Localization of Cerebral Functional Deficits in Patients with Non-Neuropsychiatric Systemic Lupus Erythematosus

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Abstract: Neuropsychiatric systemic lupus erythematosus (NP-SLE) is a common complication of systemic lupus erythematosus (SLE), and clinical interventions are of only limited efficacy despite relatively high prevalence. Such complications have been studied extensively, but the pathoetiology of NP-SLE has not yet been elucidated. Diagnosis of NP-SLE focuses primarily on psychological manifestations, and the underlying mechanisms leading to neuropsychiatric complications remain unknown. To address potential changes in brain function before NP-SLE development, we used resting-state functional magnetic resonance imaging (MRI) to compare regional brain activity in SLE patients versus matched controls. We report that regional activity in cerebellum and in areas of the default mode network are attenuated in patients with SLE, and moreover individual alterations in cerebellar activity correlated positively with the disease activity index. These findings provide direct evidence that significant alteration of brain function, resembling that observed in patients with NP-SLE, is already present in SLE patients without neuropsychiatric complications, highlighting the need for early evaluation and intervention in SLE patients. Furthermore, the disease activity rating correlated with regional functional alterations in the cerebellum, suggesting that the cerebellum could play a role in the pathogenesis of NP-SLE. *Hum Brain Mapp* 32:1847–1855, 2011. © 2010 Wiley Periodicals, Inc.

Key words: systemic lupus erythematosus; cerebral functional deficits; non-neuropsychiatric systemic lupus erythematosus; resting state functional magnetic resonance; regional homogeneity

INTRODUCTION

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Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multisystem involvement and diverse clinical manifestations [Rahman and Isenberg, 2008]. Neuropsychiatric systemic lupus erythematosus (NP-SLE) is a common complication of SLE and has been studied extensively, but the pathoetiology of NP-SLE has not been elucidated. Possible damage mechanisms include vasculopathy, autoantibodies, and inflammatory mediators, but these have not yet been confirmed [Boumpas et al., 1995]. Currently, the diagnosis of NP-SLE is based on case categorization into one of 19 neurological and

psychological syndromes as proposed by the American College of Rheumatology (ACR) in 1999. Because the underlying mechanisms leading to the development of neuropsychiatric complications have not yet been elucidated, the ACR system focuses primarily on psychological manifestations [ACR, 1999]. The prevalence of NP-SLE among patients with SLE was estimated to be as high as 76% [Sibbitt et al., 2002], and the condition is associated with a significantly reduced quality of life [Hanly et al., 2004]. Given the severe long-term impact of these prevalent psychiatric disorders, it is important to address whether changes in cerebral function in SLE precede the evolution of NP-SLE. This would lead to a better understanding of how SLE progresses to NP-SLE and, by casting light on potential mechanisms of pathogenesis, could facilitate the development of early interventions.

Brain activity can be imaged using blood oxygen-level-dependent functional MRI (BOLD-fMRI). This method uses deoxyhemoglobin as an endogenous contrast agent to identify areas of altered perfusion. Earlier fMRI studies reported that brain functions including working memory [Fitzgibbon et al., 2008], motor control [Rocca et al., 2006] and cognitive function [DiFrancesco et al., 2007] are altered in SLE patients with central nervous system (CNS) involvement. However, because these studies were generally performed with NP-SLE patients, it is unclear whether the observed changes represent alterations that progressively give rise to neuropsychiatric complications or are a consequence of disease progression following the emergence of neuropsychiatric symptoms. To the best of our knowledge, fMRI studies have not yet been performed on non-NP-SLE patients and no investigations to date have addressed possible brain functional deficits in SLE.

