main clusters of WM alterations found by ALE meta-analysis of DTI studies. The second row shows the coronal view, while the third row shows the axial view. We used a Talairach template to represent the clusters found by the meta-analysis. Left and right sides of the brain are flipped. The WM bundles involved are listed in Table 2, with peak coordinates and average ALE *p*-values. The images are visualized using BrainVoyager QX software.

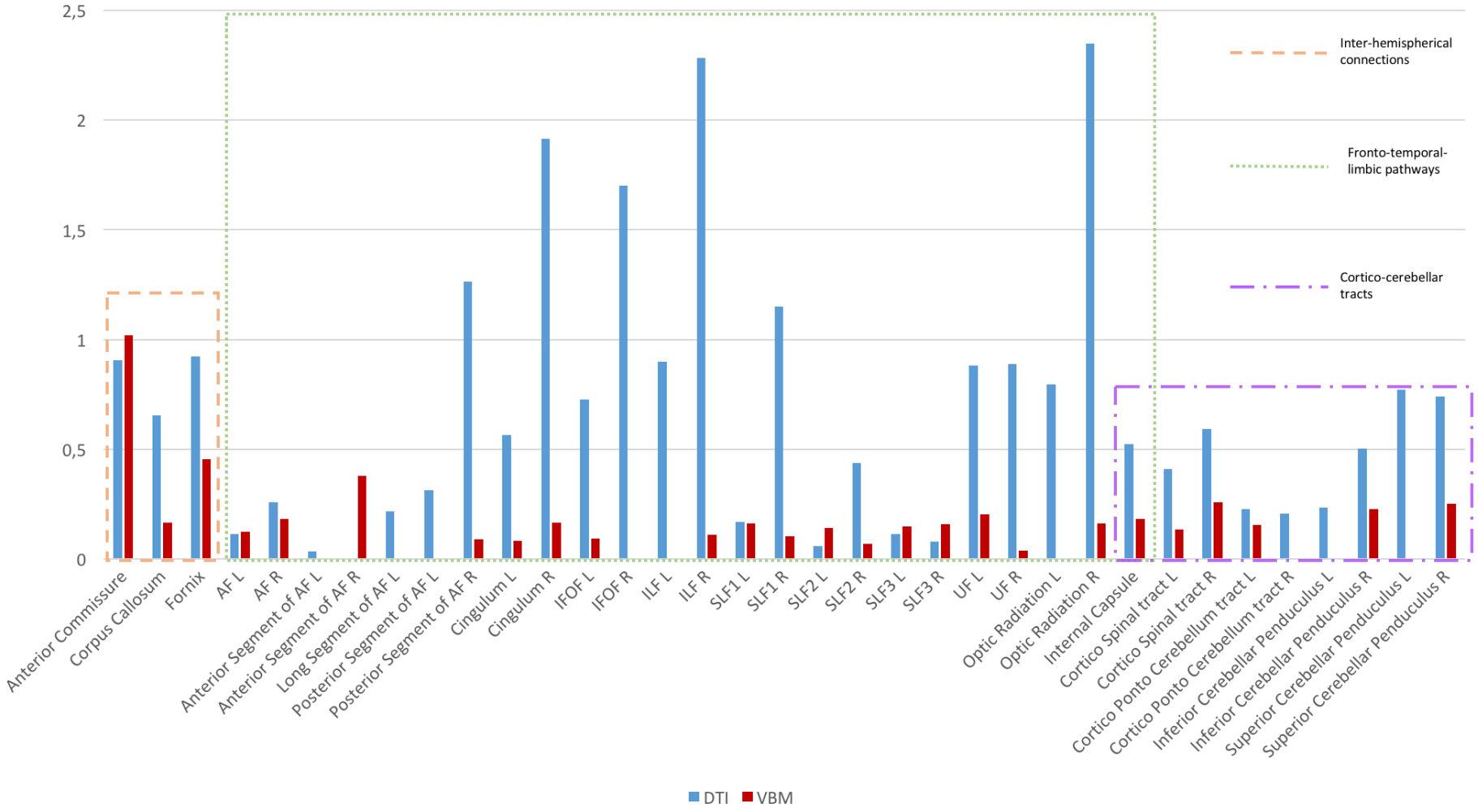
3.3. Conjunction analysis

The conjunction analysis between ALE maps from VBM and DTI studies found no overlapping clusters on the same WM tract, indicating that DTI and VBM actually detected different aspects of WM alteration (i.e., volumetric/macrostructural vs. diffusion/microstructural) and, consequentially, the clusters identified by VBM or DTI were different for the same WM tract

3.4. VBM-DTI comparison

Figure 4 shows ALE scores for each significant WM bundle emerged from ALE analysis. On the vertical axis we represented the ALE scores , whereas on the horizontal axis we listed the WM bundles emerged from our data analysis, according to Catani's WM atlas. We found that the left superior cerebellar penduculus, the left long segment of AF, the right cortico-ponto-cerebellum tract, and the left anterior segment of AF were activated (occurred) only in DTI studies, whereas the right anterior segment of AF was activated (occurred) only in VBM studies. The other tracts that were activated in both type of studies were the bilateral IFOF, the bilateral ILF, the bilateral posterior segment of AF, the bilateral optic radiation, the bilateral inferior cerebellar penduculus, the bilateral UF, the bilateral cingulum, the bilateral SLF1, the bilateral SLF2, the corpus callosum, the bilateral cortico-spinal tract, the right superior cerebellar penduculus, the internal capsule, the fornix, the left cortico-ponto-cerebellum tract, the bilateral AF, the anterior commissure, and the bilateral SLF3 (see Figure 4).

