Original Article
Right frontal white matter hyperintensities is associated with poor portrait memory

Congyang Li, Dazhi Duan, Jian Zheng

Department of Neurology, Xinqiao Hospital, Third Military Medical University, Xinqiao Street, Chongqing 400037, P. R. China

Received December 6, 2015; Accepted March 19, 2016; Epub June 15, 2016; Published June 30, 2016

Abstract: Background: It is unclear whether a single white matter lesion, is related to the type and extent of cognitive impairment. The aim of this study was to investigate whether individuals with frontal periventricular white matter hyperintensity (PVWMH) have a specific cognitive impairment. Methods: We compared 14 individuals with PVWMH with 14 matched healthy controls. All participants underwent T2-weighted fluid attenuated inversion recovery imaging (FLAIR) and diffusion tensor imaging, and neuropsychological assessment. We compared cognitive function and fractional anisotropy (FA) between the two groups. Results: The subjects with frontal (PVWMH) had decreased FA of frontal white matter and poor performance on Portrait Memory (PM) testing compared with the controls. There were no significantly differences in overall cognitive scores between the two groups. FA of right frontal white matter significantly positively correlated with PM performance ($r = 0.796; P = 0.001$). These differences were found in those participants whose overall cognitive scores were normal and whose overall memory quotient (MQ) was not significantly different from that of the controls. Conclusion: The findings in this study suggest that frontal white matter integrity as determined by DTI is associated with PM decline before overall cognitive performance and overall memory decrease.

Keywords: Periventricular white matter, white matter hyperintensity, diffusion tensor imaging, fractional anisotropy, cognition, neuropsychological testing

Introduction

White matter hyperintensities (WMH), which appear as an abnormally high signal in white matter regions on images of fluid attenuated inversion recovery (FLAIR), are common on magnetic resonance imaging (MRI) in clinically healthy older individuals [1-4]. WMH can be divided into periventricular white matter hyperintensities (PVWMH) and deep white matter hyperintensities (DWMH) according to their location [5]. Generally, histopathologic changes of WMH are different between PVWMH and DWMH [6]. DWMH and irregular PVWMH are ischemic, but smooth PVWMH, which can be divided into “caps” and “halos”, are non-ischemic [5]. Frontal PVWMH, so called “caps” around the anterior horn of the lateral ventricle, is a common early manifestation of PVWMH in normal elderly persons, and shows a tendency for progressing to deep and periventricular white matter areas [7].

Neuroimaging studies have shown that WMH have a direct relationship with cognitive impairment and dementia [8]. There is growing evidence showing that a high WMH load is significantly associated with overall cognitive decline, executive decline, and memory decline [9-12]. PVWMH occur in more than half of asymptomatic persons even in the age group of 45 to 55 years and also have shown a considerable tendency to progress even though they are assumed to be of non-ischemic origin [7]. Longitudinally, the progression of PVWMH actually parallels the decline in mental processing speed and the decrease of Mini-Mental State Examination (MMSE) scores [13], which indicates that PVWMH probably have caused a decline in cognitive domains. Also, PVWMH highly correlate with scores on cognitive tests [14, 15]. PVWMH are associated with an increased risk of progression from amnestic mild cognitive impairment (aMCI) to Alzheimer’s disease (AD) [13].
To our knowledge, it is yet unclear if a single white matter lesion, such as frontal PVWMH is related to specific cognitive impairment. Therefore, we studied the memory, executive, and total cognitive function in individuals with frontal PVWMH and evaluated the location of white matter lesions using diffusion tensor imaging (DTI) [16]. The aim of this study was to investigate whether the white matter surrounding frontal PVWMH was associated with extraordinary cognitive function impairment.

Materials and methods

Participants

Fourteen individuals (age range, 45 to 65 years) with frontal PVWMH who underwent a health checkup at the Medical Examination Center of Chengdu Military General Hospital were evaluated. Patients did not have a previous neuropsychiatric history, and they had more than 9 years of education. Conventional MRI indicated frontal PVWMH on a T2 image or FLAIR image, and the rest of the brain structures had no abnormalities such as Figure 1. The exclusion criteria included: 1) significant history of alcohol or drug abuse; 2) history of learning disability; 3) history of severe psychiatric illness; 4) history of hypertension or diabetes; 5). MRI contraindications.

The control group comprised 14 healthy volunteers, who were matched by age, sex, handedness, and education, were recruited from the local community. None had a previous history of neurological or psychiatric diseases or any WMH on their MRI scan.

