Disruption of brain white matter microstructure in primary Sjögren’s syndrome: evidence from diffusion tensor imaging

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Abstract

Objectives. The relationship between cognitive symptoms and underlying neuropathology in primary SS (PSS) is poorly understood. We used high-resolution quantitative brain MRI to identify potential structural correlates of cognitive symptoms.

Methods. Subjects completed a comprehensive neuropsychometric evaluation. Imaging was performed on a 3 T MRI scanner with T1 and proton density-weighted, fluid-attenuated inversion recovery (FLAIR) and diffusion tensor imaging (DTI) sequences. We compared MRI group metrics (impaired PSS, not-impaired PSS and controls) and tested for correlations between DTI results and neuropsychological measurements (significance threshold

Results. Nineteen PSS patients (who met American–European Consensus Group 2002 criteria) and 17 healthy controls completed the cognitive evaluation. MRI scans were performed in six impaired PSS, seven not-impaired PSS and seven controls. No differences were found in regional volumetrics, nor was there a difference in T2 lesion load between groups. Fractional anisotropy (FA) in the inferior frontal white matter (WM) was lower (P = 0.021) and mean diffusivity higher (P = 0.003) in the impaired PSS relative to the control group. Inferior frontal FA was correlated with cognitive symptoms (P = 0.0064) and with verbal memory (P = 0.0125).

Conclusions. In this exploratory study, frontal region WM microstructure alterations accompanied cognitive symptoms and were associated with mild cognitive impairment in PSS. While additional study is warranted to assess the specificity and stability of these results, DTI could provide novel insight into the pathological processes accompanying the subtle cognitive dysfunction commonly experienced by PSS patients.

Key words: Sjögren’s syndrome, Neurological involvement, Brain magnetic resonance–diffusion tensor imaging.

Introduction

Primary SS (PSS) is a chronic systemic autoimmune disease characterized by exocrine gland inflammation and symptoms of oral and ocular dryness. Females are affected more frequently than males in a ratio of nine to one with onset of symptoms typically in the fifth decade of life [1]. Persistent fatigue affects as many as 70% of persons living with PSS [2]. Additionally, patients often report difficulties with attention and memory [3]. While cognitive symptoms are commonly experienced, very little is known concerning the mechanisms of cognitive dysfunction in PSS.
Both white matter (WM) lesions and cerebral atrophy have been noted in MRI studies of PSS patients [4–6]. However, the functional significance of MRI abnormalities detected in PSS patients is unclear from previous studies. While conventional brain MRI sequences lack sufficient sensitivity to assess potential association between cognitive function and brain microstructure, recent technological advances have made possible more detailed imaging studies that provide a precise evaluation of brain tissue integrity and volume loss.

We used diffusion tensor imaging (DTI) to provide a detailed analysis of brain WM microstructure. DTI is a special form of diffusion-weighted imaging that allows the assessment of WM integrity and the organization of WM tracts [7, 8]. Barriers such as cell membranes, cellular structures and myelin restrict water diffusion and, in highly ordered WM tissue, diffusion occurs more readily in the direction of the axons with comparatively little diffusion in the plane perpendicular to the axons. The technique is called DTI because a diffusion tensor, a mathematical description of the orientation and magnitude of diffusion, is computed for each voxel. Further calculations result in summary measurements that reflect the magnitude or amount of diffusion in each direction. Fractional anisotropy (FA) is a measurement of the asymmetry in the diffusion along the direction of maximum diffusion relative to diffusion perpendicular to this direction, ranging from 0 (isotropic diffusion) to 1 (diffusion only in one direction). Mean diffusivity (MD) is the average diffusion parameter along the direction of maximum diffusion and two perpendicular directions.

To date, DTI has been used to characterize normal brain development as well as ageing, and has shown potential as a biomarker for the degree of diffuse axonal injury in a variety of brain disorders including multiple sclerosis (MS) [9]. In Type I diabetes, DTI analysis demonstrated WM abnormalities that were associated with deficits found by neurocognitive tests [10]. DTI has also provided evidence of alteration in brain microstructure that correlated with symptom intensity in FM suggesting that MR–DTI could serve as an additive diagnostic technique [11].

