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White matter integrity affected by depressive symptoms in migraine without aura: a tract-based spatial statistics study

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Previous studies have proven that migraine and depression are bidirectionally linked. However, few studies have investigated white matter (WM) integrity affected by depressive symptoms in patients suffering from migraine without aura (MWoA). Forty patients with MWoA were divided into two groups according to their self-rating depression scale (SDS) score in the present study, including 20 in the SDS (+) (SDS $>$ 49) group and 20 in the SDS (−) (SDS $\leq$ 49) group. Forty healthy participants were also recruited as the control group. Tract-based spatial statistics analyses with multiple diffusion tensor imaging-derived indices [fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), axial diffusivity (AD)] were employed collectively to investigate WM integrity between all patients with MWoA and all healthy controls, between each subgroup (SDS (−) group and SDS (+) group) and healthy controls, and between the SDS (−) and SDS (+) groups. Compared with healthy controls, decreased AD was shown in several WM tracts of the whole MWoA group, SDS (−) group and SDS (+) group. In addition, compared with the SDS (−) group, the SDS (+) group showed decreased FA and increased MD and RD, with conserved AD, including the genu, body and splenium of the corpus callosum, bilateral superior longitudinal fasciculi, the right anterior corona radiata and some other WM tracts, similar to previous findings in depression disorder. Furthermore, mean FA and RD in some of the above-mentioned WM tracts in the SDS (+) group were correlated significantly with SDS scores, including the genu and splenium of the corpus callosum, the right anterior corona radiata and the superior longitudinal fasciculi. Our results suggest that WM integrity may be affected by both depression symptoms (more sensitive as RD) and migraine (more sensitive as AD). The findings may serve as a sensitive biomarker of depression severity in MWoA. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: migraine without aura (MWoA); tract-based spatial statistics (TBSS); depressive symptoms; corpus callosum (CC); anterior corona radiata (ACR); superior longitudinal fasciculi (SLF)

INTRODUCTION

Migraine is a common type of primary headache syndrome with a prevalence range from 8.4% to 12.7% in the Asian population (1). Frequent migraine attacks may have an enormous impact on both the individual sufferer and society as a result of pain, environmental sensitivity or disability (2), and may be associated with a number of physiological and emotional stressors (3,4). Previous studies have revealed bidirectional associations between migraine and depression, with each disorder increasing the risk of the other (4,5). This bidirectional relationship suggests

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Abbreviations used: *ACC, anterior cingulate cortex; ACR, anterior corona radiata; AD, axial diffusivity; ALIC, anterior limb of the internal capsule; BET, Brain Extraction Tool; CC, corpus callosum; CR, corona radiata; DLPFC, dorsolateral prefrontal cortex; DTI, diffusion tensor imaging; EC, external capsule; FA, fractional anisotropy; FDT, FMRIB's Diffusion Toolbox; FOV, field of view; FSL, FMRIB Software Library; IC, internal capsule; MD, mean diffusivity; MNI, Montreal Neurological Institute, MT+, middle temporal area complex; MWoA, migraine without aura; OR, optic radiation; PCR, posterior corona radiata; PFC, prefrontal cortex; PLIC, posterior limb of the internal capsule; PTR, posterior thalamic radiation; RD, radial diffusivity; RIC, retrolenticular part of the internal capsule; ROI, region of interest; SCR, superior corona radiata; SDS, self-rating depression scale; SLF, superior longitudinal fasciculus/fasciculi; SMA, supplementary motor area; TBSS, tract-based spatial statistics, V3A, visual area 3A; WM, white matter.*

that there may be certain etiological risk factors shared between migraine and depression (6,7). A possible causal relationship and genetic, psychological or environmental etiology have been proposed for migraine and depression (8). The pathophysiological relationship between migraine and depression remains unclear.

Advanced neuroimaging approaches have been employed to investigate the structural and functional brain changes in patients with migraine (9) (details shown in Table 1), and have transformed our perception of migraine from a purely vascular hypothesis to a neurovascular hypothesis and, most recently, to a central nervous system theory (9). In particular, diffusion tensor imaging (DTI) can offer a unique noninvasive insight into the microstructure of white matter (WM) tracts in the living brain. Abnormalities of local diffusion characteristics are often a sign of alterations in functional, clinical or behavioral measures (10–12). Previous DTI studies have revealed abnormal WM integrity in patients with migraine and depression (13–33). Moreover, using DTI techniques, WM abnormalities in patients with migraine have been investigated. In comparison with healthy volunteers, Rocca *et al.* (13) reported that patients with migraine had lower mean diffusivity (MD) histogram peak height of the normal-appearing WM. Solid evidence has been obtained confirming that patients with migraine show abnormal diffusion characteristics, detected as decreased fractional anisotropy (FA), in several other WM tracts, such as the corpus callosum (CC), optic radiation (OR), subjacent WM of the middle temporal area complex (MT+) and visual area 3A (V3A), superior colliculus, lateral geniculate nucleus, periaqueductal gray, ventroposterior medial thalamus and corona radiata (CR) (14–19). Recently, using tract-based spatial statistics (TBSS) analysis, Szabó *et al.* (20) found reduced FA in the right frontal WM cluster of patients with migraine and increased MD and radial diffusivity (RD) in this region by a region of interest (ROI) analysis. Reduced FA, MD and RD in multiple brain regions were found in another TBSS study of migraine (21). All of these DTI findings strongly indicate that repeated migraine attacks may have cumulative effects and result in reduced FA in several WM tracts (13–21). However, the abnormalities of WM properties in patients with migraine have been reported inconsistently for different regions and for changes in other DTI indices (13–21).

