Cognitive disorders and brain MRI correlations in primary Sjögren's syndrome: unlocking the secret of cognitive symptoms

Little is known concerning the mechanisms of cognitive impairment in primary Sjögren's syndrome. However, recent technological advances have made detailed brain imaging studies possible, which have the potential to estimate more precisely the prevalence of CNS lesions in primary Sjögren's syndrome and to provide information on the severity and mechanisms of CNS tissue damage. Novel neuroimaging protocols can provide a window into cerebral organization that is not accessible with conventional imaging methods. Investigation of cognitive function with state of the art high-resolution structural and functional brain MRI could illuminate the mechanisms contributing to subtle cognitive dysfunction and guide the development of specific therapeutic approaches.

KEYWORDS: brain MRI ■ cognitive disorders ■ mood ■ Sjögren's syndrome

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Psychiatric disorder & cognitive dysfunction in primary Sjögren's syndrome: challenges in diagnosis & therapy

Sjögren's syndrome (SS) is a systemic autoimmune disorder that causes inflammation and dysfunction of the exocrine glands. Approximately one half of the cases are associated with another connective tissue disorder and are classified as secondary according to current classification criteria [1]. Primary SS (PSS) has a worldwide prevalence of 0.1–0.6% [2–4]. The prevalence is highest in those over the age of 55 years and is sevenfold higher in those aged 71–74 years compared with adults aged 40–44 years [2,3]. Based on Olmsted County, Minnesota data and the 2005 US Census bureau population prevalence estimates, there are between 0.4 and 3.1 million persons with PSS in the USA [2]. The female gender predilection is exceptional. Women, predominantly those in the perimenopausal age group, comprise over 95% of most PSS cohorts. While the cardinal symptoms are dryness in the eyes and mouth, anxiety and depression are also frequently associated with SS and cognitive dysfunction is a common complaint [5–9].

Persistent abnormal fatigue is also extremely common among patients with PSS. Fatigue contributes to decreased quality of life and affects approximately 70% of PSS patients [10]. Factors associated with fatigue include sleep disorder, pain and depression. Because the clinical presentation frequently overlaps with fibromyalgia (FM), a detailed physical and neurologic exam ination as well as an evaluation for oral and ocular dryness, confirmatory histopathology on biopsy of salivary gland tissue or positive serologic tests are required to distinguish patients with PSS who are defined as meeting current American European Consensus Group criteria [1] from those with primary FM. FM is a nonautoimmune condition characterized by tender points and chronic widespread pain alongside fatigue, cognitive symptoms and frequently mild oral and ocular dryness. While primary FM occurs in approximately 1% of the general population, approximately 20% of patients with PSS or with systemic lupus erythematosus (SLE) have coexisting FM [11–13]. The cause of the increased incidence of FM in patients with PSS and SLE is unknown.

Both FM and depression are important confounders of cognitive function in PSS. Cognitive disorders can arise from depression; however, both affective disorder and cognitive dysfunction could be immune mediated, and hence PSS patients with affective disorder and cognitive complaints present vexing therapeutic dilemmas. In the majority of studies describing neurologic involvement, patients with mild cognitive dysfunction were not classified as CNS SS, hence the impact of subtle cognitive impairment, and the relationship of mild cognitive dysfunction to pathologic processes specific to PSS, have not been adequately investigated [14–17]. Lack of consensus regarding the criteria for diagnosis of nervous system disorders associated with PSS has impeded development of effective therapeutic approaches.

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Inter-relationship of mood & cognition in PSS

The prevalence of depression is approximately 30% in most PSS cohorts [18,19]. In a recent large survey of PSS patients and healthy nonautoimmune peers in the USA, the prevalence of depression was 37% in patients with PSS compared with 12% in controls. PSS patients reported more frequent cognitive difficulties, as well as greater fatigue, pain and reduced function in all eight domains of the SF-36 [5]. Patients who were unemployed owing to disability reported significantly more pain, depression and cognitive dysfunction than those who were employed [5]. Similarly, in SLE, even mild impairment appears to interfere with employment and quality of life in general [20]. While substantial evidence suggests a role played by fatigue and depression in reduced health quality in PSS, data on the neuropsychological function of patients with PSS is limited and interpretation of data from different centers is complicated by lack of agreement on a standardized cognitive evaluation for SS patients [14,21–24].