All of the subjects underwent MRI scanning and neuropsychological assessment between April 16, 2013 and October 30, 2013. The study was approved by the Research Ethics Committee of the Third Military Medical University and in accord with the ethical standards established by the institution or in accord with the Helsinki Declaration. All participants gave written informed consent.

Neuropsychological assessment

The Clinical Memory Scale was introduced by the Psychology Institute of the Chinese Academy of Science to evaluate memory ability [17]. The scale is composed of five subtests: Directional Memory (DM), Associative Learning (AL), Graphic Free Recall (GFR), Meaningless Graphics Recognition (MGR), and Portrait Memory (PM). The Memory Quotient (MQ) was calculated according to the manual. Each participant was assessed individually in a quiet and comfortable room without any interruption. The detailed procedure and scaling scores were performed according to the handbook of the Clinical Memory Scale [18].

Directional memory

The test material consists of two groups of Chinese words. The first group of words includes 12 fruit terms and 12 non-fruit food terms. The other group of words consists of 12 animal names and 12 human organ names. The 24 words in each group are randomly arranged, and are heard at the speed of a word per second by participants, who are asked to say the fruit name just heard. Then there is a test with another group of words, in which participants are asked to say the animal name just heard. Participants are scored a point for every fruit or animal they remember. The total score is 24 points for this test.

Associative learning

The test material is composed of six pairs of “easy” Chinese words, in which each pair of words has a logical relationship, and six pair of “difficult” Chinese words, in which each pair of words has no logical relationship. All 12 pairs of
words are heard at a speed of a word per 3 seconds by participants. Then participants are asked to say the next word when they hear the first word, and the score is 0.5 point if the “easy” pair of Chinese words answer is correct, and 1 point if the “difficult” pair of Chinese words answer is correct. The above process is repeated three times. The total score is 27 points for this test.

**Graphic free recall**

The test material is composed of two groups of general item sketches. Each group contains 15 randomly arranged sketches. The 15 sketches are presented to participants at a speed of 4 seconds per sketch and interval of 2 second. Then the participants are asked what they have seen, and scored 1 point for each item they remember. And then the next group of sketches is presented. The total score is 30 points for this test.

**Meaningless graphics recognition**

The test material is composed of 20 stimulus pictures and 40 recognition pictures of meaningless lines and curves. The 20 stimulus pictures are randomly presented to participants at a speed of 3 seconds per picture. Then participants are asked which picture is the stimulus picture in 40 recognition pictures that consist of 20 stimulus pictures and 20 other interference pictures. If answer is correct, then 1 point is added, and if the answer is wrong 1 point is subtracted. The total score is 2 times the total points.

**Portrait memory**

The test material is composed of six simple portrait pictures which are randomly arranged and are presented to subjects for 3 seconds in 9 second intervals. When presenting each picture, the experimenter told subjects the name, occupation, and interests, of the portrait and repeated this two times. After being presented all six pictures, subjects were presented the 6 simple portrait pictures according to another random order, and responded with each portrait’s name, occupation, and hobbies. Each correct occupation added one point, each correct interest added one point, and each correct name added 2 points. The sum total score is 24 points.

**Other neuropsychological assessment**

The MMSE and the Montreal Cognitive Assessment (MoCA) [18] were employed to test overall cognitive ability. The Center for Epidemiological Studies Depression scale (CES-D) [19] and the Trail Making Test-A (TMT-A) [20] were employed to detect the possibility of depressive symptoms and impairment of executive function.

**MRI acquisition**

Magnetic resonance imaging scans were carried out at the Chengdu Military General Hospital using a Philips 3.0-Tesla Achieva Quasar Dual MR scanner (Philips Medical systems, Best, The Netherlands) with an 8-channel head coil. Each participant underwent T2-weighted fluid attenuated inversion recovery (FLAIR) imaging and DTI. The diffusion tensor data were acquired using a single-shot spin-echo echo-planar (EPI) sequence with the following protocol: 16 directional diffusion sensitizing gradients (b = 1000 s/mm²) with one no-diffusion-weighted (b = 0 s/mm²) pulse, echo time (TE) = 76 ms, repetition time (TR) = 6500 ms; flip angle = 90°, number of excitation (NEX) = 1, 60 contiguous axial slices with 2 mm thickness and no gap, field of view (FOV) = 224 × 120 × 224 mm, matrix size = 128 × 128, in-plane image resolution = 1.75 × 1.75 mm. The FLAIR sequence was acquired with TR = 7000 ms, TE = 125 ms, TI = 2250, matrix size = 512 × 512, slice thickness = 6.6 mm, yielding spatial resolution of 0.45 × 0.45 × 6.6 mm³/voxel.