FIGURE 4. VBM-DTI comparison [a]



a Average ALE-scores of WM tracts emerged from ALE analysis. Blue columns are DTI ALE-scores, while red columns are VBM ALE-scores. The scores on vertical axis must be multiplied by 10^{-3} to obtain ALE-scores. On horizontal axis are represented the WM tracts organized by the main cerebral circuits; the orange dotted line includes the inter-hemispheric connections, the green dotted line includes the fronto-temporal-limbic pathways, while the purple dotted line includes the cortico-cerebellar tracts.

3.5. Meta-Regression

Meta-regression analyses of VBM and DTI studies suggested that age, duration of illness, and gender were associated to WM reductions. Table 3 summarizes the results of meta-regression analysis, while Figure 5 and Figure 6 show significant clusters ($p < 0.005$) both positively and negatively associated with each regressor respectively from analyses of VBM and DTI studies.

As for VBM studies, older patients (higher mean age) showed significant WM reductions in the left AF and left splenium of corpus callosum, compared to younger patients (lower mean age) that showed significant associations with WM reduction in left ILF and the right genu of corpus callosum. Longer duration of illness was significantly associated with WM reductions in the internal capsule and the right AF, whereas shorter duration of illness was associated with WM reductions in the fornix and the left genu of corpus callosum. Finally, a higher percentage of male patients showed significantly reduced WM traits in the left UF, the right SLF3, and the left cingulum, whereas a higher percentage of females showed significantly reduced WM traits in the right cortico spinal tract and the anterior commissure.

Meta-regressions of DTI studies reported that older patients showed significantly reduced WM in the right splenium of corpus callosum and the right cortico spinal tract, whereas younger patients showed significant associations with WM reductions of left cortico spinal tract, the right cingulum bundle, the WM of right superior temporal gyrus, and the left SLF3. Association between a longer duration of illness, and WM reductions in the bilateral UF, the left ILF, the right IFOF and the right posterior cingulum bundle was found, whereas shorter duration of illness was associated with significant WM reductions in the right anterior cingulum bundle, the WM of right median cingulate gyrus, and the left SLF3. Finally, a higher percentage

of male patients showed significantly reduced WM traits in the right SLF2, the WM of left inferior temporal gyrus, the bilateral SLF3, the WM of right superior temporal gyrus, the right posterior segment of AF, and the left body of corpus callosum, whereas a higher percentage of female patients showed significantly reduced WM traits in the right genu of corpus callosum, the right IFOF, the right SLF3, the left superior cerebellar penduculus, the left optic radiation, and the left long segment of AF.