We used a recently developed fMRI method known as “resting-state” fMRI to assess brain function in a cohort of non-NP-SLE patients. Resting-state fMRI not only avoids possible performance confounds, but in the context of clinical studies to assess resting-state brain physiology, the method is easier to implement than positron emission tomography (PET)/single photon emission computed tomography (SPECT) because of its lower cost, greater availability, and noninvasiveness [Lui et al., 2009]. Low-frequency (0.01–0.08 Hz) fluctuations of the BOLD signal in resting-state fMRI are thought to reflect spontaneous neural activity in nonhumans [Leopold et al., 2003; Shmuel and Leopold, 2008] and humans [Goncalves et al., 2006; Laufs et al., 2003]. Regional homogeneity (ReHo), a method developed to analyze resting-state data, assumes that the hemodynamic characteristics of each voxel within a functional cluster are similar and/or synchronous, and the hemodynamic characteristics of each are modulated in parallel under different conditions [Zang et al., 2004]. This method has been successfully used to investigate functional resting-state changes in Parkinson disease [Wu et al., 2009], schizophrenia [Liu et al., 2006], and Alzheimer disease [He et al., 2007]. Before experimentation, we hypothesized that (1) changes in brain functional activity

TABLE I. Demographic data and clinical characteristics of subjects

Characteristics	SLE (<i>n</i> = 31)	Controls (<i>n</i> = 23)	<i>P</i> value
Mean age (years)	34.4	31.5	0.79
Education (years)	11.9	12.9	0.22
Height (cm)	157.5	159.6	0.06
Weight (kg)	54.5	54.2	0.44
Illness duration (months)	60	—	—
SLEDAI	6.3	—	—
GC dosage (mg)	18.9	—	—

in non-NP-SLE patients could be located in multiple cerebral regions and (2) individual ReHo values in specific regions could correlate with disease activity or glucocorticoid (GC) dosage of patients.

SUBJECTS AND METHODS

Participants

We initially recruited 33 right-handed female non-NP-SLE patients. Of these, two were excluded from the study, because overt cerebral deficits were visible on T1 and T2 scans. The study therefore included 31 female patients (ages 34.4 ± 7.6 years, education 11.9 ± 3.2 years). The study was approved by the Southwest Hospital Ethical Committee, and all participants gave written informed consent to their participation. Diagnosis of SLE and non-NP-SLE was performed by a consensus of the attending physicians based on ACR SLE criteria [Hochberg, 1997] and ACR case definition [ACR, 1999]. As a control group, 23 right-handed healthy female volunteers were recruited from the local community by poster advertisement; age, height, handedness, weight, and years of education were matched between groups (Table I). The following exclusion criteria applied to all subjects: organic brain disorder, alcohol or drug abuse, pregnancy, or any physical illness such as hepatitis, brain tumor, or epilepsy. Brain MR images (T1 and T2-weighted images) were inspected by two experienced neuroradiologists to exclude any gross structural abnormalities of the brain.

Data Acquisition

MR images sensitized to changes in BOLD signal levels were obtained using a 3-T MR imaging system (TRIO TIM; Siemens) with a gradient-echo echo-planar imaging (EPI) sequence: repetition time/echo time (TR/TE), 2,000/30 ms, flip angle 90° , slice thickness 4 mm (no slice gap), matrix 64×64 , FOV 256×256 mm, isotropic voxel $4 \times 4 \times 4$ mm. Each brain volume comprised 36 axial slices, and each functional run contained 210 image volumes preceded by five dummy volumes, resulting in a total scan time of 430 s. All participants were instructed not to focus

their thoughts on any particular topic and to keep their eyes closed during resting-state fMRI acquisition. A further high-resolution structural T1-weighted image was scanned using a volumetric 3D magnetized prepared rapid gradient echo (MP-RAGE) sequence: TR/TE 1900/2.52 ms, flip angle 15°, slice thickness 1 mm; 144 partitions, matrix 256×256 , isotropic voxel $1 \times 1 \times 1$ mm.

Data Processing

Functional image preprocessing and statistical analyses were carried out using SPM8 software (Statistical Parametric Mapping; <http://www.fil.ion.ucl.ac.uk/spm/>). For each subject, the first five volumes of functional images were discarded to allow for steady-state magnetization and stabilization of participant status. EPI images were slice-time corrected to the middle slice acquired in time and realigned and resliced to correct for head motion with a mean volume created. Structural images were co-registered with the mean volume of functional images and subsequently segmented by an inbuilt unified segmentation routine in SPM8 [Ashburner and Friston, 2005]. The parameter created by segmentation was then applied to functional images, nonlinear normalization to the Montreal Neurological Institute template brain, and each voxel was resampled to isotropic $3 \times 3 \times 3$ mm. To avoid manipulation error confounds and standardize the process, a batch processing tool DPARSF (data processing assistant for resting-state fMRI; <http://www.restfmri.net>) [Chao-Gan and Yu-Feng, 2010] was used. The head motion of all participants during resting-state fMRI acquisition was observed, and data were excluded from this study if the translation exceeded 1 mm or if rotation exceeded 1°.