The first systematic prospective study of neurologic manifestations of PSS was published in 1985 [18]. Cognitive testing of 40 patients with PSS demonstrated deficits in attention and memory impairment suggestive of subcortical dementia [18]. Interestingly, depression and cognitive impairment were found much more frequently in PSS patients who had neurological deficits, suggesting that there was an underlying neuropathologic basis for their mood disorder. Referral bias complicates the interpretation of these findings, however, as the patients were drawn from a tertiary center recognized for expertise in neurologic SS. The results of a recent population-based study in Norway support a high frequency of cognitive dysfunction in association with PSS [9]. Among unselected PSS patients referred to a university center, the prevalence of mild cognitive impairment was 22%, moderate impairment 21% and severe cognitive impairment 6% in the Norwegian study. The prevalence of cognitive dysfunction in patients with PSS and patients with SLE was identical [9].

Pattern of cognitive impairment suggests frontal–subcortical brain involvement in PSS

Despite the impact of psychological distress and cognitive symptoms on quality of life in PSS, much remains to be learned regarding the prevalence and mechanisms of neuropsychological features in PSS. Short attention span, poor concentration, memory deficits and cognitive slowness are described in PSS (Table 1). PSS patients are highly sensitive to subtle attention and recall deficits, and self-reported cognitive function correlates moderately with objective performance on tests of verbal memory [25]. Detailed neuropsychological evaluation has demonstrated deficits in verbal fluency, verbal reasoning, psychomotor processing and visual memory as well as tests of executive function in PSS patients compared with age-matched controls [18,21–23,25]. The pattern of cognitive deficits suggests frontal–subcortical brain involvement, as opposed to the cortical pattern of decline associated with Alzheimer's disease.

Neuroimaging abnormalities & cognitive function: how is the brain altered in PSS?

In an early brain MRI study in which subjects with PSS were compared with age-matched controls, abnormal results on MRI were reported in 75% of patients with PSS who had active CNS disease, defined as psychiatric dysfunction, or cognitive dysfunction, with or without focal neurologic deficits [26]. The most common MRI finding was small (5–10 mm) white matter hyperintensities (WMH), small distinct areas of increased signal intensity observed on T2-weighted images [26]. As is the case in a high percentage of neurologically impaired individuals, lesions in PSS are most often detected exclusively as WMH, although some PSS patients present with both deep cortical gray matter lesions and WMH [26–29]. Involvement of basal ganglia is also found in PSS, whereas posterior fossa lesions are rare [30].

The histopathological findings associated with WMH are variable. A variety of pathologic processes including ischemia, which results in microinfarcts, and inflammation, which leads to demyelination and gliosis, have a uniform appearance. The severity of the WMH lesion load can be assessed semiquantitatively by assigning a score, which takes into account the spatial localization, size and number of lesions to measure WMH burden [31]. In SLE, lesion load and global brain atrophy are correlated with cognitive impairment, particularly in patients with a history of neuropsychiatric involvement [32]. In subjects with PSS, however, the significance of WMH seen on conventional MRI T2-weighted images or fluid-attenuated inversion recovery scans is less clear.

Two small studies demonstrated a statistically significant increase in WMH in PSS patients compared with age-matched healthy controls, although the patient populations examined were relatively small [28,33]. The precise relationship of

Table 1. Evaluation of cognitive disorders and MRI correlations in primary Sjögren's syndrome†.