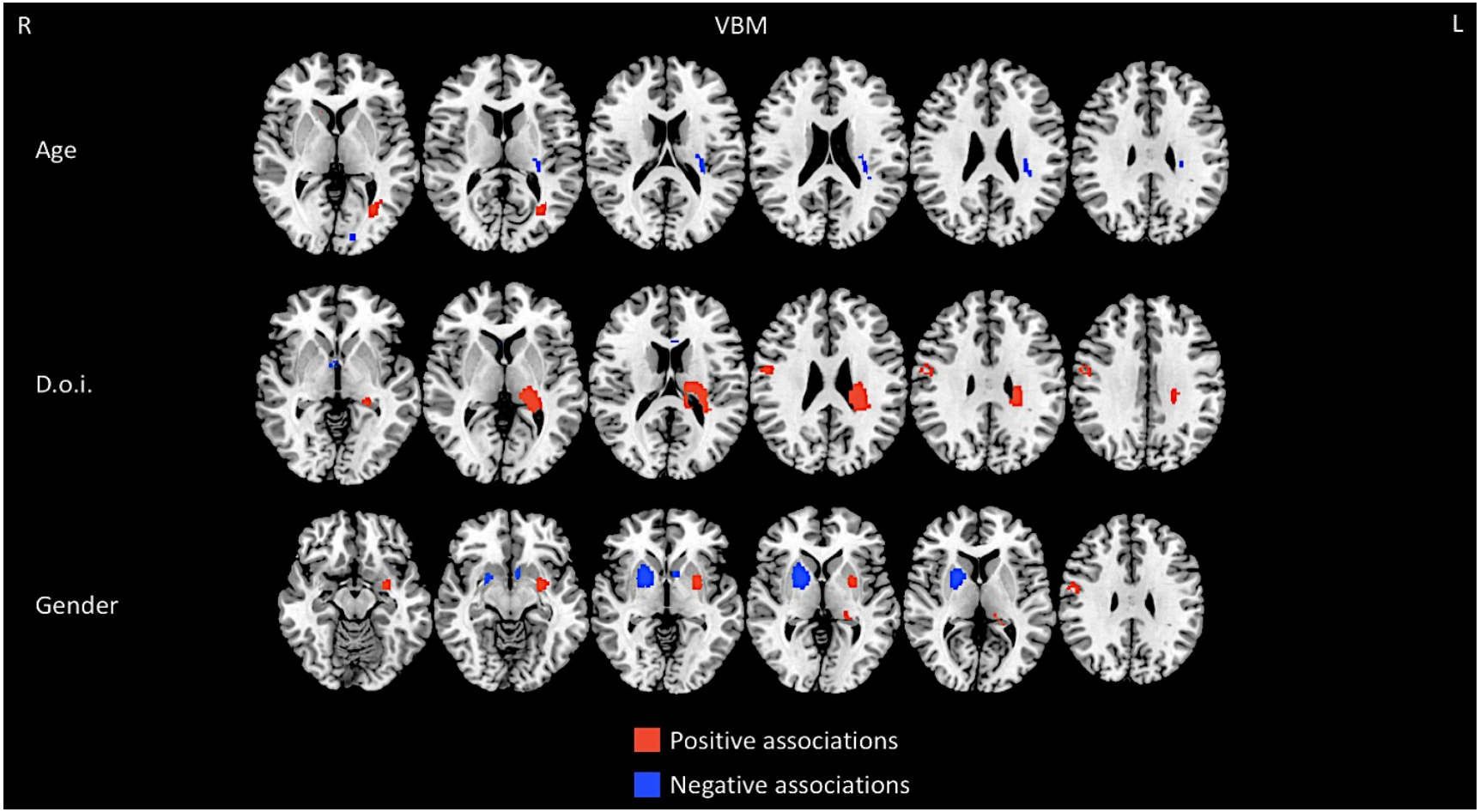
TABLE 3. Blob report for regressions of VBM and DTI studies [a]

	VBM						DTI					
	Peak coordinates			*SDM-Z* score	Voxels	Description	Peak coordinates			*SDM-Z* score	Voxels	Description
	x	y	z				x	y	z			
Age	-29	-27	18	1.745	137	AF L	17	-49	25	2.352	2102	Corpus Callosum, Splenium R
	-14	-86	-1	1.328	29	Corpus Callosum, Splenium L	27	-35	45	1.273	76	Cortico Spinal Tract R
	-35	-62	4	-2.365	175	ILF L	-24	-17	36	-1.469	560	Cortico Spinal Tract L
	12	17	11	-1.977	16	Corpus Callosum, Genu R	10	36	9	-1.970	323	Cingulum R
							44	-26	2	-1.436	81	WM of Superior Temporal Gyrus R (near SLF3)
							-31	46	3	-1.086	11	SLF3 L
D.o.i.	-25	-30	6	3.145	1313	Internal Capsule	27	6	5	1.811	394	UF R
	47	-6	31	1.831	73	AF R	-27	-1	3	1.441	120	UF L
	6	-1	-2	-1.885	39	Fornix	-42	-27	-10	1.597	100	ILF L
	-3	15	12	-1.779	25	Corpus Callosum, Genu L	40	-35	-6	1.699	91	IFOF R
							4	0	34	1.368	11	Cingulum R (posterior)
							7	36	5	-2.151	167	Cingulum R (anterior)
							8	15	39	-1.768	19	Median Cingulate Gyrus R (near SLF1)
							-31	46	3	-1.607	19	SLF3 L
Gender	-29	-1	-2	2.146	208	UF L	32	3	37	1.788	154	SLF2 R
	51	-6	33	2.341	69	SLF3 R	-44	-51	-8	1.691	112	WM of Inferior Temporal Gyrus L (near Posterior segment of AF)
	-18	-30	3	2.179	44	Cingulum L	-52	-6	15	1.594	112	SLF3 L
	18	6	10	-1.963	525	Coritco Spinal Tract R	44	25	19	1.611	78	SLF3 R

	VBM						DTI					
	Peak coordinates			*SDM-Z* score	Voxels	Description	Peak coordinates			*SDM-Z* score	Voxels	Description
	x	y	z				x	y	z			
	-7	9	-1	-1.188	52	Anterior Commissure L	48	1	-5	1.536	48	WM of Superior Temporal Gyrus R (above ILF)
							-48	-34	17	1.533	26	SLF3 L
							42	-59	16	1.349	23	Posterior Segment of AF R
							-12	-9	25	1.213	10	Corpus callosum, Body L
							18	28	15	-3.118	1915	Corpus callosum, Genu R
							36	-35	-4	-2.676	785	IFOF R
							28	-35	45	-1.996	181	SLF3 R
							-5	-30	-20	-1.714	128	Superior Cerebellar Penduculs L
							-27	-19	-7	-1.698	119	Optic Radiation L
							-33	-22	30	-1.851	110	Long segment of AF L