WM abnormalities in patients with depression have also been investigated and are characterized by reduced FA in several WM pathways, such as the CC, internal capsule (IC), superior longitudinal fasciculus (SLF), uncinate fasciculus, cingulum bundle, thalamic projection fibers and other association fibers (22–33). Moreover, some WM regions have shown increased MD and RD with reduced FA in several meticulous depression

Table 1. Structural and functional brain changes in patients with migraine compared with healthy controls

Study	Findings
VBM (34–37)	Significant gray matter reduction in the cingulate cortex, bilateral insula, superior temporal gyrus, orbitofrontal cortex (OFC), inferior frontal gyrus and precentral gyrus (34–37)
Histogram analysis in DTI (13,38,39)	Lower mean diffusivity (MD) histogram peak height of the normal-appearing gray matter (39), normal-appearing white matter (WM) (13) and normal-appearing brain tissue (38) of patients with migraine compared with controls
VBA in DTI (14–18)	Reduced fractional anisotropy (FA) in the corpus callosum (CC), optic radiation (OR), subjacent WM of MT+ and V3A, superior colliculus, lateral geniculate nucleus, periaqueductal gray, ventroposterior medial thalamus and corona radiata (CR) (14–18)
TBSS in DTI (20,21)	Reduced FA with increased MD and increased radial diffusivity in the right frontal white matter cluster was detected in migraine patients (20) Lower FA, MD and axial diffusivity (AD) in the genu, body and splenium of the CC, right anterior limb of the internal capsule (ALIC) and posterior limb of the internal capsule (PLIC) (21)
Task-related fMRI (17,40,41)	Abnormal activation of some brain regions in migraine patients, such as the anterior cingulate cortex (ACC), prefrontal cortex (PFC), OFC, insula and supplementary motor area (SMA) (17,40,41)
fMRI during the resting state (42–46)	· Significant reduced regional homogeneity (ReHo) values in the right rostral anterior cingulate cortex (rACC), PFC, OFC and SMA (42) · Increased functional connectivity between several regions and the left dorsal ACC, i.e. the bilateral middle temporal lobe, OFC and left dorsolateral prefrontal cortex (DLPFC) (43) · Stronger functional connectivity between the periaqueductal gray (PAG) and several brain areas (44) · Significant reduced functional connectivity within the right fronto-parietal networks (FPN) and specifically in the middle frontal gyrus (MFG) and the dorsal ACC (45) · Reduced FA values of the genu of CC and decreased interhemispheric resting-state functional connectivity of the ACC was found by voxel-mirrored homotopic connectivity (VMHC) analysis, and the correlation between the above structural and functional changes suggested that the reduced FA of CC modulates interhemispheric VMHC in patients with migraine (46)
Perfusion-weighted MRI (47,48)	· Decreased cerebral blood flow and blood volume and increased mean transit time in the occipital lobe (47) · Hyperperfusion in the left medial frontal gyrus in migraineurs and in the inferior and middle temporal gyrus in patients with MWoA; hypoperfusion in the postcentral gyrus and inferior temporal gyrus in migraine patients with aura and in the inferior frontal gyrus in patients with MWoA (48).

DTI, diffusion tensor imaging; fMRI, functional MRI; TBSS, tract-based spatial statistics; VBA, voxel-based analysis; VBM, voxel-based morphometric.

Table 2. Clinical details of patients suffering from migraine without aura (MWoA) and healthy controls (data are means ± standard deviations and minimum–maximum values)

Clinical details	Controls ($n = 40$)	MWoA ($n = 40$)	SDS (−) ($n = 20$)	SDS (+) ($n = 20$)	F or χ^2	df	p
Age (years)	33.2 ± 9.5 23 – 55	35.9 ± 10.3 22 – 57	33.6 ± 11.7 22 – 57	38.2 ± 8.4 22 – 55	1.355	3	0.26
Sex (F, female; M, male)	16 F, 4 M	29 F, 11 M	13 F, 7 M	16 F, 4 M	0.655	3	0.581
Disease duration (years)	—	10.8 ± 7.1 1 – 31	12.4 ± 8.0 1 – 31	9.2 ± 5.8 2 – 20	1.027	2	0.363
Attack frequency (times in past 4 weeks)	—	5.2 ± 3.6 1 – 15	4.2 ± 2.7 1 – 10	6.3 ± 4.1 1 – 15	1.679	2	0.193
VAS (0–10)	—	5.1 ± 1.7 1 – 9	4.8 ± 1.4 2.2 – 7.5	5.5 ± 1.9 1 – 9	0.816	2	0.446
SDS scores	37.6 ± 4.0 25 – 42	49.7 ± 12.2 29 – 69	39.1 ± 5.0 29 – 45	60.3 ± 6.6 50 – 69	42.102	3	0.000

VAS, visual analogue scale; SDS, self-rating depression scale.