The aim of this study was to perform high-resolution computer-assisted brain imaging to identify potential neuroanatomical correlates of cognitive symptoms in PSS. We assessed PSS patients and healthy controls with a comprehensive neuropsychometric evaluation. Subjects were imaged with a multisequence MRI protocol designed to evaluate the degree and extent of cerebral tissue abnormality. We hypothesized that evidence of frontal and subcortical cognitive dysfunction would be detected in the PSS patients and that association would be found between cognitive symptoms and microstructural abnormalities detected with high-resolution computer-assisted imaging.

Methods

Subjects

Seventy-four females between the ages of 18 and 65 years from the University of Minnesota PSS cohort who were residents of the greater Minneapolis metropolitan area were invited to participate. Our sampling strategy was not based on consecutive patients; instead we recruited patients from a large community-based PSS cohort who indicated their interest in participating. The first 24 PSS subjects who indicated an interest in participating were screened to determine eligibility. Inclusion required diagnosis of PSS according to American–European Consensus Group criteria (AECG) [12]. Exclusion criteria included diabetes, history of cardiac illness, stroke, aPL syndrome, neurodegenerative disorder, history of alcohol dependence or substance abuse, seizure disorder or brain trauma. Seventeen female controls who did not have a history of systemic autoimmune disorder and who were free of the exclusion criteria were recruited from the University of Minnesota community.

No subject had a history of cognitive disorder other than complaints of memory and concentration difficulties. Subjects with contraindications were not included in the MRI part of the protocol. The study was approved by the Institutional Review Board of the University of Minnesota and all subjects gave informed written consent according to the Declaration of Helsinki.

Neuropsychological evaluation

Validated questionnaires were used to assess psychological symptoms including fatigue with the Fatigue Severity Scale (FSS), symptoms of depression with the Center for Epidemiologic Studies Depression Scale (CES-D), sleep quality with the Pittsburgh Sleep Quality Index (PSQI) and pain with the Brief Pain Inventory (BPI) [13–16]. Subjective cognitive function was evaluated with the mental domain of the Profile of Fatigue mental domain (Prof-M) and with the Thinking Index [17, 18]. The tests selected for the psychometric evaluation were chosen to examine a range of cognitive domains, including language, visual spatial processing, attention, mental processing speed, executive function, short-term learning and memory. (See supplementary file 1 for detailed description of the questionnaires and the cognitive test battery, available as supplementary data at Rheumatology Online.) Each session lasted 1.5–2 h and was administered and scored by trained personnel.

Patient selection for MR brain imaging

The results of the cognitive battery of tests were used to rank subjects according to the number of test scores less than or equal to —1.5S.D. below the age-adjusted norm. Patients were grouped according to their cognitive test results into PSS subjects with cognitive impairment and those with no cognitive impairment. A test result was considered to reflect impairment, according to generally accepted convention, if the result was greater than or equal to —1.5S.D. below the age-adjusted norm. Seven subjects with at least one test result equal to or below —1.5S.D. comprised the impaired group. Eight of 19 PSS subjects had no cognitive impairment on any test. These subjects comprised the not-impaired PSS group. Subjects from the
control group were invited to participate in the MRI study without regard to cognitive test results. All subjects underwent a screening neurological exam on the day of the MRI scan.

We grouped patients for analysis of the MRI results based on the results of the cognitive tests. Accordingly, seven PSS patients with cognitive impairment, eight PSS patients with no cognitive impairment and seven controls underwent the MRI portion of the study. One of the patients without cognitive impairment was unable to tolerate the MR scanning due to claustrophobia and was dropped from the imaging portion of the study. One subject with cognitive impairment was excluded from the image analysis because she was an outlier in age (10 years younger than any other MRI participant). Analysis of the imaging data was performed on the remaining 13 patients and 7 controls.

**Brain imaging**

For details, see supplementary file 2, available as supplementary data at Rheumatology Online.