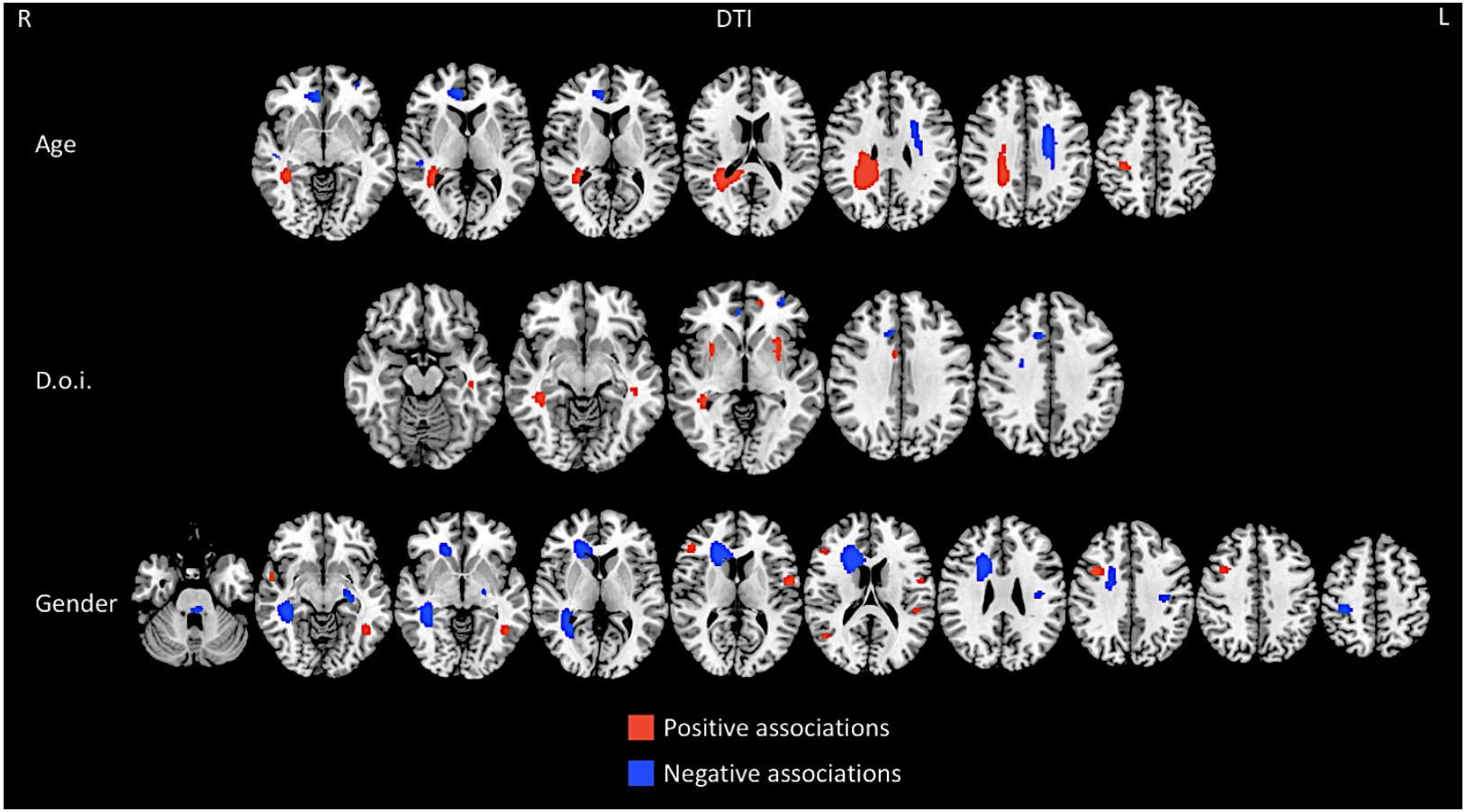
[a] Each cluster is thresholded at $p < 0.005$ with and additional extent cluster thresholding of minimum 10 voxels. Peak coordinates are expressed in Talairach space. Description of WM tracts is based on WM atlas developed by Catani and Thiebaut de Schotten (2008). "Age" section contains the results of meta-regression on the mean age of patients, "D.o.i" section contains the results of meta-regression on the mean duration of illness, while "Gender" section contains the results of meta-regression on ratio of male patients.