Study	Study design	Country	Cognitive function	Psychological symptoms	Results of imaging	Ref.
Segal *et al.* (2010)	13 PSS subjects compared with 7 controls	USA	Deficits in verbal reasoning and psychomotor response	Depression in 37% of PSS subjects versus 14% of controls	DTI abnormality localized to the inferior frontal lobe WM correlated with cognitive symptoms and verbal memory	[25]
Le Guern *et al.* (2010)	10 PSS subjects prospectively evaluated and compared with 10 controls	France	Deficits in visual spatial and executive function	None, depressed subjects were excluded	MRI: no difference in lesion load (WMH) SPECT: hypoperfusion of left hemisphere cortical areas	[23]
Massara *et al.* (2010)	424 PSS subjects retrospectively evaluated, uncontrolled	Italy	6/424 (1.4%) recurrent encephalopathy	Excluded depression and mild cognitive complaints	Multiple focal perfusion defects and diffuse WM damage	[17]
Harboe *et al.* (2009)	68 unselected PSS subjects prospectively selected compared with 68 controls	Norway	24% mild, 21% moderate, 6% severe cognitive dysfunction	Mood disorders in 33% of patients	Increase in WM lesion score in PSS subjects with cognitive dysfunction	[34]
Delalande *et al.* (2004)	82 PSS subjects retrospectively evaluated, uncontrolled (referrals to neurology)	France	9/82 (11%) severe cognitive dysfunction and 'subcortical dementia'	Details not given	Normal conventional MRI in patients with cognitive dysfunction	[14]
Mataro *et al.* (2003)	15 PSS subjects prospectively evaluated compared with 15 subjects with migraine	Spain	47% deficits in three or more tests; primarily memory and frontal lobe function	Higher levels of fatigue and depression in PSS subjects	Psychomotor speed correlated with WM lesion load and with fatigue score, ventricular volume correlated with attention	[35]
Lafitte *et al.* (2001)	36 subjects prospectively evaluated, uncontrolled	France	8/36 (22%) cognitive dysfunction	No patients experienced depression	No correlation, normal conventional MRI	[22]

†Selection criteria: studies reporting neuropsychological status and MRI findings in PSS. A Medline search was performed that included studies published in English between 2001 and the present day. Search terms included: MRI and Sjögren's syndrome, or cognitive disorders and SS, or CNS and SS. A total of 201 were reviewed for relevance. Studies were selected if they included an assessment of cognitive function and used current diagnostic criteria for primary Sjögren's (AECG 2002) or specified that patients were classified as meeting the definition of PSS with either anti-SSA/SSB seropositivity or minor salivary gland biopsy with a positive focus score of at least 1. Case series as well as observational cohort studies were included in the list.
DTI: Diffusion tensor imaging; PSS: Primary Sjögren's syndrome; SS: Sjögren's syndrome; WM: White matter; WMH: White matter hyperintensities.

small focal T2 hyperintense lesions detected on MRI to the evolution of gradual cognitive decline is difficult to define owing to the prevalence of white matter lesions in otherwise healthy subjects, and the correlation of lesion load with aging. WMH frequency increases with both age and the presence of cerebrovascular risk factors; hence, a large sample size is required in order to provide adequate power. In the largest controlled study to date, Harboe *et al.* imaged 68 unselected PSS patients and 68 controls [34]. No difference in total or in regional WMH scores between PSS patients and healthy subjects was observed; however, even this study may have been inadequately powered to detect a difference. WMH load was, however, higher in PSS patients with cognitive dysfunction, as is the case in healthy elderly people [34].

Very few studies have investigated the correlation of cerebral imaging results with cognitive abilities in PSS (Table 1). In a small study in which 15 patients with PSS were compared with 15 subjects who suffer from migraines, Mataro found a high prevalence of ventricular dilatation and cortical atrophy in both patient groups [35]. Differences in the presence and severity of signal hyperintensities between SS patients and the migraine group did not reach statistical significance. Lesion severity was correlated with psychomotor speed and with fatigue in both PSS and migraine subjects. Likewise, a significant relationship was also observed between ventricular volume and attention in both patient groups. Unfortunately, the specificity of these changes is unknown, as healthy controls were not included in this study.