**Image acquisition.** MRI was performed on a 3 T Siemens TIM Trio MR scanner. The MRI scan protocol included sequences with: T1- and proton density weighting for structural analysis, fluid-attenuated inversion recovery (FLAIR) imaging for analysis of WM lesion load and DTI for analysis of WM microstructure.

**Image processing.** Images were processed and analysed using custom software that utilized tools (FSLVIEW, BET, FLIRT, FAST, FUGUE and FDT) from the Oxford Centre for Functional MRI of the Brain (FMRIB) software library (http://www.fmrib.ox.ac.uk/) and the FreeSurfer software library (FSL; http://surfer.nmr.mgh.harvard.edu/).

**FLAIR analysis.** FLAIR images were visually scored using FSLVIEW. Deep WM hyper-intensities (WMHs) were rated on a scale of absent (0) to highly confluent (3), and the number of each degree of WMH was counted for each subject. Periventricular hyper-intensities (PVHs) were also scored from absent (0) to irregular (3). Each subject was given an overall score for WMH and PVH according to the most severe levels observed for each type [19].

**Regions of interest.** The same semi-automated procedures reported by Wozniak et al. [20] were used in this work to define regions of interest (ROIs). Two ROIs were selected for analysis: the inferior frontal region (INF), which is all WM voxels rostral to the genu of the callosum and inferior to the anterior and posterior commissure (AC–PC) plane, and the superior frontal region (SPF), which is all WM voxels rostral to the genu of the callosum and superior to the AC–PC plane (Fig. 1). A trained operator determined the boundary of the ROIs on the Montreal Neurological Institute-aligned T1 image for each subject; these planes were aligned on the DTI image and convolved with the WM mask to define the WM ROI masks. Mean values for MD and FA were computed for the WM voxels within the two ROIs.

**Statistical methods.** Descriptive statistics were used to characterize the study population according to demographics and psychological symptom severity. Student’s t-test or chi-squared P-values for proportions were used to compare PSS subjects and controls. Cognitive tests were grouped into neuropsychological domains by principle components analysis. Individual raw scores on each test were converted to age-corrected Z-scores for comparison of PSS subjects and controls.

Analysis of variance (ANOVA) was used to compare cognitive test scores and psychological symptom measurements between groups (P-value set at significance threshold of 0.05). ANOVA was used to compare MRI group metrics: impaired, not-impaired and controls (P-value set at significance threshold of 0.05). MRI measurements of potential brain morphometry differences included whole brain volume, ventricular volume, brain parenchymal volume fraction and cortical thickness in 70 cortical ROIs as well as lobar ROIs. Tukey’s test was used to correct the FreeSurfer cortical thickness analysis.

**Fig. 1** Frontal regions defined to be superior to a plane at the genu of the corpus callosum. INF is also inferior to the plane formed by the AC–PC; SPF is also superior to the AC–PC plane.
for multiple comparisons. WM lesion load was assessed using the FLAIR images. For DTI analysis of WM differences, the FA and MD values were computed for each voxel in the DTI volume. Mean FA and MD were computed for WM voxels in the superior and inferior frontal ROIs.

Spearman’s correlation coefficients were calculated to test for relationships between measurements of cognitive function and selected MR parameters. Due to the exploratory nature of our study, we did not correct the correlation data for multiple comparisons. We tested the prediction that memory impairment would be associated with abnormalities in frontal WM ROI, and tested for correlations between DTI parameters in the specific frontal ROIs with psychological symptoms.

Results

Neuropsychological status of PSS and control subjects

Nineteen female PSS and 17 healthy female subjects completed the neuropsychometric evaluation. Patients and controls were similar in age and education. Controls and patients were similar in overall intellectual ability, and therefore comparable as indicated by results of the Wide-Range Achievement Test (WRAT-3; Table 1). Cognitive function was perceived as significantly worse ($P = 0.0086$) and depression, fatigue and pain scores were significantly higher in PSS subjects compared with controls (Table 1).