FIGURE 5. Significant clusters of WM reductions associated with each regressor from analyses of VBM studies



[a] Axial views of the significant clusters ($p < 0.005$) of minimum 10 voxels of WM reductions associated with each regressor. Meta-regression showed both positive (red clusters) and negative (blue clusters) associations with the mean age of patients, the mean duration of illness and the ratio of male patients. Images are visualized with MRIcron. [For a complete graphical overview of meta-regressions results see figures in Supplementary Materials].

FIGURE 6. Significant clusters of WM reductions associated with each regressor from analyses of DTI studies



[a] Axial views of the significant clusters ($p < 0.005$) of minimum 10 voxels of WM reductions associated with each regressor. Meta-regression showed both positive (red clusters) and negative (blue clusters) associations with the mean age of patients, the mean duration of illness and the ratio of male patients. Images are visualized with MRIcron. [For a complete graphical overview of meta-regressions results see figures in Supplementary Materials].

4. Discussion

The results of this meta-analysis showed a widespread WM disruption in schizophrenia involving specific cerebral circuits instead of well-defined regions. Long projection fibers, callosal and commissural fibers, part of motor descending fibers, and fronto-temporal-limbic pathways were the most frequent WM bundles detected by both VBM and DTI techniques. We may hypothesize that differences in results of previous meta-analytic works (Ellison-Wright and Bullmore 2009; Di et al., 2009; Yao et al.; 2013) compared with those of the current meta-analysis were found due to the number of eligible articles considered. Indeed, Ellison-wright and Bullmore (2009) included 15 studies in their meta-analytic work, Di et al. (2009) and Yao et al. (2013) included respectively only 17 and 8 studies whereas the present work included 59 studies. Given that the ALE algorithm is sensitive to sample size (Eickhoff et al., 2009; Eickhoff et al., 2012), a larger number of selected studies would produce more consistent and substantial results compared to the previous meta-analyses.

The current study is the first meta-analysis that investigated WM reductions in patients with schizophrenia using both VBM and DTI studies of the last 15 years analyzing and comparing WM reductions associated to each technique. The VBM-DTI comparison indicated that a group of WM bundles were activated in both VBM and DTI studies, although the conjunction analysis revealed that both methodologies outlined WM alterations in different clusters of the same tract. Indeed, the lack of overlapping clusters highlighted by the conjunction analysis may indicate that VBM and DTI actually detect different aspects of WM alteration. Although these differences may depend on data collection or different parameters implemented during the scan acquisition (Oouchi et al., 2007; Melonakos et al., 2001), another hypothesis is that the WM tracts might show single or multiple “type” of alteration

(i.e., volumetric and/or diffusion alterations). Overall, given that different clusters of WM reduction detected by both VBM and DTI were found on the same tract, our results may suggest that alterations of these tracts in different clusters are related to a more severe damage derived from both volumetric and diffusion alterations and may represent the "core tracts" of schizophrenia.

An aberrant diffusivity could be represented by anomalies in FA, as revealed by DTI methods (Poretti et al., 2012). FA is sensitive to the disruption of myelin integrity (Kubicki and Shenton, 2014). Genetic and post-mortem studies had shown the involvement of both myelin and oligodendrocytes in the pathophysiology of schizophrenia, suggesting that anomalies in axonal communication observed in schizophrenia could be partially related to aberrant WM connectivity between different brain regions (Kubicki and Shenton, 2014). Given that oligodendrocytes produce myelin and provide facility of communication between brain regions (Shenton, Whitford and Kubicki, 2010), they may play a central role in the pathophysiology of schizophrenia. Indeed, a diffusion alteration may reflect anomalies in the number or in the functions of oligodendrocytes, providing anomalies in speed conduction among myelinated axons (Whitford, Kubicki and Shenton, 2011). These anomalies could lead, at least, to confound the origin of neural signals and to a consequentially confusion between internally and externally generated events (e.g., hallucinations) (Whitford, Kubicki and Shenton, 2011).

Given that aberrant communication could represent a general disruption of functional connectivity in schizophrenia, the functional anomalies could partially arise from structural deficits (Williams, 2008; Fitzsimmons, Kubicki and Shenton, 2013). Indeed, structural deficits outlined by VBM methods could highlight synaptic and cytoarchitectural aberrations, representing a possible loss of organization in the

affected brain circuits of schizophrenia (Williams, 2008). The aberrant organization could be due to the consequentially changes in synaptic density during maturation and development (Andersen, 2003). The presence of significant structural reductions in schizophrenia could reflect an excessive pruning process involving the WM changes observed in schizophrenia. The loss of neurons cellular body and their associated neuropil due to an extensive pruning might indicate that their myelinated axons are overly eliminated in schizophrenia (Williams, 2008). Normal pruning is triggered by a reduction of the number of available trophic factors and the overpruning could depend by an abnormal largely reduction of these trophic factors. Thus, the overpruning might probably reflect the typical GM and WM reductions of schizophrenia detected by VBM methods (Williams, 2008).