Conventional brain MRI scans can be very helpful in the evaluation of severe CNS SS, particularly when cognitive symptoms are associated with focal neurologic deficits. While early multiple sclerosis (MS) can be difficult to distinguish from PSS on clinical grounds, brain MRI can be helpful in distinguishing MS from PSS, as the pattern of involvement in MS, including the presence of posterior fossa lesions, may be somewhat different [30]. Conventional MRI is especially useful for diagnosis of CNS vasculitis [36], a rare manifestation of PSS presenting as cognitive dysfunction alone or as multiple focal neurologic deficits [37]. MRI is also essential in the evaluation of SS patients with myelitis or optic neuritis in which neuromyelitis optica is a consideration [38]. Nevertheless, conventional brain MRI has limited sensitivity and specificity, as patients with mild cognitive symptoms often have normal MRI scans that often provide little clinically relevant information.

Multimodality neuroimaging reveals association of gray & white matter damage in MS & SLE

As is the case in PSS, cognitive deficits are reported in many patients with SLE who have no history of overt neuropsychiatric involvement and normal conventional brain MRI scans [39]. Metabolic abnormalities detectable with magnetic resonance spectroscopy (MRS) can reflect early white matter involvement in SLE when routine MRI findings are normal [40]. Cognitive dysfunction in SLE is also associated with selective gray matter abnormalities detectable with magnetization transfer imaging (MTI) [41]. Application of multimodality imaging with MTI and MR spectroscopy to study cognitive function has not yet been reported in PSS. In the future, the application of more sensitive techniques such as MRS and multimodality imaging with MTI and diffusion tensor imaging (DTI) could extend what is known about the neural substrate of cognitive symptoms in PSS.

Brain imaging studies of MS and SLE have also suggested a neural basis for the symptom of fatigue. Lesion load is correlated with fatigue in SLE [42]. The severity of fatigue was correlated with widespread axonal dysfunction in MS in a study that examined axonal damage using MR spectroscopy [43], as well as with both T2 lesion load and frontal gray matter atrophy, suggesting that fatigue is associated with disruption of brain networks involved in attention and cognitive processes in MS [44]. Thus, with the arrival of novel techniques such as voxel-based morphometry, DTI, MTI and MRS, there are more precise measures to assess the neural processes associated with cognitive dysfunction, fatigue and affective disorders in PSS. As the field develops and optimal methods to acquire and process the data are determined, these quantitative imaging techniques are likely to provide more robust correlations with clinical disability than has been possible with conventional imaging (Table 2).

DTI reveals brain white matter microarchitecture damage in PSS subjects with cognitive symptoms

Diffusion tensor imaging is a special form of diffusion-weighted imaging that allows the assessment of white matter integrity and the organization of white matter tracts [45]. Barriers such as cell membranes, cellular structures and myelin restrict water diffusion and, in highly ordered white matter tissue, diffusion occurs more readily in the direction of the axons with

Table 2. Comparison of conventional brain MRI with quantitative structural and functional MRI methods.

Technique	Advantages	Limitations
Conventional MRI		
T2-weighted and FLAIR scans	Sensitive detection of small lesions on WMH and calibration of the degree and distribution of brain tissue damage	Lack of specificity Often poor correlation between MRI lesions and clinical features
Nonconventional MRI		
MTI	Increased specificity for myelin, may be helpful in differentiating ischemic from demyelinating lesions especially when utilized in combination with other techniques	Comparison across studies can be difficult owing to complexity of the mathematical modeling and lack of standardized protocols
DTI	Provides a measure of WM connectivity, organization of WM tracts and abnormalities in brain microarchitecture potentially useful for diagnosis and evaluation of treatment response	Spatial resolution large compared with the intrinsic size of the structures (axons and even some fiber bundles). Optimal methods to acquire and process data must be refined and validated
MRS	Alterations in metabolite concentration in tissue may predict future damage, particularly useful in detecting neuronal dysfunction	Low signal-to-noise ratio results in limited brain coverage
fMRI	Allows identification of areas of increased or decreased neuronal activity or functional connectivity	More data are needed to assess and optimize signal-to-noise ratio and study design