studies, suggesting a pattern of decreased myelination or other degeneration changes (22,25,26). According to previous DTI findings, it is not known how the WM integrity is affected by depressive symptoms frequently occurring in patients with migraine. It is noteworthy that, compared with patients suffering from migraine without aura (MWoA) without depressive/anxious disorder, Li *et al.* (16) revealed that MWoA complicated with depressive/anxious disorder showed lower FA values in the CC, which were significantly negatively correlated with the Hamilton depression score in MWoA (16). This suggests that there may be different WM properties in MWoA with and without depressive/anxious disorder; however, the type of WM abnormality (e.g. radial or axial) is unknown. To specify the neuropathological features of WM integrity affected by migraine and depression symptoms in MWoA, a multiple DTI-derived indices analysis [FA, MD, axial diffusivity (AD), RD] may be used to provide different details related to migraine and depression bidirectionally (10,49). To this end, patients with MWoA were divided into two groups according to their self-rating depression scale (SDS) score (50), including the SDS (+) group (MWoA with severe depressive symptoms, SDS > 49) and the SDS (−) group (MWoA with a low depressive tendency, SDS ≤ 49). The TBSS method with multiple DTI-derived indices analysis (i.e. FA, MD, RD, AD) was employed collectively to investigate the WM abnormalities among the whole MWoA group, SDS (−) group, SDS (+) group and healthy controls in the present study (10–12,23,49).

Given that previous migraine and depression DTI studies have reported abnormal structural properties of WM involved in pain and emotional processing, we hypothesized that the whole MWoA group, SDS (−) group and SDS (+) group might show different patterns of FA, MD, AD and RD in these brain regions compared with healthy controls. Moreover, a pattern similar to the findings in previous depression DTI studies may be expected in the SDS (+) group compared with the SDS (−) group. Finally, a correlation analysis was introduced to investigate the relationship between severe WM abnormalities of the brain regions and the SDS scores of MWoA.

EXPERIMENTAL DETAILS

This study was approved by the Medical Ethics Committee of the West China Hospital at Sichuan University. All participants signed informed consent after the experimental procedure had been fully explained.

Subjects

Eighty-seven patients with MWoA were screened following the diagnostic criteria of the International Headache Society (51), such that MWoA must include the occurrence of at least five headache attacks and fulfill the following criteria: (i) headache attacks lasting 4–72 h (untreated or unsuccessfully treated); (ii) featuring at least two of the following characteristics: unilateral location, pulsating quality, moderate to severe pain intensity and aggravation by causing avoidance of routine physical activity (e.g. walking or climbing stairs); (iii) during headache, at least one of the following: nausea and/or vomiting, photophobia and phonophobia; and (iv) not attributed to another disease.

In addition, 53 age- and gender-matched healthy controls, who had no family members suffering from any type of headache or depression disorder, were enrolled. The exclusion criteria for both groups were as follows: (i) any physical illness, such as brain tumor, hepatitis, diabetes or epilepsy, as assessed according to clinical evaluations and medical records; (ii) pregnancy or menstrual period in women; (iii) alcohol, nicotine or drug abuse; (iv) existence of a psychiatric disease; (v) organic brain defects on T_1 or T_2 images (examined by two experienced radiologists); (vi) claustrophobia; and (vii) any antidepressant treatment. All of the participants were right-handed as measured by the Edinburgh Handedness Inventory (52).

Finally, 40 patients with MWoA (11 men and 29 women; age, 22–57 years; mean age, 35.9 ± 10.3 years) and 40 age- and gender-matched healthy controls (10 men and 30 women; age, 21–54 years; mean age, 33.2 ± 9.5 years) participated in our study. Prior to scanning, the SDS test was used to evaluate the depression symptoms of all participants (50). The SDS consists of 20 items presented in a four-point multiple-choice format. Each item is scored on a scale of 1–4, with higher scores indicating an increased level of depressive symptoms. The scores range from 20 to 80 with four possible outcomes as follows: 20–49, normal range; 50–59, mildly depressed; 60–69, moderately depressed; 70 and above, severely depressed (53). According to the SDS scores, the whole MWoA group (SDS scores of 49.7 ± 12.2) were divided into two groups. Those who scored

under 49 were assigned to the SDS (−) group (seven men and 13 women; age, 22–57 years; mean age, 33.6 ± 11.7 years; SDS score, 39.1 ± 5.0) and the rest were assigned to the SDS (+) group (four men and 16 women; age, 22–55 years; mean age, 38.2 ± 8.4 years; SDS score, 60.3 ± 6.6) (50). The SDS score in healthy controls was 37.6 ± 4.0. In addition, urine drug screening was performed on all subjects to exclude the possibility of substance abuse. The average pain intensity of the SDS (−) group was rated as 4.8 ± 1.4 and that of the SDS (+) group was rated as 5.5 ± 1.9 on a visual analogue scale (VAS) of 0–10 based on attacks in the past 4 weeks, with 10 being the most intense pain imaginable. The attack frequency in the past 4 weeks and the duration of migraine attacks were also rated. None of the patients had a migraine precipitated during or on the day following the scan or a migraine attack at least 72 h prior to the scan (17). The clinical and demographic characteristics of the participants are shown in Table 2.