The WM disruptions showed in our met-analysis, did not involve only single regions, but a large number of whole-brain connecting areas. Thus, WM abnormalities in schizophrenia may reflect a disruption of neural circuits and a GM dysfunctional communication (Friston and Frith, 1995; Friston, 1998), affecting inter-hemispheric connectivity (Crow, 1998), fronto-temporal-limbic connections, (McGuire and Frith, 1996; Ardekani et al., 2003) and cortical-cerebellar-thalamic-cortical circuit (Andreasen et al., 1998). The alteration of inter-hemispheric commissural fibers such as the anterior commissure, corpus callosum, and fornix, is a critical evidence of the disruption of inter-hemispheric connectivity (Crow, 1998). A damage of these structures implicates impaired integration of motor, perceptual, and cognitive information crossing both hemispheres because of specific alterations in the anterior commissure (Hulshoff Pol et al., 2004; Schlösser et al., 2007), the corpus callosum (Sigmundsson et al., 2001; Spalletta et al., 2003; Sugranyes et al., 2012; Ellison-

Wright et al., 2011; Reidet al., 2015), and the fornix (Witthaus et al., 2008; Kanaan et al., 2009; Guo et al., 2012; ; Sugranyes et al., 2012; Reid et al., 2015).

Different authors (Friston and Frith, 1995; Frith, 1995; McGuire and Frith, 1996; Ardekani et al., 2003) have postulated the existence of a cortical-thalamic network disruption in patients with schizophrenia involving frontal, temporal, and limbic regions. Similarly, our analysis showed an involvement of the main WM tracts that link frontal, temporal, and limbic areas, such as the internal capsule, the cingulum bundle, the AF, the SLF, the ILF, and the IFOF. These WM tracts may be involved in cognitive and behavioral outcomes, and in positive and negative symptomatology.

The alteration of the internal capsule is consistent with several VBM (Paillère-Martinot et al., 2001; Sigmundsson et al., 2001; Suzuki et al., 2002; Hulshoff Pol et al., 2004; Chua et al., 2007; Yoshihara et al., 2008; Yao et al., 2014; Lyu et al., 2015) and DTI (Szeszko et al., 2005; Buchsbaum et al., 2006; Cheung et al., 2008; Jeong et al., 2009; Kanaan et al., 2009; Guo et al., 2012; Knöchel et al., 2012; Nakamura et al., 2012; Ellison-Wright et al., 2014) findings. The WM loss in the internal capsule may lead to a functional disconnection between cerebral cortex and other subcortical structures (Kubicki et al., 2005), reflecting the impairment of executive function, emotional stability, and motivation (Guo et al., 2012; Yao et al., 2014; Lyu et al., 2015). Alterations of the internal capsule are also correlated with the severity of both positive (Sigmundsson et al., 2001) and negative (Paillère-Martinot et al., 2001) symptoms, and are found also in patients with FES and/or never-medicated patients (Sigmundsson et al., 2001; Suzuki et al., 2002; Szeszko et al., 2005; Cheung et al., 2008; Yoshihara et al., 2008; Guo et al., 2012; Yao et al., 2014; Lyu et al., 2015). Therefore, this type of alteration may not be a secondary effect of medication or

chronicity, and may represent one of the core features of the pathophysiology of schizophrenia.

The internal capsule is a central structure in motor pathways: motor descending fibers as the cortico-spinal tract or the cortico-ponto-cerebellum tract run through the internal capsule (Catani and Thiebaut de Schotten, 2008; Guo et al., 2012; Yao et al., 2014) and the abnormalities we found of both the internal capsule and descending motor pathways may represent the neural basis of motor dysfunctionality in schizophrenia (Perez-Iglesias et al., 2010; Walther and Strik, 2012). Moreover, alterations in cerebellar WM (Farrow et al., 2005; Hao et al., 2006; Chua et al., 2007; Seok et al., 2007; Kyriakopoulos et al., 2008; Yoshihara et al., 2008; Bai et al., 2009; Kanaan et al., 2009; Kyriakopoulos et al., 2009; Sugranyes et al., 2012; Watson et al., 2012; Singh et al., 2014; Lyu et al., 2015; Singh et al., 2015; Spalletta et al., 2015) support the role of motor pathways in schizophrenia. Motor descending fibers, in addition to internal capsule and cortical-cerebellar tracts, form part of the cortical-cerebellar-thalamic-cortical circuit. A disruption of this pathway may be related to dysfunctionalities of circuits involved in cognitive and motor functions and may prompt further evidence supporting the concept of "cognitive dysmetria" (Andreasen et al., 1998). Taken together, the structural alterations of motor pathways, in addition to the further common GM and motor areas hypofunctionality, may partially explain one of the essential features of the schizophrenia, i.e. the presence of behavioral and motor dysfunctionality (Perez-Iglesias et al., 2010; Walther and Strik, 2012).