DTI: Diffusion tensor imaging; FLAIR: Fluid attenuated inversion recovery; fMRI: Functional MRI; MRS: Magnetic resonance spectroscopy; MTI: Magnetization transfer imaging; WM: White matter; WMH: White matter hyperintensities.

comparatively little diffusion in the plane perpendicular to the axons. The technique is called DTI because a mathematical description of the orientation and magnitude of diffusion, known as a diffusion tensor, is computed for each voxel. White matter microstructure alterations detected with DTI may reflect abnormalities in axonal size, the myelin sheath and/or directional coherence of fiber tracts.

To date, DTI has been used to characterize normal brain development as well as aging brain development, and has demonstrated potential usefulness as a tool to assess the degree of axonal injury in a variety of brain disorders [46–48]. In patients with depression, structural abnormalities have been detected in areas of the brain involved in emotional regulation and memory processing including the hippocampus, amygdala, basal ganglia and prefrontal cortex. In FM, a neural basis for fatigue was suggested by the finding that fatigue severity was correlated with abnormal DTI measurements localized to the left superior frontal and left anterior cingulate gyrus [49]. Likewise, PSS fatigue and pain severity were correlated with injury to the left anterior cingulate cortex [50]. Interestingly, the areas of the brain mapped to information processing and attention to information from the inside world of an individual include the superior frontal gyrus and cingulate, indicating the possibility that structural changes in these brain areas could lead to increased attention to symptoms of fatigue and pain [49].

Diffusion tensor imaging has been used to search for clues to the mechanisms of cognitive dysfunction in multiple sclerosis and systemic lupus [40,51–54]. DTI is more sensitive than conventional MRI and quantitative measurements can be used in detecting early signs of SLE [51]. DTI combined with detailed neuropsychiatric assessment could also provide insight into the pathophysiologic processes underlying cognitive dysfunction in PSS. A recent exploratory study in PSS suggested that abnormal white matter connectivity is associated with cognitive impairment in PSS subjects with no history of CNS disorders other than subjective memory loss and concentration difficulties [25]. White matter abnormalities localized to the inferior frontal region were detected, which were correlated with both the severity of cognitive symptoms and objectively measured verbal memory in PSS.

Subtle deficits on tests of verbal reasoning, verbal fluency, psychomotor speed, verbal memory and executive function were associated with abnormal DTI metrics in the frontal lobe

white matter in the PSS cognitively impaired group relative to nonimpaired PSS subjects and to healthy age-matched controls, while there was no evidence of volume loss or increased WMH lesion load in this exploratory study [25]. Cognitive deficits and white matter abnormality detected in these PSS subjects were not age related; however, more data from appropriate control subjects and larger sample size is needed to assess the specificity of the pathologic process.

Putative mechanisms of neuronal damage in PSS

Vasculopathy

Very limited histopathologic data and data demonstrating cerebral hypoperfusion have been interpreted to indicate that small vessel vasculopathy contributes to the pathophysiologic processes leading to cognitive symptoms in PSS [17,23,55]. Small vessel disease can result in impairment of attention and executive function (typically with preservation of memory) and result in subtle cognitive dysfunction. However, hypoperfusion is nonspecific and is detectable in less than 60% of PSS patients with CNS involvement [56].