The medical history of the patients and controls was similar with regard to the proportion with a history of depression (reported by 37% of the PSS subjects and 22% of the controls), anti-depressant medication use (16% of the PSS subjects and 18% of the controls) and history of migraine headaches (reported by 37% of the patients and 24% of the controls). A history of FM was reported by three patients (17%) and none of the controls. Three of the PSS patients and none of the controls had a history of hypothyroidism. None of the patients had a history of systemic vasculitis or lymphoma.

Cognitive test results

Subjective cognitive function and the results of tests of memory and attention were significantly correlated in the PSS patients but not in the controls. The Prof-M correlated with performance on tests of verbal memory [Hopkins Verbal Learning Test (HVLT-total)], sustained attention (digit symbol) and working memory (Trails B; Table 2). Digit symbol and Trails B scores were also negatively correlated with depression (CES-D) and with the Thinking Index.

PSS subjects were more likely to perceive problems with memory and attention; however, cognitive deficits in the patient group were subtle. Deficits in verbal memory and cognitive efficiency tests were more frequent in the PSS subjects than in the controls. Eight of the 19 PSS subjects had one or more test results equal to or less than $-1.5 \text{ S.D.}$ Three PSS subjects had borderline

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographical and clinical characteristics of 19 PSS and 17 controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>PSS ($n = 19$)*, mean (s.d.)</strong></td>
</tr>
<tr>
<td>Age, years</td>
<td>53 (10)</td>
</tr>
<tr>
<td>Education, years</td>
<td>15.6 (2.4)</td>
</tr>
<tr>
<td>Mental fatigue (Prof-M)</td>
<td>3.68 (2.04)</td>
</tr>
<tr>
<td>Depression (CES-D)</td>
<td>14.16 (12.78)</td>
</tr>
<tr>
<td>Pain (BPI)</td>
<td>2.93 (2.43)</td>
</tr>
<tr>
<td>Fatigue (FSS)</td>
<td>5.46 (1.47)</td>
</tr>
<tr>
<td>Overall intellectual function (WRAT-3)</td>
<td>106.22 (6.90)</td>
</tr>
</tbody>
</table>

*Serological status: (PSS subjects) 61% Ro positive, minor salivary gland biopsy positive 100%.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Correlations between cognitive tests and psychological symptoms in 19 subjects with PSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>$r$ (P-value)*</td>
</tr>
<tr>
<td>Verbal learning and memory (HVLT-total)</td>
<td>$-0.48$ ($0.0453$)</td>
</tr>
<tr>
<td>Psychomotor speed and sustained attention (Digit Symbol)</td>
<td>$-0.48$ ($0.0446$)</td>
</tr>
<tr>
<td>Working memory, attention (Trails B)</td>
<td>$-0.55$ ($0.0186$)</td>
</tr>
<tr>
<td>Concentration (Stroop C)</td>
<td>$-0.23$ ($0.3775$)</td>
</tr>
<tr>
<td>Verbal fluency (COWAT)</td>
<td>$-0.05$ ($0.8474$)</td>
</tr>
<tr>
<td>Verbal reasoning and executive function (Similarities)</td>
<td>$-0.01$ ($0.9270$)</td>
</tr>
<tr>
<td>Executive function (WCST)</td>
<td>$-0.07$ ($0.7976$)</td>
</tr>
</tbody>
</table>

Numbers in bold are significant. Test names are given in parentheses in column 1. $r$: Spearman’s correlation coefficient ($P$-value significant at 0.05). COWAT: Controlled Oral Word Association Test; WCST: Wisconsin Card Sorting Test.
cognitive decline between $-1.33$ and $-1.5$ on a single test. In the control group of 18 patients, three subjects had one test result equal to or less than $-1.5$. Three of the patients and one of the controls were impaired on tests of verbal memory. Two patients and one control were impaired on the test of verbal fluency (Fig. 2).