**DTI data post-processing**

All DTI data were processed off-line with Dti-Studio software [21], Version 3.0.3 (Johns Hopkins University, Baltimore, MD). First, image co-registration was performed to remove small bulk motions that occurred during the scans by Automatic Image Registration (AIR) maps. Color-coded directionality maps of diffusion were calculated and created in individual images. The color-coded directionality maps (red: X direction, green: Y direction, blue: Z direction) provided easy visualization of the white matter fiber tracts. After rectangular regions of interest (ROI) were drawn based on the identification of white matter tracts on the color-coded maps, FA maps of each participant were overlaid on their color-coded maps. Then, the mean
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values of FA values within each ROI were calculated.

We measured the inferior occipito-frontal fascicle (IOFF), genu and splenium of the corpus callosum (GCC, SCC), central and posterior segments of the cingulum bundle (CCB, PCB), segment II of the superior longitudinal fascicle (SLFII), and frontal white matter (fWM). We used two methods to select the ROI: 1) overlap FA maps on color-coded maps for choice of long association fiber tracts; 2) overlap FA maps on b0 maps for choice of frontal white matter. Examples of ROI traced for DTI analyses are presented in Figures 2 and 3.

Inferior occipito-frontal fascicle (IOFF): an axial plane of color-coded maps was selected in which IOFF displayed most were clearly seen as a green trace from frontal lobe to occipital lobe. Three ROI on each side with in-plane size of 2 × 4 pixels were separately placed (one frontal, one fronto-temporal, one temporal). Care was taken not to overlay with the tract boundary. FA

Figure 2. An example of placement of frontal white matter ROI (Left: The image of b = 0; right: The same ROI overlaid on the FA map).

Figure 3. Illustration of ROI selection on the long fiber tracts. Upper row: Color-coded map; lower row: Same ROI overlaid on the FA map. From left to right: Inferior occipito-frontal fascicle (IOFF); corpus callosum (GCC and SCC); segment II of the superior longitudinal fascicle (SLFII); posterior cingulate bundles (PCB); mid-cingulate bundles (MCB).
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Table 1. Comparison of demographic and neuropsychological data between frontal PVWMH group and control group

<table>
<thead>
<tr>
<th></th>
<th>PVWMH (n = 14)</th>
<th>Controls (n = 14)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50.21±5.83</td>
<td>48.64±1.98</td>
<td>0.780</td>
</tr>
<tr>
<td>Education</td>
<td>10.4±2.38</td>
<td>10.64±2.06</td>
<td>0.863</td>
</tr>
<tr>
<td>Gender</td>
<td>8 m/6 f</td>
<td>8 m/6 f</td>
<td>-</td>
</tr>
<tr>
<td>MMSE</td>
<td>27.64±2.17</td>
<td>28.86±1.46</td>
<td>0.160</td>
</tr>
<tr>
<td>MoCA</td>
<td>26.57±1.02</td>
<td>26.36±1.01</td>
<td>0.778</td>
</tr>
<tr>
<td>Trail Making Test-A (s)</td>
<td>65.57±32.71</td>
<td>52.07±17.60</td>
<td>0.206</td>
</tr>
<tr>
<td>DM</td>
<td>14.21±5.07</td>
<td>15.79±4.04</td>
<td>0.402</td>
</tr>
<tr>
<td>AL</td>
<td>18.79±4.10</td>
<td>20.64±5.36</td>
<td>0.405</td>
</tr>
<tr>
<td>GFR</td>
<td>17.00±5.59</td>
<td>19.00±4.51</td>
<td>0.354</td>
</tr>
<tr>
<td>MGR</td>
<td>16.93±7.25</td>
<td>19.64±4.89</td>
<td>0.256</td>
</tr>
<tr>
<td>PM</td>
<td>13.36±3.39</td>
<td>17.29±4.12</td>
<td>0.017</td>
</tr>
<tr>
<td>MQ</td>
<td>85.57±12.57</td>
<td>95.00±10.13</td>
<td>0.059</td>
</tr>
<tr>
<td>CES-D</td>
<td>21.71±11.47</td>
<td>19.50±13.82</td>
<td>0.461</td>
</tr>
</tbody>
</table>

Values are given as mean and standard deviation; m: male; f: female; MoCA: Montreal Cognitive Assessment; MMSE: Mini-Mental State Examination; DM: Directional Memory; AL: Associative Learning; GFR: Graphic Free Recall; MGR: Meaningless Graphics Recognition; PM: Portrait Memory; MQ: Memory Quotient; CES-D: The Center for Epidemiological Studies Depression scale.