Role of autoantibodies & inflammatory cytokines in mediating cognitive disorders in PSS

In PSS, a role for cholinergic receptor antibody in cognitive dysfunction has been envisioned [57]. It is intriguing that areas of the brain involved in regulating emotion are rich in cholinergic receptors. In a single study, anticerebral IgG antibodies that negatively inhibited the function of acetylcholine receptors of cerebral frontal cortical membranes were present in 40% of PSS patients, suggesting that autoantibodies targeting acetylcholine receptors might have a role in the pathogenesis of cognitive dysfunction present in some PSS patients [58]. Modulation of brain cholinergic receptors and neuron function by intrathecal antibody, while speculative at present, is a potential mechanism of cognitive dysfunction, which could account for the relapsing course and steroid responsiveness described recently in patients with PSS and encephalopathy [17].

Frontal lobe white matter abnormality in PSS is consistent with current theories that suggest a relationship between cognition, affective disorders and frontal connectivity. The prefrontal cortex is particularly sensitive to stress exposure. The effects of chronic and acute stress and the alterations in cytokine networks are presumed to be quite different. Inflammatory cytokines (IL-1, IL-6 and TNF-α) provide trophic support to neurons under physiologic conditions and contribute to normal cognitive function in laboratory animals, whereas excessive or prolonged activation of CNS cytokine networks induces apoptosis in relevant cell types (astrocytes and oligodendrocytes) and dysregulates neuronal interactions and function [59,60]. Psychosocial stress induces cytokine-mediated remodeling of neural circuitry [61,62]. Cytokines are thought to play a role in illness behavior in animals as well as in a wide variety of neurologic and psychiatric disorders in humans [61–64]. Changes in neural architecture, including the observation of abnormal dendrite morphology, have been observed in animals subjected to experimental stress [65]. A study by Harboe *et al.* demonstrates the association of fatigue with increased levels of IL-1Ra in the cerebrospinal fluid consistent with the hypothesis that inflammatory cytokines contribute to neuronal dysfunction and fatigue in PSS [63]. Hence, an attractive hypothesis for future study is that WM DTI abnormality in PSS observed in the inferior frontal cortical region is the result of stress-induced cytokine-mediated remodeling of neural architecture.

Resting state functional connectivity: alteration of spontaneous neural activity in depression & FM

The development of functional MRI (fMRI), beginning in the 1980s, has facilitated neuroscience research aimed at elucidating links between mental processes and behavior. Task-based fMRI has been used to identify brain areas associated with the processing of a variety of different types of stimuli and the performance of various cognitive tasks. As an example, fMRI demonstrated the abnormal activation of the cortical pain matrix in patients with FM [66,67]. The role of the inferior frontal cortex in controlling the impact of task-irrelevant emotional distraction on memory performance has also been demonstrated using fMRI [68]. However, the application of task-based fMRI to the study of disease states has been slowed by several inherent problems. Task-based stimuli often allow multiple interpretations of the differences observed and acquisition of information during task activation studies is frequently limited by design issues, as well as poor signal-to-noise ratio.

Recently, resting state fMRI (rs-fMRI) techniques have shown great promise for expanding the application of fMRI to the study of clinical populations. rs-fMRI is a method for evaluating regional brain interactions when a subject is at

rest (i.e., not performing a specific task). During the fMRI scan, the subject is asked to remain awake but still, and not to think about anything in particular. Surprisingly, consistent patterns of functional connectivity are observed in resting state scans across subjects. Coherent, low-frequency blood–oxygen level-dependent (BOLD) signal fluctuations with specific spatial patterns are observed to be temporally correlated across the brain. Signal variations are of neuronal origin and correspond to functionally related regions that characterize the human brain in the absence of deliberate or externally stimulated neuronal activity. Intrinsic connectivity involves information transfer between disparate brain regions, comprising known primary sensory, executive and associative networks [69]. For the investigation of group differences between patients and controls, or for monitoring of treatment effects or following disease progression, the evaluation of rs-fMRI correlation patterns has significant advantages over the traditional task-based fMRI protocols [70].