**Description of the MRI groups: impaired PSS, not-impaired PSS and control subjects**

The demographic and clinical characteristics of the six patients in the impaired group, seven patients in the not-impaired group and seven controls are shown in Table 3. Demographics (age and education) were similar between the three groups. Fatigue, sleep quality and pain ratings were similar in the impaired group compared with the not-impaired group. There was a tendency towards higher CES-D scores in the impaired vs not-impaired group ($P = 0.083$) and between the impaired and control group ($P = 0.102$ (Table 3).

The impaired and not-impaired PSS groups were similar in terms of extra-glandular manifestations. Abnormal fatigue, defined by an FSS $>3$ was present in the majority of both groups of PSS subjects: $4/7$ in the impaired group and $7/7$ in the not-impaired.

**Table 3** Comparison of demographics, psychological symptom severity and cognitive outcomes in six impaired PSS, seven not-impaired PSS and seven control subjects

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Impaired PSS</th>
<th>Not-impaired PSS</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (s.d.), years</td>
<td>52 (7.2)</td>
<td>52 (5.3)</td>
<td>57 (4.1)</td>
</tr>
<tr>
<td>Education, mean (s.d.), years</td>
<td>15 (2.7)</td>
<td>16 (1.2)</td>
<td>16 (2.0)</td>
</tr>
<tr>
<td>Symptoms, mean (s.d.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prof-M</td>
<td>4.7 (2.2)*</td>
<td>2.5 (1.5)</td>
<td>1.6 (0.4)</td>
</tr>
<tr>
<td>CES-D</td>
<td>20.0 (16.7)</td>
<td>7.4 (7.9)</td>
<td>5.1 (5.4)</td>
</tr>
<tr>
<td>FSS</td>
<td>5.9 (0.8)*</td>
<td>4.9 (1.6)**</td>
<td>3.2 (1.2)</td>
</tr>
<tr>
<td>BPI</td>
<td>3.2 (2.2)*</td>
<td>2.7 (2.2)**</td>
<td>0.6 (0.5)</td>
</tr>
<tr>
<td>PSQI</td>
<td>9.7 (5.6)*</td>
<td>7.4 (3.0)**</td>
<td>4.8 (3.5)</td>
</tr>
<tr>
<td>Cognitive tests, mean Z-score (s.d.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HVLT per cent retained (verbal memory)</td>
<td>$-0.48$ (1.36)</td>
<td>$0.46$ (0.79)</td>
<td>$0.21$ (1.07)</td>
</tr>
<tr>
<td>COWAT (verbal fluency)</td>
<td>$-1.02$ (1.19)</td>
<td>$-0.28$ (0.66)</td>
<td>$0.07$ (0.80)</td>
</tr>
<tr>
<td>Digit symbol (attention and speed)</td>
<td>$0.17$ (1.19)</td>
<td>$0.81$ (0.57)</td>
<td>$0.71$ (0.52)</td>
</tr>
<tr>
<td>Similarities (verbal reasoning)</td>
<td>$0.56$ (0.46)*</td>
<td>$1.62$ (0.85)</td>
<td>$1.38$ (0.85)</td>
</tr>
<tr>
<td>WCST (executive function)</td>
<td>$-0.30$ (0.80)</td>
<td>$0.16$ (0.40)</td>
<td>$0.13$ (0.74)</td>
</tr>
</tbody>
</table>

* $P \leq 0.05$ impaired vs controls. ** $P \leq 0.05$ not-impaired vs control. COWAT: Controlled Oral Word Association Test; WCST: Wisconsin Card Sorting Test.
not-impaired group and 5/6 in the impaired group. There were two PSS subjects (both in the not-impaired group) who had a history of cutaneous vasculitis. A history of recurrent swelling of the parotid glands was reported by 8/13 PSS subjects: four in the impaired group and four in the not-impaired group. A history of migraines was reported by 2/6 of the not-impaired and 3/6 of the impaired PSS subjects and none of the controls. FM was reported by 2/7 not-impaired and 1/6 impaired subjects.