Right frontal white matter: an axial plane of b0 imaging was selected at the middle of the genu of the corpus callosum (GCC) in which three ROI on each side with in-plane size of 3 × 3 pixels were carefully placed (one in the appearing normal white matter region in front of the anterior horn of the lateral ventricle or in front of “caps” of the anterior horn of the lateral ventricle; one in front of the first ROI with the intervals of at least one pixel; one lateral of the first ROI with the intervals of at least one pixel. Further small adjustments in position were then made, if necessary, to ensure the ROI had not moved into regions of CSF or into frontal periventricular WMH regions. Then on each side FA values in those ROI can be calculated and averaged in FA maps.

Mid-cingulate bundles (MCB): the highest green tracts were the center line in color-coded maps, and one ROI on each side with in-plane size of 2 × 4 pixels was drawn on the center.

To determine reliability of the post-processing measurements, the same rater repeated ROI drawings on 12 randomly selected subjects, blinded to the previous evaluation. The correlation coefficient between previous and repeated measures was 0.9.

Statistical analysis

Nonparametric Mann-Whitney U-tests (MWU) were employed to assess the group comparisons of demographic data, neuropsychological performance, and ROI values with statistical significance set at P < 0.05. Spearman bivariate correlations analyses were used to calculate relationships between ROI values and neuropsychological performance. These statistical analyses were carried out using the Statistical Package for the Social Sciences Statistics program 13.0 software (SPSS, Inc., Chicago, IL, USA).

Results

Demographic characteristics and neuropsychological data are presented in Table 1. There were no significant differences in age and gender between the two groups. Furthermore, neu-
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Table 2. Comparison of FA values of frontal white matter between frontal PVWMH group and control group

<table>
<thead>
<tr>
<th>Items</th>
<th>PVWMH (n = 14)</th>
<th>Controls (n = 14)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>L frontal white matter</td>
<td>0.40±0.034</td>
<td>0.45±0.054</td>
<td>0.032</td>
</tr>
<tr>
<td>R frontal white matter</td>
<td>0.39±0.035</td>
<td>0.45±0.073</td>
<td>0.015</td>
</tr>
<tr>
<td>L inferior front-occipital fascicles</td>
<td>0.55±0.058</td>
<td>0.56±0.047</td>
<td>0.8</td>
</tr>
<tr>
<td>R inferior front-occipital fascicles</td>
<td>0.54±0.055</td>
<td>0.53±0.066</td>
<td>0.58</td>
</tr>
<tr>
<td>Genu of corpus callosum</td>
<td>0.82±0.051</td>
<td>0.85±0.056</td>
<td>0.167</td>
</tr>
<tr>
<td>Splenium of corpus callosum</td>
<td>0.83±0.051</td>
<td>0.83±0.068</td>
<td>0.678</td>
</tr>
<tr>
<td>L mid-cingulate bundles</td>
<td>0.69±0.072</td>
<td>0.70±0.052</td>
<td>0.73</td>
</tr>
<tr>
<td>R mid-cingulate bundles</td>
<td>0.65±0.111</td>
<td>0.66±0.078</td>
<td>0.908</td>
</tr>
<tr>
<td>L posterior cingulate bundles</td>
<td>0.65±0.050</td>
<td>0.61±0.076</td>
<td>0.231</td>
</tr>
<tr>
<td>R posterior cingulate bundles</td>
<td>0.57±0.079</td>
<td>0.60±0.071</td>
<td>0.29</td>
</tr>
<tr>
<td>L superior longitudinal fascicle</td>
<td>0.61±0.074</td>
<td>0.60±0.064</td>
<td>0.927</td>
</tr>
<tr>
<td>R superior longitudinal fascicle</td>
<td>0.60±0.052</td>
<td>0.61±0.072</td>
<td>0.612</td>
</tr>
</tbody>
</table>

Values are given as mean and standard deviation. L: left; R: right.