Data acquisition

All DTI data were acquired on a 3-T Siemens MR scanner (Allegra; Siemens Medical System, Erlangen, Germany) at the Huaxi MR Research Center, West China Hospital, Sichuan University, Chengdu, China. The heads of the subjects were positioned carefully with restraining foam pads to reduce head motion, and ear plugs were used to reduce scanner noise. Prior to the DTI run, high-resolution T_1- and T_2-weighted images were acquired for each subject by two expert radiologists to exclude the possibility of clinically silent lesions. The diffusion tensor images were obtained with a single-shot, echo-planar imaging sequence. The diffusion sensitizing gradients were applied along 30 non-collinear directions ($b = 1000$ s/mm^2) with an acquisition without diffusion weighting ($b = 0$ s/mm^2) (11). The imaging parameters were 45 contiguous axial slices with a slice thickness of 3 mm, TR = 6800 ms, TE = 93 ms, data matrix of 128 × 128 and field of view (FOV) of 240 × 240 mm^2. Diffusion tensor images were acquired with two averages.

Data processing

The data processing and analysis in this study were mainly carried out using FMRIB Software Library (FSL) software 4.1.9 (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library; http://www.fmrib.ox.ac.uk/fsl). First, the Brain Extraction Tool (BET) 2.1 (54) in FSL was used for brain extraction. Then, the eddy current distortion and head motion of raw diffusion data were corrected using FMRIB's Diffusion Toolbox (FDT) 2.0. Second, FA, MD and first, second and third eigenvalue maps (L1, L2 and L3 maps) were calculated by fitting a tensor model at each voxel of the diffusion data using FDT. The L1 map was the AD image. The RD images were calculated via the mean of the L2 and L3 maps using fslmaths command-line utilities. Third, TBSS analyses were performed using TBSS 1.2 (55) [(i) between all healthy controls and all patients with MWoA; (ii) between each subgroup (the SDS (−) group and SDS (+) group) and controls; and (iii) between the SDS (−) group and SDS (+) group] to examine differences in FA, MD, AD and MD. In detail, all subjects' FA images were nonlinearly registered to an FMRIB58-FA standard-space template (FMRIB Centre, University of Oxford, Department of Clinical Neurology, John Radcliffe Hospital, Headington, Oxford, UK; http://www.fmrib.ox.ac.uk/fsl/data/FMRIB58_FA.html) and aligned to the Montreal Neurological Institute (MNI) space. The mean image of all aligned FA images was created and thinned to provide a skeletonized mean FA image with the FA value threshold at 0.2 (55). Each aligned FA image of all participants was projected onto this skeleton. Next, the MD, AD and RD images were also aligned into MNI space and projected onto the mean FA skeleton using the protocol of non-FA images in TBSS.

Statistical analysis

After controlling for age and gender as covariates, the permutation-based nonparametric inferences within the framework of the general linear model were performed to investigate the differences among the SDS (−) group, SDS (+) group and healthy controls in FSL. The results were corrected using threshold-free cluster enhancement with the family-wise error correction for multiple comparisons ($p < 0.05$, corrected, 5000 permutations) (55). Finally, compared with the SDS (−) group, the regions in which the SDS (+) group showed significantly different DTI properties were overlapped to investigate the greater severity produced by depressive symptoms. A series of partial correlation analyses controlling for age with Bonferroni correction for multiple testing of the overlapped regions was performed to examine the correlation of the mean DTI index values of these overlapped brain regions with the SDS scores in the MWoA groups. The clinical and demographic characteristics of the participants and correlation analysis were analyzed using SPSS statistical analysis software (version 17.0, SPSS Inc., Chicago, IL, USA) and MATLAB (2010b, The Mathworks Inc., Natick, MA, USA).

RESULTS

The clinical and demographic characteristics of the participants are shown in Table 1. Some WM regions which were identified by the ICBM-DTI-81 white-matter labels atlas (56) showed significantly different DTI properties in the SDS (−) group, SDS (+) group and whole MWoA group. First, the whole MWoA group was compared with the control group. The MWoA group showed decreased FA in the left anterior limb of the internal capsule (ALIC), left anterior corona radiata (ACR), thalamus, brainstem, left cerebral peduncle, splenium of the CC and left cingulate gyrus; decreased MD in the genu, body and splenium of the CC, right ALIC, right ACR, bilateral superior corona radiata (SCR), right posterior corona radiata (PCR), bilateral SLF and left posterior thalamic radiation (PTR); decreased AD in the genu, body and splenium of the CC, bilateral IC, bilateral ACR, right external capsule (EC), bilateral PCR, bilateral SLF, bilateral SCR, bilateral cerebral peduncle and brainstem; and no difference in RD (Fig. 1, part 1). Second, the SDS (+) and SDS (−) groups were contrasted against the control group. The SDS (−) group showed decreased MD in the genu, body and splenium of the CC, right ACR, left PTR, bilateral SLF and bilateral SCR; decreased AD in the genu, body and splenium of the CC, right ACR, right IC, right PTR, right EC and bilateral IC; decreased RD in the genu and splenium of the CC, right ACR, right SCR, right EC, right posterior limb of the internal capsule (PLIC), right retrolenticular part of the internal capsule (RIC), bilateral PTR and bilateral SLF; and no difference in FA (Fig. 1, part 2). The SDS (+) group showed decreased FA in the genu, body and splenium of the CC, left IC, left ACR, left EC, left SLF, left PTR and left cerebral peduncle; decreased AD in the genu, body and splenium of the CC, bilateral SCR, bilateral SLF, left cerebral peduncle, bilateral EC,

bilateral IC and bilateral PTR; increased RD in the genu and body of the CC, left cingulum and right ALIC; and no difference in MD (Fig. 1, part 3). Third, the SDS (+) group was compared with the SDS (−) group. Compared with the SDS (−) group, the SDS (+) group showed reduced FA in the genu, body and splenium of the CC, bilateral ACR, bilateral SCR, bilateral SLF, bilateral EC, bilateral PLIC, bilateral PTR, bilateral RIC and left ALIC; increased MD and increased RD in similar brain regions and right ALIC; and no difference in AD (Fig. 1, part 4).