Calculation of ReHo

ReHo analysis was performed by using REST software (<http://resting-fmri.sourceforge.net/>). Functional images were bandpass filtered ($0.01 \text{ Hz} < f < 0.08 \text{ Hz}$) to reduce low-frequency drift and physiological high-frequency respiratory and cardiac noise, and linear trends were removed to reduce the influence of the rising temperature of the MRI equipment [Biswal et al., 1995]. For each voxel, KCC (Kendall's coefficient of concordance) values [Kendall, 1990] were calculated to measure ReHo or similarity of the ranked time series with the nearest 26 neighboring voxels. By calculating the KCC value for every voxel throughout the whole brain, individual ReHo maps were generated. For standardization purpose, each individual ReHo map was divided by that subject's global mean brain KCC value. This procedure is similar to that employed in PET studies [Raichle et al., 2001]. Finally, processed images were smoothed with an isotropic Gaussian kernel (full-width at half-maximum, 8 mm).

Statistical Analysis

ReHo maps in the SLE and control groups were compared on a voxel-wise basis by using the two-sample *t*-test in SPM8. Results were displayed by REST software with a threshold of $P < 0.05$ with multiple comparison corrected by the Alphasim inbuilt routine for whole-brain analysis, which applies a Monte-Carlo simulation and calculates the probability of false-positive detection by taking into consideration both the individual voxel probability threshold and cluster size [Cox, 1996].

Finally, to explore whether individual ReHo correlated with SLE disease activity index (SLEDAI) or GC dosage, the mean ReHo values in multiple ROIs were extracted from each individual ReHo map, with ROIs selected using the WFU_PickAtlas (Wake Forest University, Wake Forest, NC) [Maldjian et al., 2003, 2004]. A total of 22 ROIs were extracted based on (1) the results of current study, (2) previously reported to be related to SLE including bilateral amygdala [Emmer et al., 2006] and limbic areas comprising the anterior cingulate cortex (ACC), the hippocampus, and thalamus. Regional ReHo values were extracted and explored for correlation with SLEDAI score or GC dosage using the Spearman correlation test and SPSS 16.0 software (SPSS, Chicago, IL).

RESULTS

Resting-state fMRI was used to compare regional brain activity in non-NP-SLE patients and matched normal volunteers. The ReHo maps of both subject groups are shown in Figure 1. Both subject groups displayed significant activation of the default mode network in the generated ReHo maps.

Two sample *t*-test (whole brain analysis) indicated that, compared to the controls, SLE subjects displayed significantly decreased ReHo values in multiple areas including the bilateral posterior lobes of the cerebellum (predominantly in crus I and II of the neocerebellum), the vermis, left inferior frontal gyrus, left precuneus, right limbic lobe, and cingulate gyrus; ReHo was increased in bilateral cuneus and in the calcarine gyrus (in all cases $P < 0.05$ following correction; Fig. 2 and Table II).

We then explored the possibility that disease activity or GC dosage might be associated with regional ReHo. For this analysis, we extracted ReHo values from ROIs selected either, because they presented significantly altered ReHo in this study and/or were previously reported to associate with SLE [Appenzeller et al., 2007a; Emmer et al., 2006]. These values were compared with SLEDAI score and daily GC dosage in individual non-NP-SLE patients; groupwise correlations were analyzed using the Spearman correlation test. This revealed that the SLEDAI score was positively correlated with mean ReHo value from left cerebellum posterior lobe and left ACC ($P < 0.01$), whereas

Figure 1.