Table 3. Correlation analysis between FA values of frontal PVWMH and cognitive function

<table>
<thead>
<tr>
<th></th>
<th>Right frontal</th>
<th></th>
<th></th>
<th>Left frontal</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
<td>r</td>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>0.278</td>
<td>0.336</td>
<td>0.449</td>
<td>0.108</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MoCA</td>
<td>-0.044</td>
<td>0.882</td>
<td>-0.114</td>
<td>0.698</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>-0.033</td>
<td>0.911</td>
<td>0.625</td>
<td>0.017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AL</td>
<td>0.184</td>
<td>0.529</td>
<td>-0.002</td>
<td>0.994</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR</td>
<td>0.067</td>
<td>0.819</td>
<td>0.241</td>
<td>0.406</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MGR</td>
<td>0.173</td>
<td>0.553</td>
<td>0.563</td>
<td>0.036</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM</td>
<td>0.796</td>
<td>0.001</td>
<td>0.36</td>
<td>0.207</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MQ</td>
<td>0.365</td>
<td>0.2</td>
<td>0.647</td>
<td>0.012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CES-D</td>
<td>-0.025</td>
<td>0.934</td>
<td>-0.348</td>
<td>0.223</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT-A (s)</td>
<td>-0.106</td>
<td>0.718</td>
<td>-0.134</td>
<td>0.649</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MoCA: Montreal Cognitive Assessment; MMSE: Mini-Mental State Examination; DM: Directional Memory; AL: Associative Learning; GFR: Graphic Free Recall; MGR: Meaningless Graphics Recognition; PM: Portrait Memory; TMT-A: Trail Making Test-A.

Neuropsychological data showed no significant differences in performances on the MMSE, MoCA, Trail Making Test-A, DM, AL, GFR, MGR, MQ, and CES-D between the two groups. However, compared with control group, the frontal PVWMH group had poorer performance on PM (P = 0.017).

Fractional anisotropy values of participants are presented in Table 2. There were no significant differences in the long association fiber tracts bilaterally that could be detected between the groups. FA values of the frontal white matter were significantly decreased in the participants with frontal PVWMH (right: P = 0.015; left: P = 0.032).

Table 3 shows the relationship between FA values and the memory components in participants with frontal PVWMH and Figure 4 shows the results of correlation analyses. FA values of right frontal white matter displayed a significantly positive correlation with PM performance (r = 0.782, P = 0.01). At the same time, FA values of left frontal white matter displayed significantly positive correlation with DM performance (r = 0.625, P = 0.017) and MGR (r = 0.536, P = 0.036), and MQ (r = 0.647, P = 0.012). FA values of frontal white matter did not significantly correlate with any other neuropsychological performances by the participants with frontal PVWMH.

Discussion

In this study, we explored white matter microstructure changes and cognitive impairments in normal-appearing individuals with frontal PVWMH. The results showed that in normal-appearing participants with frontal PVWMH: 1) PM performance was poorer compared with the control group; 2) frontal white matter FA was significantly reduced; 3) the poorer PM performance was associated with increased right frontal lobe FA. We believe that the most important finding in our study was that frontal PVWMH in normal-appearing individuals paralleled difficulties with PM while their overall cognitive and memory function performance was “normal”.

We used the TMT-A to measure executive function. Table 1 shows that there was no difference between the two groups in TMT-A performance. Studies have shown that executive function is closely related to the frontal lobe [22], especially the prefrontal cortex [23]. The differences in brain structure between the two groups in our study were limited to white matter; there were no differences in gray matter. Meanwhile, there was no difference between the two groups in scores on the CES-D. With regard to depression-related cognitive deficits, depressive patients suffer from short-term memory decrease, and attention extent, stabil-
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Figure 4. A-D. Correlations of FA and memory performance of the participants with frontal PVWMH.

ity and rearrangement are decreased [24]. In our two groups, differences in cognitive functions were not due to the depressive state since there was no significant difference in the CES-D scores between the groups.

Although hypertension and/or diabetes has been linked with cognitive impairments [25], individuals with either condition were excluded in from our study because these conditions can cause small vessel chronic ischemia not only in the frontal lobe but also the other areas of the brain [26]. Since our aim was to investigate the relationship between frontal white matter and cognitive function, if it was found that cognitive function declined in patients with hypertension and/or diabetes we could not be sure that the result was due to the frontal lobe lesion.

A study has shown that temporal WMH were associated with face recognition deficits [27]. The difference in results from our study may be attributable to differences in selection of participants. In our research, the overall cognitive level of participants was normal. In other words, PM decreased prior to cognitive function being impaired and overall memory decline.