As shown in Fig. 2, compared with the SDS (−) group, the brain regions with decreased FA and increased MD and RD in the SDS (+) group overlapped and are shown in red, including the genu, body and splenium of the CC, bilateral SCR, SLF, EC, PLIC, RIC, left PTR and right ACR. These overlapped ROIs may suggest more severely disrupted integrity of myelin sheaths without axonal loss than in other regions with abnormal DTI-derived indices (10,23,49). Furthermore, correlation analysis results demonstrated that there were significant correlations

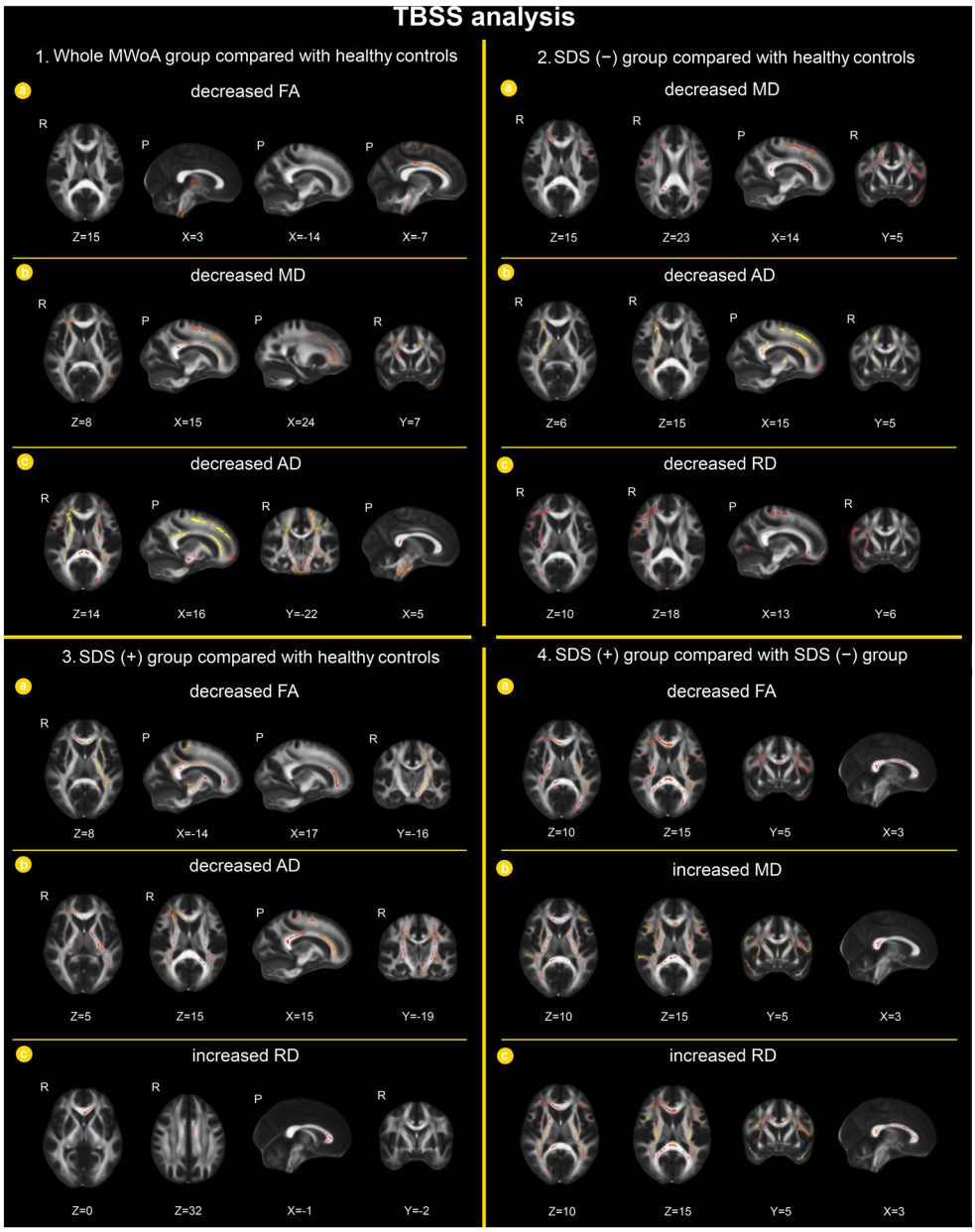

Figure 1. Part 1: compared with the control subjects, patients suffering from migraine without aura showed significantly decreased FA (a), decreased MD (b) and decreased AD (c) in multiple brain regions ($p < 0.05$, corrected), whereas no difference was observed in RD. Part 2: compared with control subjects, the SDS (−) group showed significantly decreased MD (a), decreased AD (b) and increased RD (c) in multiple brain regions ($p < 0.05$, corrected), whereas no difference was observed in FA. Part 3: compared with the control subjects, the SDS (+) group showed significantly decreased FA (a), decreased AD (b) and increased RD (c) in multiple brain regions ($p < 0.05$, corrected), whereas no difference was observed in MD. Part 4: compared with the SDS (−) group, the SDS (+) group showed significantly decreased FA (a), increased MD (b) and increased RD (c) in multiple brain regions ($p < 0.05$, corrected), whereas no difference was observed in AD. AD, axial diffusivity; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; SDS (+) group, patients suffering from migraine without aura with high depressive symptoms [self-rating depression scale (SDS) score > 49]; SDS (−) group, patients suffering from migraine without aura with low depressive symptoms (SDS score ≤ 49).

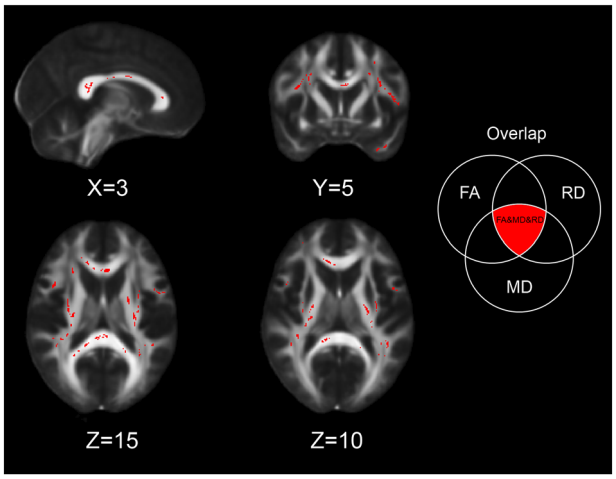

Figure 2. Compared with the SDS (−) group, brain regions in which patients in the SDS (+) group showed significantly different diffusion tensor imaging (DTI) properties were overlapped. The overlap of the decreased fractional anisotropy (FA) (Fig. 1, part 4a), increased mean diffusivity (MD) (Fig. 1, part 4b) and increased radial diffusivity (RD) (Fig. 1, part 4c) is shown in red. The diagram on the right shows the red overlap and the relationship of the overlap. SDS (+) group, patients suffering from migraine without aura with high depressive symptoms [self-rating depression scale (SDS) score >49]; SDS (−) group, patients suffering from migraine without aura with low depressive symptoms (SDS score ≤ 49).