We also found WM reductions of bilateral cingulum that may represent one of the main feature of schizophrenia. Indeed, cingulum alterations occurred in patients with FES (Hao et al., 2006; Tang et al., 2010), EOS (Kumra et al., 2005), and LOS (Chen et al., 2013), and also never-medicated patients (Burns et al., 2003).

Interestingly, Mori et al. (2007) found that FA reductions in the cingulum bundle are age-related and depend on the progress of the disorder. Given the critical role of the cingulum in the limbic system (Catani and Thiebaut de Schotten, 2008), one may speculate that cingulum reductions may implicate the disruption of fronto-cingolo-thalamic circuits, with consequent emergence of both positive (Seok et al., 2007; Rotarska-Jagiela, 2009) and negative symptoms such as apathy, lack of drive, and poor perseveration (Cummings, 1993; Paillère-Martinot et al., 2001; Sigmundsson et al., 2001).

Our meta-analysis shows a general WM reduction of long projection fibers such as AF, SLF, ILF, and IFOF in patients with schizophrenia compared to control subjects. Interestingly, several studies found a relationship between patients who showed aberrant patterns of these WM tracts and the occurrence of auditory hallucinations (Hubl et al., 2004; Ashtari et al., 2007; Szeszko et al., 2008; Knöchel et al., 2012). Moreover, a schizophrenic-in-group comparison showed a FA increase of the auditory and speech production connections, especially AF or SLF, in patients with auditory hallucinations compared to non-hallucination patients (Hubl et al., 2004), suggesting an hyperactivation of the auditory and language production areas. Thus, increasing connectivity may cause a hyperactivation of these regions and may be responsible for the occurrence of hallucinations (Hubl et al., 2004; Shergill et al., 2007; Szeszko et al., 2008; Rotarska-Jagiela et al., 2009). The ILF and the IFOF seem also to be involved in hallucinatory experiences (Ashtari et al., 2007; Szeszko et al., 2008) and several studies demonstrated the involvement of these tracts in patients with EOS (Szeszko et al., 2008; Witthaus et al., 2008) and with FES (Cheung et al., 2008), as well as chronic (Jeong et al., 2009) and never-medicated patients (Cheung et al., 2008; Liu et al., 2014), and adolescents (Ashtari et al., 2007; Yoshihara et al.,

2008; Kyriakopoulos et al., 2009). Given the anatomical pathways of these WM tracts (Catani and Thiebaut de Schotten, 2008), it may be plausible an involvement of ILF and IFOF in aberrant visual processes such as visual hallucinations. Indeed, Ashtari et al. (2007) recently found FA reductions in the ILF of their adolescent sample of patients with visual hallucinations compared to those without hallucinations. These findings are in contrast with other studies that reported a FA increase in AF or SLF (Hubl et al., 2004; Seok et al., 2007; Shergill et al., 2007; Rotarska-Jagiela et al., 2009) and in ILF or IFOF (Szeszko et al., 2008) in patients with hallucination episodes. The contradictory results between these studies may depend on the age difference (adult vs. adolescent) (Kyriakopoulos et al., 2009) or the nature of the auditory and visual experiences (Ashtari et al., 2007).

The meta-regression results suggested a potential effect of age, duration of illness, and gender in both positive and negative directions, so that the WM tracts that already showed an alteration worsen in male patients and with progression of age-dependent factors. Indeed, older patients showed a stronger reduction in the corpus callosum, the WM of the left AF and the right cortico spinal tract compared to younger patients that contrarily showed stronger reductions in the left ILF, the right part of genu of corpus callosum, the left cortico spinal tract, the right cingulum, the WM of right superior temporal gyrus (near SLF3), and the left SLF3. A longer duration of illness was associated with stronger WM reductions of the internal capsule, the right AF, the bilateral UF, the left ILF, the right IFOF and the right posterior cingulum, whereas a shorter duration of illness was associated with stronger WM reductions in the fornix, the left part of genu of corpus callosum, the right anterior cingulum bundle, the WM of right median cingulate gyrus (near SLF1), and

the left SLF3. Generally, the effect of age may be related with the progression of illness, because the duration of illness generally increases with aging.

The results outlined by our meta-regression may suggest different WM trajectories associated to the age and stage of illness. Thus, it might be possible to compare WM alterations in different stages of schizophrenia, i.e., comparing FES and chronic patients. Indeed, a shorter duration of illness may indicate an early stage of schizophrenia as experienced by FES patients, whereas a longer duration of illness may be characteristic of chronic patients. Our findings may highlight significant difference in WM reductions of FES and chronic patients, showing different WM tracts involved in early or late stage of illness (Bora et al., 2011).

Moreover, these patterns of WM reductions may be due not only to the disease progression itself but also to the physiological WM reductions observed in healthy subject because of aging. It has already been demonstrated that WM reductions trajectories in healthy subject worsen with aging (Bartzokis et al., 2012). The physiological aging process of WM reductions trajectories may play a crucial role in WM trajectories observed in patients with schizophrenia. Indeed, the physiological aging may prompt to disruptions extended to several tracts of the cortical lobes and the cerebellum that widen with age and progression of illness (Mori et al., 2007; Kochunov et al., 2014; Cropley et al., 2017).