Our research also showed that only the right frontal lobe white matter FA was positively correlated with PM. Positron emission tomography (PET) and functional MRI (fMRI) provide sufficient experimental evidence for exploring the memory functions of the frontal lobe [28]. The areas more active in the free recall task were the right dorsolateral frontal cortex (DLFC), while in the cued recall task the right ventrolateral frontal cortex (VLFC) was more active, which is the area associated with monitoring components needed in tasks. It can be presumed that white matter of the right frontal lobe may play an important role in connecting different regions of frontal cortex and modulating their activity. Our research also showed that
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participants with frontal PVWMH did not have a decrease in DM, AL, GFR, or MGR, for which less of this region is needed. Since PM calls for visual information, auditory information, and the need to combine them together, difficulties in performing this task suggest that the right frontal lobe white matter may play a liaison role for dealing with various aspects of comprehensive information. Although the left frontal lobe white matter FA values were correlated positively with DM, MGR, and MQ (Figure 4), there were no significant differences between the two groups. Therefore, these correlations were not due to WMH, probably because of the property of frontal white matter itself.

In our neuropsychological assessment, PM involved hearing, vision, attention, association memory, and other cognitive features. A study using fMRI has shown that frontal, temporal, and occipital regions were activated in face recognition tasks [29]. Research on developmental neuroscience suggested that the temporal lobe participates in face recognition tasks before the frontal lobe and that the frontal lobe is mainly associated with the processing speed of face recognition tasks [30]. Those findings also indicated that the frontal lobe has a regulation role in PM tasks. Our research has also shown that frontal white matter impairment may first affect the delivery of information between the frontal lobe, temporal lobe, and occipital lobe, which results in PM tasks becoming difficult. A longitudinal study found memory training can improve frontal lobe white matter FA, and improve memory test scores [31].

The relationship between cerebral WMH and cognitive impairment has been reported elsewhere [11, 30, 32-34]. These studies were aimed at WMH, except two studies showed that white matter microstructural abnormalities emerged in a wider range of white matter regions surrounding WMH but were seen as “normal” on traditional MRI [35, 36]. Our study also confirmed this with the finding that white matter FA surrounding frontal PVWMH decreased. Several studies found negative correlations between BOLD signal and FA value [37, 38], and an association of lower white matter integrity with reduced frontal cortex efficiency [39]. These results were in agreement with the histopathological finding in frontal PVWMH that there was a lack of U-fibers and oligodendrocyte decomposition in the frontal lobe subcortex, and microglia reaction activity in the frontal periventricular region [40]. Microglia are a group of static state immune cells in the central nervous system that mediate the death of oligodendrocytes by the actions of the neurotransmitter system (such as adenosine triphosphate, glutamic acid) [41], which leads to myelin and axonal damage. These pathological processes hint that white matter injury areas may occur more widely then WMH on T2 or FLAIR imaging. Follow-up studies have confirmed that the microstructure of normal white matter organization would evolve into actual WMH in the future [42]. Therefore, as we discovered, the white matter damaged areas in individuals with frontal PVWMH are wider than the hyperintensities.

Our study had some limitations. First, this study is not a longitudinal study, so whether frontal PVWMH finally progresses to a wider region still needs to be observed; and whether it will lead to overall cognitive function impairment also needs further study. Second, executive function measures in our study provide only rough estimates of the decrease in test time. Perhaps executive function also had some impairment that we did not find. Third, we did not find that left frontal lobe white matter integrity decreased the effects on cognitive function in neural psychological measurement. In this study, these problems did not affect the results since we focused on overall cognition and memory, and found difficulties with PM. However, further study is needed in order to explore frontal PVWMH. Although this is not a longitudinal study that does not affect our finding that there is a relationship between right frontal WMH and PM.

Conclusion

In short, this is the first exploration of the white matter microstructure damage in normal participants with frontal PVWMH using diffusion tensor imaging, and assessment of cognitive function through neuropsychological assessment. The neuropsychological data showed that frontal PVWMH was associated with more difficulty with PM when the frontal PVWMH group was compared with the control group, and that there was parallel frontal lobe white matter microstructure impairment. Furthermore, if the right frontal lobe white matter is associated with PM this indicates that in mem-
memory disorder in participants with frontal PVWMH there may be an abnormality of monitoring function that is needed in the process of memory.

Acknowledgements

We thank the study participants. This study was supported by Sichuan Provincial Health and Family Planning Commission of China (4241-2101) and Chongqing science and technology project, People’s Republic of China (cstc2012- gg-yjs0726).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jian Zheng, Department of Neurology, Xinqiao Hospital, Third Military Medical University, Xinqiao Street, Chongqing 400037, P. R. China. Tel: +86-23-68763203; Fax: +86-23-68763203; E-mail: jzheng59@hotmail.com

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