between the DTI properties (i.e. average FA and RD values) in 15 overlapped regions and the SDS scores of MWoA (Fig. 3). After Bonferroni correction for multiple testing (15 tests), there was a significance level of $p=0.0033$; the correlation results remained significant in the right ACR, genu and splenium of the CC and left SLF. In more detail, there were significant negative correlations between the average FA values and the SDS scores, including the right ACR ($r=-0.5127$, $p=0.0008$), genu of the CC ($r=-0.5058$, $p=0.0010$), splenium of the CC ($r=-0.5011$, $p=0.0012$) and left SLF ($r=-0.5374$, $p=0.0004$). There were significant positive correlations between the average RD values and the SDS scores, including the genu of the CC ($r=0.5240$, $p=0.0006$), splenium of the CC ($r=0.5262$, $p=0.0006$) and left SLF ($r=0.4670$, $p=0.0027$). The correlation between the average RD values in the ACR and SDS scores ($r=0.4558$, $p=0.0035$) did not survive after Bonferroni correction, but showed a significant trend.

DISCUSSION

Previous research supports the view that migraine and depression are bidirectionally linked and may share certain similar physiopathological features (4,5). Furthermore, the inconsistent abnormalities of WM properties in patients with migraine have been reported in numerous DTI studies (13–18,20,21). To our knowledge, few studies have investigated WM integrity affected by depressive symptoms in MWoA. As a powerful tool to deduce the more specific pathophysiological features of WM, multiple DTI-derived indices (FA, MD, AD and RD) may provide more specific biomarkers of WM neuropathology collectively (10,12,49,57). The most frequently used DTI-derived index is FA, which is highly sensitive to microstructural changes, but not very specific to the types of change (e.g. radial or axial) (10,12,49). Reduced FA may result from several conditions, such as demyelination, axon loss, gliosis and inflammation, observed in a broad spectrum of diseases (10,49). As a supplementary measure, MD, AD and RD may provide more information about WM microstructure for the evaluation of myelin loss and axonal injury, which may improve the understanding of the neuropathological basis of specific diseases (10,12,49). MD is a measure of the average molecular diffusion, which may be affected by longitudinal diffusion along axons (AD) or in the transverse direction (RD) (57). A decrease in AD suggests axonal loss or loss of bundle coherence (23,49), and an increase in RD suggests demyelination or dysmyelination (10,12,23,49,57).