Finally, a higher percentage of males showed significantly stronger WM reductions of the left UF, the right SLF2, the bilateral SLF3, the left cingulum, the bilateral WM of temporal gyrus, the right posterior segment of AF, and the left portion of the body of corpus callosum, whereas females were characterized by stronger WM reductions of the right portion of the genu of the corpus callosum, the right IFOF, the right SLF3, the left superior cerebellar penduculus, the left optic

radiation, and the left long segment of AF. These differences may be related to different WM reductions trajectories in male and female patients (Hawco et al., 2016; Cropley et al., 2017) that probably even depends on gender differences in normal brain development trajectories (Giedd et al., 2012).

Some limitations of our study should be noted. The majority of the selected studies for our analysis included patients under antipsychotic treatment, with the exception of some studies that did not report this information or others that included first-episode and/or drug-naïve patients. This aspect might partially affect our results because of the reported association of increase (Ozcelik-Eroglu et al., 2014) and decrease (Bartzokis et al., 2011) WM changes with antipsychotic treatments. However, we decided to include every type of patients (i.e., both medicated and non-medicated patients) in our meta-analysis to have a better understanding of the general distribution of WM alteration among schizophrenic patients. Moreover, although the studies reported the diagnosis of schizophrenia based on a psychiatric manual for diagnostic assessment (i.e., DSM-IV or ICD-10), we were not able to verify the accuracy of the diagnostic procedure in the selected studies. This might bring us to consider a sample of patients more heterogeneous than expected.

Furthermore, given that the ALE method requires a dataset of selected coordinates to compute the analysis and build the MA maps, we did not include in our analysis studies that did not report the coordinates of alteration foci. A general bias might be introduced in considering alteration peak values. Indeed, imaging studies reported only coordinates of alteration peaks, excluding all the significant voxels in the examined (altered) cluster. This may suggest the researchers to evaluate only alterations peaks instead of an entire altered cluster. However, reporting and evaluating peak coordinates instead of an entire cluster is a common procedure in

imaging studies that implemented ALE methodology (Turkeltaub et al., 2002; Eickhoff et al., 2009; Radua et al., 2012). This procedure allows the researcher to make probabilistic observations based on the probability significance of the peak value that represents the highest point of the coordinates distribution around it (Laird et al., 2005; Eickhoff et al. 2009; Eickhoff et al., 2012). Thus, evaluating peak coordinates instead of all coordinates of the investigated cluster reduces the probability of making errors due to spatial uncertainty, making inferences more significant.

An additional limitation of our study that might partially influence the results, was the inclusion of studies using different acquisition field scans (1.5T and 3T). Some authors outlined a variability of cortical thickness measurements comparing MRI-field strengths (Han et al., 2006). However, we do not expect a strong bias in our results because the ALE analysis investigates the concordance degree of the results across the selected studies (Laird et al., 2005; Eickhoff et al., 2009; Eickhoff et al., 2012; Eickhoff et al., 2016) regardless of field strength (Duerden et al., 2012). This is further supported by a recent voxel-based meta-analysis that did not found any confounding effects of filed strength on anatomical results (Fusar-Poli et al., 2011).

5. Conclusions

Our meta-analytic study found a widespread alteration of WM bundles mostly included in frontal, temporal, and limbic pathways. Moreover, our results highlighted the presence of alterations in other circuits, such as callosal and commissural circuits, and cortical-cerebellar-thalamic-cortical circuit. Similarly, Dong et al. (2017) found a widespread disruption of several WM bundles forming part of the most relevant circuits involved in the illness, such as the corpus callosum, the thalamic radiations, the IFOF, the UF, the cingulum, and the SLF. These WM alterations are generally

associated with some clinical features of schizophrenia (e.g., see Minichino et al., 2017), such as positive and negative symptoms, or cognitive and motor dysfunctionalities. Taken together, these considerations may prompt further evidence to the "disconnection hypothesis" and underline the conceptualization of the schizophrenia as a mental illness characterized by a disrupted cerebral network. Moreover, the present meta-analysis highlighted the existence of a group of WM tracts that occurred in both VBM and DTI studies. Furthermore, the conjunctions analysis revealed the presence of different clusters of reduction on the same WM tract detected by both VBM and DTI. Given that the two techniques individuate different features of WM alteration, we can consider that both of them are required to detect efficiently WM reductions widespread over the entire brain. Thus, the group of WM tracts detected by both methodologies may consequentially show both volumetric and diffusion alterations. These tracts may be the most commonly involved bundles in schizophrenia and may represent the "core tracts" of the illness. Overall, our findings may improve in our understanding of WM alterations in patients with schizophrenia and may help clinicians to foster advance treatment planning.

Conflict of interest

All authors declare that they have no conflicts of interest.

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