There were no significant differences (P-value by Fischer’s exact test) between impaired and not-impaired subjects regarding symptoms: poor sleep quality (PSQI > 5) was frequently reported by PSS subjects (5/7 not-impaired and 5/6 impaired) and by 3/6 controls; moderate to severe pain (BPI > 4) was reported by one-third of both patient groups and none of the controls. Depression as indicated by the CES-D > 16 was present in 3/6 of the impaired group compared with 1/7 of the not-impaired (P = 0.26) and 1/7 of the controls. Medication use for depression, pain and sleep was similar in patient groups and controls. Medication for Sjögren’s such as cevimeline, topical ciclosporin eyedrops and HCQ were commonly used in the patient group and were used by none of the controls. Although treatment effects, such as use of corticosteroids, could modulate DTI parameters, there was no difference in steroid medication use by the PSS subjects in the two groups. One PSS subject was taking prednisone (intermittently for asthma). One PSS subject was taking lipid-lowering medication (in the not-impaired group) and three PSS subjects were taking thyroid supplement (two in the not-impaired group, one in the impaired group).

### MRI results

Neither was there any evidence of decreased cortical thickness in the FreeSurfer ROIs in any group after correction for multiple comparisons, nor was there evidence for reduced cortical thickness in the lobar analysis. Brain parenchymal fraction and ventricular volume were not significantly different between groups. Small WMHs in the periventricular WM were common, but there was no difference in WM lesion load or lesion severity between patients and controls.

DTI revealed significant differences between groups in the inferior frontal WM, with impaired PSS subjects significantly different from not-impaired PSS and controls. Lower FA and higher MD reflecting disruption of normal brain tissue microstructure were observed in the impaired PSS group. Three-way ANOVA revealed higher MD (impaired > not-impaired > controls, P = 0.004) and lower FA (impaired < not-impaired < controls, P = 0.018) in PSS subjects relative to controls in the INF, while in the SPF trend level differences were observed in MD (impaired > not-impaired = controls, P = 0.054) and FA (impaired < not-impaired = controls, P = 0.067). Post hoc analysis of the INF data revealed significant differences between controls and impaired PSS in FA (P = 0.049) and MD (P = 0.003) as well as between controls and not-impaired PSS in FA (P = 0.049) and MD (P = 0.046).

There were significant correlations in the patient group between verbal memory (HVLT-total) and WM FA localized to the INF. Depression and subjective cognitive function were correlated with inferior frontal FA and MD in the PSS subjects (Table 4). The correlation between subjective cognitive function as measured by the Prof-M and inferior frontal FA shown in Fig. 3 was significant in the patients (r = −0.72, P = 0.008) and not in the controls (r = 0.11).

### Discussion

The major finding of this exploratory study is that PSS subjects with mild cognitive dysfunction had abnormal

<table>
<thead>
<tr>
<th>DTI parameter</th>
<th>r (P-value)</th>
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<tbody>
<tr>
<td>Depression (CES-D)</td>
<td>FA -0.53 (0.0631)</td>
</tr>
<tr>
<td></td>
<td>MD 0.78 (0.0008)</td>
</tr>
<tr>
<td>Subjective cognitive function (Prof-M)</td>
<td>FA -0.72 (0.0064)</td>
</tr>
<tr>
<td></td>
<td>MD 0.75 (0.0030)</td>
</tr>
<tr>
<td>Verbal learning (HVLT-total)</td>
<td>FA 0.65 (0.0150)</td>
</tr>
<tr>
<td></td>
<td>MD -0.40 (0.1817)</td>
</tr>
</tbody>
</table>

**Table 4** Correlation of symptoms and cognitive abilities with DTI inferior frontal plane parameters in 13 patients with PSS.

**Fig. 3** Scatterplot of subjective cognitive function (Prof-M) and inferior frontal FA in 13 patients and 7 controls.

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Disruption of brain white matter in primary SS
DTI findings localized to the INF. While previous DTI studies have demonstrated abnormalities in a variety of neuropsychiatric disorders including SLE and geriatric depression, to our knowledge, this is the first study to apply DTI methodology to assess the integrity of WM and to address the correlation between DTI findings and neuropsychological measures in PSS [21, 22]. WM microstructural alterations, detectable with DTI, may reflect abnormalities in the myelin sheath or directional coherence of fibre tracts (or both) [23]. We found significantly lower FA and higher MD values in the impaired PSS group compared with the not-impaired subjects and controls suggesting that injury to inferior frontal WM is associated with the pathological process leading to mild cognitive impairment in PSS. The comparison with healthy controls suggests that this process is not attributable to age-related changes.