In the present study, multiple DTI-derived indices (i.e. FA, MD, RD and AD) were used to specify the pathophysiological features of WM (49), which may reflect different details related to migraine and depression bidirectionally. Consistent with previous findings (13–18,20,21), all patients with MWoA showed similar patterns of decreased FA in several WM tracts compared with the control group (Fig. 1, part 1). In particular, compared with healthy controls, the whole MWoA group, SDS (−) group and SDS (+) group showed decreased AD in the genu, body and splenium of the CC, bilateral IC and right EC (Fig. 1, parts 2 and 3). This might suggest that decreased AD in several WM tracts of patients with MWoA is more strongly associated with migraine, implying axonal loss (21). Furthermore, decreased FA and increased MD and RD with conserved AD in the genu, body and splenium of the CC, bilateral SCR, SLF, EC, PLIC, RIC, left PTR and right ACR were shown in the SDS (+) group compared with the SDS (−) group (Fig. 1, part 4 and Fig. 2), which is similar to previous findings in depression disorder (22,25,26). This might suggest that decreased FA and increased MD and RD in several WM tracts of the SDS (+) group are more strongly associated with depression symptoms in patients with MWoA and may cause disrupted integrity of myelin sheaths. The inconsistent abnormalities of WM properties in patients with migraine have focused on AD and RD in previous TBSS studies (20,21). Szabó *et al.* (20) suggested increased RD and conserved AD in the WM region with decreased FA. The different findings on AD and RD in TBSS studies might be related to the different enrollment criteria of the subjects or different depressive conditions, which need to be resolved by a more comprehensive experimental design in future studies.

WM differences between SDS (+) and SDS (−) groups

Similar to the findings in previous depression DTI studies (22,25,26), our results validated the WM abnormalities of the CC in the SDS (+) group compared with the SDS (−) group. As the main fiber tract interconnecting the two cerebral hemispheres, the CC serves as an important role in interhemispheric functional integration and communication of emotional, perceptual, cognitive, motor and volitional information (58). There are three subdivisions of the CC: the genu of the CC connects the prefrontal cortex (PFC) and anterior cingulate cortex (ACC), premotor cortex and supplementary motor area (SMA) of the two hemispheres; the body of the CC contains fibers projecting into the primary somatosensory cortex located in the postcentral gyrus of the parietal lobe between the two halves of the brain; and the splenium of the CC communicates information between the parietal lobe, the occipital lobe and the temporal lobe of the two hemispheres (58). Abnormalities of CC have been consistently reported in depression studies (22,29,59), suicidal

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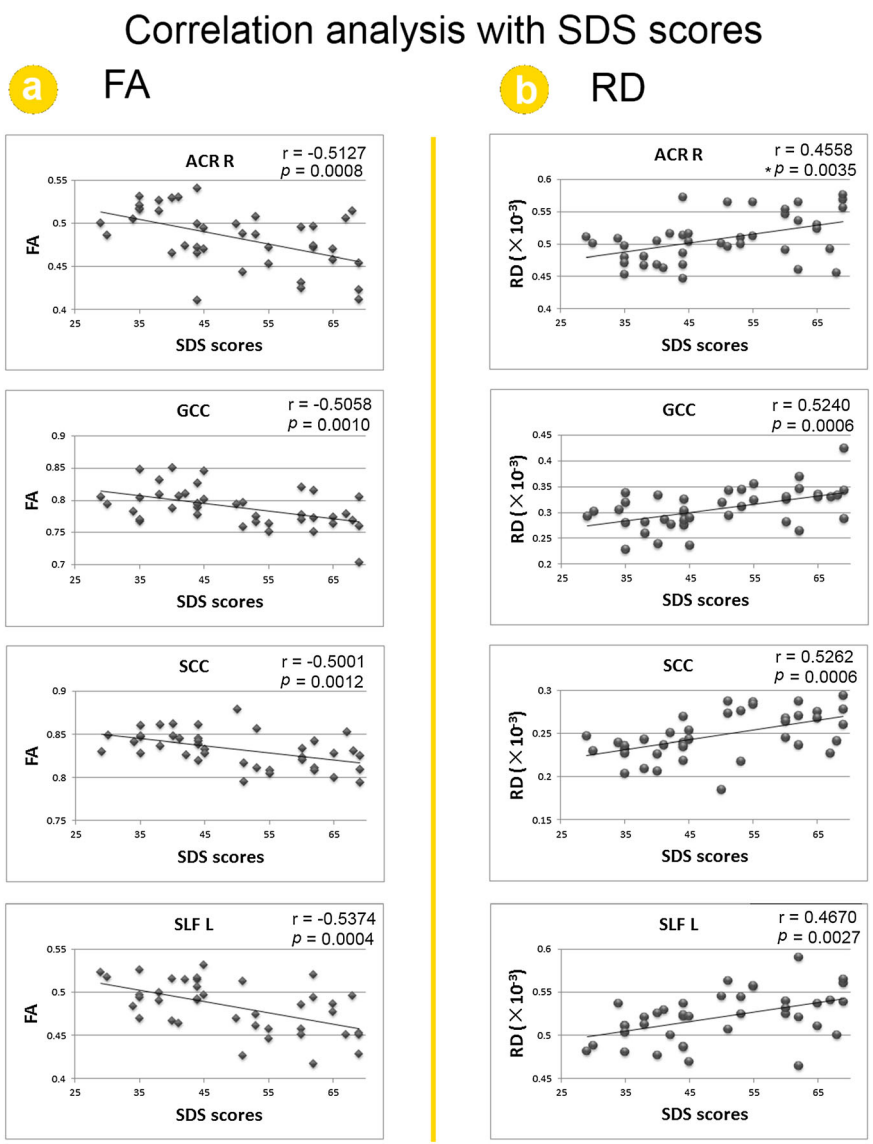