Two important intrinsic connectivity networks indentified in the human brain are the default mode network (DMN) and the executive attention network. The DMN is a constellation of brain regions thought to be engaged in self-referential thinking that are 'deactivated' during various externally focused task conditions. The application of rs-fMRI to the study of cognitive function is being explored in PSS. We have acquired resting state data on a cohort of patients with PSS and age- and gender-matched healthy controls and have applied the technique of independent component analysis to these data to study the DMN. The resulting spatial maps are shown in Figure 1.

Intrinsic brain connectivity is altered by chronic pain

A growing body of evidence supports the view that chronic pain syndromes, including FM, are accompanied by altered brain neurophysiology [71]. In a recent rs-fMRI study of FM, elevated intrinsic brain connectivity in multiple networks was correlated with spontaneous pain [67]. This study suggests that rs-fMRI might be used to identify cortical activation pathways associated with different types of pain in PSS, including both neuropathic and FM pain, which can be difficult to distinguish clinically. The effect of pain on networks involved in attention and working (short-term memory) could also be evaluated.

DMN & depression: overactivity of emotional regulation within the DMN

Three different brain networks – the cognitive control network, the DMN and the affective network (involved in mood and regulation of visceral functions) – were investigated in depressed subjects compared with controls. The discovery that these three networks are linked

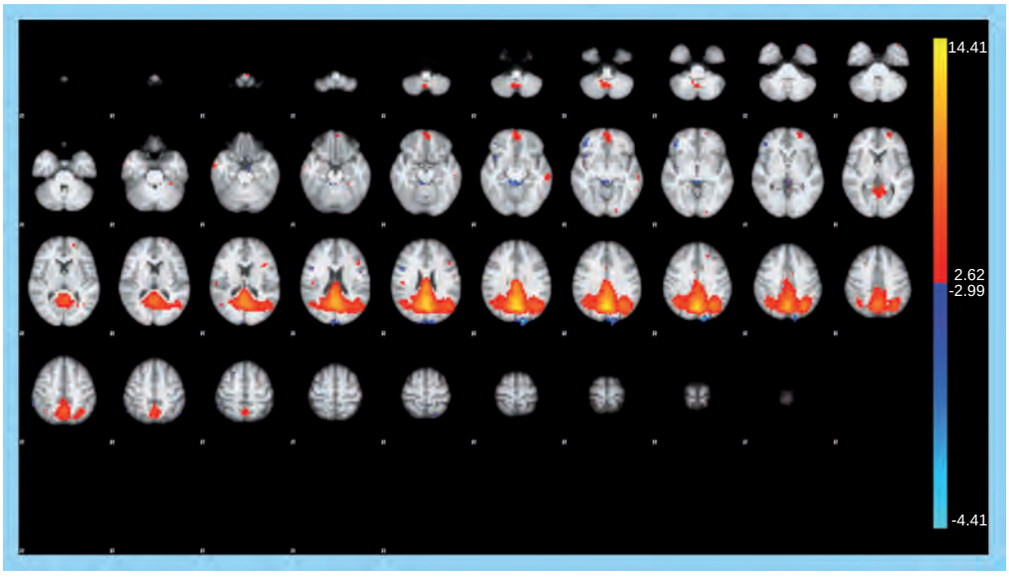

Figure 1. Group independent component analysis demonstrating areas of regional connectivity in 13 primary Sjögren's syndrome patients and seven controls for the default mode network. Brain regions shown in color identify large-scale patterns of functional connectivity in the study group. Regions from red to yellow represent increasing connectivity, while regions in blue represent voxels with negative correlation to the component.

together in patients with depression provides a potential mechanism to explain some aspects of the effect of negative emotion on cognition, particularly deficits in attention and working memory [72]. These data suggest an approach that could be used in future studies of PSS to illuminate the contribution of depression to cognitive dysfunction. One possible strategy would be to identify patterns of resting state activation that characterize subsets of PSS patients with different clinical features such as anxiety and depression.