Previous studies in patients with SLE have shown alterations in normal WM in patients with SLE suggesting that DTI may be useful in early diagnosis of neuropsychiatric lupus (NPSLE). Increased general diffusivity in brain parenchyma compared with normal controls has been demonstrated in patients with NPSLE suggesting subtle and widespread damage [24]. Our study, in contrast, demonstrates the absence of increased general diffusivity, as well as the absence of both volume loss and reduced cortical thickness in any brain region, suggesting that subtle widespread damage is not likely in the majority of SS patients who do not have clinical CNS involvement apart from mild cognitive symptoms.

Mild impairment in cognitive efficiency and difficulties with verbal memory consistent with a subcortical type of cognitive dysfunction have been reported previously in unselected PSS patients defined by current American European Consensus Group criteria [25]. Previous studies have not clarified the contribution of depression to cognitive dysfunction [26–28]. There was a trend towards more psychological distress, as reflected by higher CES-D scores in the PSS subjects with impairment in our study. The correlations we observed between mood, subjective cognitive function, attention and memory are consistent with data indicating that mood and cognition are inter-related. In future studies of PSS, to determine the strength and specificity of the relationship between MRI findings, cognition and mood, it will be important to assess whether cognitive deficits are greater in PSS patients with depression.

A relationship between depression and cognitive deficits has been demonstrated in previous studies of late life depression and correlation has been found between cognitive deficits and prefrontal WM abnormalities in patients with HIV [29, 30]. Additional data are needed to clarify the relationship between affective disorder and the processes leading to cognitive dysfunction and frontal WM abnormality. The INF WM differences we observed could arise through remodelling of neural circuits secondary to primary affective disorder, or both depressed mood and learning deficits could be modulated by the indirect effects of pain, disease-related stressors affecting the individual’s ability to cope or the direct effects of an underlying CNS disorder in PSS.

Our 19 PSS subjects were high-functioning individuals. However, over half our PSS patients reported, as do many Sjögren’s patients, problems with learning and processing of information. While group differences in cognitive performance in our PSS subjects were small compared with the control group, perceived cognitive dysfunction among the patients did reflect objective deficits in verbal learning and attention. The present study does support the conclusion that perceived difficulties in cognitive performance among PSS patients have a neuroanatomic substrate. Given the association of DTI WM abnormalities with cognitive deficit, it will be important to address in future studies whether PSS patients with cognitive dysfunction and depression progress to more serious cognitive impairment over time. DTI may also prove useful in studies designed to address the neurobiological substrate of cognitive disorders and depression. Interestingly, DTI abnormalities in WM that appear normal have been described previously in MS and in SLE [31, 32]. In MS, abnormalities in connectivity measurable by DTI were correlated with fatigue and disability suggesting that microstructural evidence of damage to WM has important clinical implications [33].

Our results were not consistent with previous conventional MRI studies, which indicated higher WM lesion load in PSS [4, 5]. However, our results are consistent with the data in a recent large controlled study of 65 PSS patients compared with age-matched healthy volunteers in which there was no difference between PSS and controls in WM lesion load [34]. Although our study was not powered to detect small differences in WM lesions between patients with PSS and controls, the absence of greater WM lesions in this study, despite the excellent lesion contrast in FLAIR imaging, is also consistent with data from Akasbi et al. [35]. MS-like WM lesions were found by conventional MRI in only 3% of PSS subjects (mean age 54 years) in the study by Akasbi et al. [35] suggesting a very low prevalence of WM lesions in unselected PSS patients.