Figure 3. After Bonferroni correction for multiple testing, the correlation analysis results demonstrated that there were significant correlations between the average fractional anisotropy (FA) and radial diffusivity (RD) in the overlapped regions (Fig. 2) and the self-rating depression scale (SDS) scores of patients with migraine. *Correlation did not survive after Bonferroni correction, but showed a significant trend. ACR R, right anterior corona radiata; GCC, genu of the corpus callosum; SCC, splenium of the corpus callosum; SLF L, left superior longitudinal fasciculi.

behavior (60), bipolar depression (23), dysthymia (61) and in adolescents with a parental history of depression (62), as well as in migraine (16). All of these findings suggest that the CC may be involved in the etiology of depressive symptoms, not only in depressive disorder itself, but also in other disorders with a depressive component in their symptomatology (63).

We also found significant WM integrity reductions in bilateral SLF, consistent with other reports in depressive disorder (24,32,59,64) and bipolar disorder (23). The SLF is a pair of long bidirectional fiber bundles of neurons interconnecting frontal, occipital, temporal and parietal lobes (65), in particular the dorsolateral prefrontal cortex (DLPFC), which is an important region in the emotion-regulating circuit (66). Previous studies have indicated that DLPFC is a contributory factor in depression, with ischemic changes even predisposing elderly individuals to major depressive disorder (67–69).

Abnormalities were also identified in the EC, which were consistent with patients in treatment-resistant depression (70) and patients with major depressive disorder and melancholic features (22). The EC contains cortico-striatal projection fibers interconnecting prefrontal and temporal areas with the basal ganglia (71), which is an integral part of the depression-related limbic–cortical network (59,64,66). Similarly, the ACR has been highlighted in several previous DTI studies in adult bipolar disorder (72–74), pediatric bipolar disorder (75) and major depressive disorder (63), and contains both descending and ascending axons between the frontal cortex and the caudal structures within the brainstem (76,77). It may be associated with affect modulation disturbance (63,78,79). Furthermore, we observed disrupted integrity of WM interconnecting cortical and limbic regions, including the PLIC, DLPFC and thalamic radiation, supporting the notion of an abnormal neural circuit in depressive symptoms (29).

Correlation between DTI indices and depressive symptoms in patients with MWoA

To further investigate the association between the WM abnormalities and depression symptoms in MWoA, a partial correlation analysis controlling for age was carried out. Our results demonstrated that the average FA and RD values of overlapped regions, including the genu and splenium of the CC, bilateral SLF and right ACR, were correlated significantly with the SDS scores in MWoA (Fig. 3). We suggest that migraine and depression symptoms in migraine are linked to different diffusion characteristics of WM, which may be a biomarker of alterations in functional, clinical, behavioral or emotional measures in patients with MWoA (10). This may indicate that demyelination, as opposed to abnormalities in axonal loss, might occur more frequently in MWoA with more severe current depression symptoms. The relationship between symptom severity and WM integrity was more significant in the genu and splenium of the CC, bilateral SLF and right ACR. In particular, the negative correlation between the decreased integrity of the CC and depression severity was consistent with a previous migraine study (16) and depression studies (63).

Our results may provide considerably greater precision for the characterization of the regions involved in depression severity in MWoA. Given the decreased AD and increased RD in multiple brain regions, our findings suggest that migraine and depression may affect the WM in similar regions, but with dissimilar types of change (axial or radial). If WM integrity is measurably plastic and related to both migraine and depression symptom severity, this may serve as a sensitive biomarker to reflect pain progression and depression severity of MWoA, and may have potential use in diagnosis, monitoring and assessment in a clinical setting. Successful treatment in depressive disorder or migraine might be accompanied by a normalization of WM integrity, as reported in several structural and functional MRI studies (63,80,81). Similarly, our results might help us to understand how antidepressants help to reduce the severity of migraine or to prevent migraine (82). With regard to migraine, interactive effects with multiple therapies may be more beneficial than a single treatment (3,83). In future studies, depressive symptoms in migraine should be considered as a bias to affect WM integrity. The previous findings in migraine (17,34–37,40–42) should be re-tested to avoid bias caused by depression symptoms.

Limitations

This study is limited in its cross-sectional design. It is not possible to postulate the inferences of causality in the relationships between current illness severity and decreased WM integrity or between migraine attack and depression symptoms. These relationships may be bidirectional, or may result from changes in correlated latent variables. Further longitudinal and analysis of variance studies are required to improve our understanding.

CONCLUSIONS

In the current study, we investigated the pathophysiological features of WM integrity affected by migraine and depressive symptoms in MWoA employing the TBSS method with multiple DTI indices (i.e. FA, MD, RD and AD). The findings suggest that migraine and depression may affect the WM in similar regions, but with dissimilar types of change (radial or axial). This may serve as a sensitive biomarker of the depression severity in MWoA. However, a more comprehensive experimental design is needed to reveal the accurate roles of these WM abnormalities in the pathology of migraine with depression symptoms. We hope that our results extend the evidence of WM changes in migraine patients and improve our understanding of migraine pathophysiology.

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