Conclusion

Cognitive dysfunction and psychological distress significantly add to the burden of illness experienced by patients with PSS. While the neural substrate of cognitive symptoms is not yet fully understood, the application of novel fMRI and high-resolution quantitative brain imaging protocols have revealed the existence of neural networks involved in regulating the effect of negative emotion, particularly pain and depression on cognitive function. Neuroanatomic and fMRI studies could lead to improved understanding of the mechanisms contributing to cognitive symptoms and fatigue and guide the development of specific therapeutic approaches in PSS.

Future perspective

Diffusion tensor imaging could prove to be a sensitive technique for assessing CNS pathology, even when routine MRI is negative or nonspecific. Quantitative neuroimaging modalities such as DTI and MTI can detect abnormalities in brain microarchitecture beyond the resolution of conventional MRI. MRS, functional techniques and rs-fMRI represent advances that could provide diagnostic and prognostic markers of value when studying disease progression.

Both DTI and fMRI techniques could be useful to follow response to therapy. Functional mapping in longitudinal studies will be especially useful to assess the impact of treatment on cognitive symptoms and affective disorders in patients with PSS.

Cognitive and affective disorders will be modeled with MRI to investigate the underlying mechanisms. Alteration in dendrite morphology induced by stress could account for the localized nature of the DTI WM injury. Stress-induced architectural remodeling is an attractive hypothesis of cognitive dysfunction in PSS to be explored in future studies. Neuroanatomic and functional brain imaging tools could illuminate the pathogenic role of

Executive summary

Psychiatric disorder & cognitive dysfunction in primary Sjögren's syndrome: challenges in diagnosis & therapy

- Early studies suggested high incidence of personality and affective disorder, particularly in individuals with overt neurologic disorder.
- Primary Sjögren's syndrome (PSS) patients are very sensitive to subtle attention and recall deficits in PSS.
- Brief self-report measures of cognitive function correlate moderately with objective performance on tests of verbal and working (short-term) memory.
- Novel techniques such as functional MRI, diffusion tensor imaging (DTI) and magnetic resonance spectroscopy, can provide more precise ascertainment measures to assess the neural mechanisms contributing to cognitive dysfunction, fatigue and affective disorders in PSS.

Putative mechanisms of neuronal damage in primary Sjögren's syndrome

- Brain cytokine networks provide trophic support to neurons under physiologic conditions, while excessive or prolonged activation of the CNS cytokine network induces apoptosis of astrocytes and oligodendrocytes resulting in altered neuronal interaction and cognitive dysfunction.
- Inflammatory cytokines, as well as autoantibodies, potentially contribute to neuronal damage in PSS.
- Cognitive impairment is correlated with left hemisphere cortical hypoperfusion in PSS patients with normal conventional MRI scans.

Diffusion tensor imaging reveals brain abnormal white matter microarchitecture

- Abnormal white matter connectivity localized to the inferior frontal region is associated with cognitive impairment in PSS subjects with no history of CNS disorder other than subjective memory loss and concentration difficulties.

Resting state functional connectivity: alteration of spontaneous neural activity in patients with depression & patients with fibromyalgia

- Altered connectivity within the default mode network is associated with pain intensity in chronic pain subjects.
- Symptoms in depression could arise from increased functional connectivity in multiple brain networks involved in attention, memory and the processing and regulation of emotion.

Conclusion

- Cognitive symptoms are a frequent complaint in subjects with PSS, and cognitive deficits suggesting frontal–subcortical dysfunction is detectable in as many as 50% of PSS subjects.
- DTI could prove to be a sensitive tool for assessing CNS pathology in PSS, even when routine MRI is negative or nonspecific.
- Both DTI and functional MRI studies could be useful to follow response to therapy and illuminate the effects of pain and depression on cognition in PSS.

autoimmune and inflammatory processes associated with affective disorders and cognitive dysfunction in PSS.

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- ▪ of interest
- ▪▪ of considerable interest

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▪ **Demonstration of increased intrinsic connectivity between three important networks in bilateral prefrontal cortical regions which might underlie aspects of emotional dysregulation in patients with depression.**