The WM abnormalities that we detected are not specific for vascular pathology and could reflect demyelination or neuronal dysfunction mediated by altered dendrite morphology rather than ischaemic tissue damage. The pathogenesis of CNS disorders in PSS is likely to be heterogeneous. In a single case report of CNS Sjögren’s and severe dementia, histopathological data were interpreted as consistent with cerebral small vessel vasculopathy [36]. However, reports of CNS vasculitis and severe cognitive impairment attributable to PSS are very rare [36–38]. In this study, the absence of both a difference in WM lesion load and a difference in brain volume between groups, suggests that vasculopathy was not the aetiology of the mild cognitive dysfunction in our subjects.

An alternative hypothesis to that of vascular injury is suggested by data that support a role for inflammatory cytokines in the regulation of stress responses and the symptoms of fatigue and learning difficulties associated with sickness behaviour in animals [39, 40]. Stress-
induced abnormalities in cytokine signalling could also play a role in WM pathology in PSS. Changes in neural architecture, including observation of abnormal dendrite morphology, have been observed in animals subjected to experimental stress [41]. Chronic stress causes loss of dendrites in the prefrontal cortex associated with deficits in attention and working memory as well as memory consolidation. While brain cytokine networks provide trophic support to neurons under physiological conditions, excessive or prolonged activation of the CNS cytokine network induces apoptosis of astrocytes and oligodendrocytes resulting in altered neuronal interaction and cognitive function [41].

Interestingly, Harboe et al. [42] found that higher levels of the cerebrospinal fluid inflammatory cytokine IL-1Ra were associated with fatigue in subjects with PSS. Their study suggests the possibility that intra-cerebral production of inflammatory cytokines could play a role in fatigue and cognitive symptoms in PSS. Psychosocial stress is capable of stimulating inflammatory signalling molecules; moreover, cytokine and chemokine activity in the CNS have been implicated in the WM defects observed in demyelinating disease, brain injury and mental disorders [43, 44]. Additional data are needed on the role played by intra-cerebral cytokine production in the regulation of neural networks involved in modulation of emotional responses and memory in PSS.

Recent neuroimaging studies have demonstrated that neural networks of the medial prefrontal cortex and closely related limbic areas regulate mood and emotional expression [45]. The inferior frontal cortex is known to have a role in memory and attention, and particularly to be involved with the inhibition of negative emotion on memory processes [41]. Functional MRI data have demonstrated the role of the inferior frontal cortex in controlling the impact of task-irrelevant emotional distraction on memory performance [46]. The DTI results in this study are consistent with neurobiological models of chronic stress which posit that a defect in frontal connectivity is associated with cognitive and affective disorders.

Psychological stress impairs higher order prefrontal cortex abilities such as working memory and attention regulation [47–49]. A relationship between deficits in memory and attention, reduced ability to regulate the impact of negative emotion and alteration in brain architecture in the inferior frontal cortex in PSS remains speculative and should be addressed in future studies.

Our study has several limitations. This study was exploratory with a small sample size. We recruited patients from a large community-based PSS cohort who indicated their interest in participating, which may have resulted in oversampling of PSS subjects with perceived cognitive deficits. Neither was this study designed to assess the range of cognitive disorders among PSS patients, nor did we have sufficient power to assess the contribution of affective disorder to cognitive dysfunction among our patients. Longitudinal studies are needed to better understand the contribution of altered pain sensitivity, anxiety and depression to cognitive symptoms in PSS.

Conclusion
We found WM abnormalities in the INF, which were associated with cognitive deficits and correlated with both the severity of cognitive symptoms and objectively measured cognitive performance in PSS. If our observations are confirmed in future studies of PSS, DTI could provide clues to the pathogenesis of the subtle cognitive dysfunction associated with PSS. Additional research is warranted to evaluate the relationships between microstructural WM abnormalities, negative emotions and cognitive dysfunction in PSS.

Rheumatology key messages

- Deficits in memory and attention correlated with subjective cognitive function in PSS patients.
- Inferior frontal WM abnormalities on DTI were detected in PSS patients with mild cognitive impairment.

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Supplementary data
Supplementary data are available at Rheumatology Online.

References