Resting state regional homogeneity (ReHo) maps of healthy controls (**A**) and SLE patients (**B**) ($P < 0.05$, following correction for multiple comparisons). The left side of image corresponds to the right side of the brain (Radiological Convention).

there were no correlations between GC dosage and regional ReHo values (Table III). It is therefore possible that alterations in the left posterior lobe of the cerebellum and/or left ACC could contribute to or reflect ongoing cerebral involvement in SLE.

DISCUSSION

Structural MRI is considered to be the neuroimaging tool of choice for morphological brain evaluation in disorders such as NP-SLE, because it is capable of detecting

Figure 2.

T-statistic maps of SLE patients versus healthy subjects. In SLE patients, significantly decreased ReHo values were found in multiple areas ($P < 0.05$, corrected), including bilateral posterior lobes of the cerebellum (A), vermis (B), left inferior frontal gyrus (C), right cingulate gyrus (D), left precuneus (E), and right limbic lobe (F). Relative ReHo values appeared to be increased

in bilateral cuneus (G) and calcarine gyrus (H) ($P < 0.05$, corrected). T-score bars are shown on the right. Hot and cold colors indicate SLE-related ReHo increases and decreases, respectively. The left side of image corresponds to the right side of the brain (Radiological Convention).

different types of brain lesions including punctuate focal white matter lesions [Stimmler et al., 1993]. However, the structural MRI has been found to be of limited value in patients with diffuse neuropsychiatric disturbances such as headache, cognitive dysfunction, affective disorders, and confusional states [Rozell et al., 1998; Sabet et al., 1998]. Multiple functional neuroimaging modalities have therefore been used in SLE, including ^1H -magnetic resonance spectroscopy (MRS) [Castellino et al., 2005], SPECT [Appenzeller et al., 2007a], and fMRI [DiFrancesco et al., 2007; Fitzgibbon et al., 2008; Rocca et al., 2006]. These studies have suggested that functional alterations could precede structural changes in NP-SLE [Castellino et al., 2005], and, moreover, they allowed differentiation between patients with or without active CNS involvement

[Appenzeller et al., 2007a]. Moreover, NP-SLE patients exhibited greater activation of specific cerebral regions than healthy controls in tasks of working memory [Fitzgibbon et al., 2008], motor control [Rocca et al., 2006], and attention and language processing [DiFrancesco et al., 2007], possibly indicative of functional compensation in NP-SLE patients that could reflect impairment of cerebral functions relating to these tasks. One can therefore speculate that the functional deficits seen in NP-SLE might arise from systems-level disturbances in distributed brain networks.

Concerning non-NP-SLE subjects, cerebral functional changes were previously investigated using MRS [Filley et al., 2009; Kozora et al., 2005]. An increased choline/creatinine (Ch/Cr) ratio was found in frontal lobe white matter,

TABLE II. Brain regions with significantly altered ReHo value in SLE patients

Location	AAL area (mm ³)	Peak <i>t</i> -value MNI coordinates			Peak <i>t</i> -value	Volume (mm ³)
		<i>x</i>	<i>y</i>	<i>z</i>		
	Decreased ReHo in SLE					
L cerebellum posterior lobe	Cerebelum Crus2 L (1269)	−30	−81	−45	−3.52	1,890
L precuneus	Occipital Mid L (837)	−33	−63	27	−3.33	2,106
L inferior frontal gyrus	Frontal_Inf Tri L (1161)	−36	39	3	−4.04	1,458
R cerebellum posterior lobe	Cerebelum Crus2 R (1458)	39	−78	−21	−3.66	3,456
	Cerebelum Crus1 R (1323)					
R limbic lobe	Cingulum Mid R (2727)	6	−39	30	−4.26	18,009
	Cingulum Mid L (1458)					
	Cingulum Post R (1269)					
	SupraMarginal R (945)					
	Cingulum Post L (810)					
	Precuneus R (702)					
	Angular R (621)					
	Precuneus L (432)					
R cingulate gyrus	Cingulum Ant R (648)	3	18	45	−3.39	2,538
	Cingulum Mid R (594)					
Vermis	Cerebelum 6 L (864)	−3	−69	−12	−3.24	1,485
	Vermis 6 (594)					
	Increased ReHo In SLE					
Calcarine and R cuneus	Calcarine L (4293)	0	−90	15	3.76	10,098
	Calcarine R (2781)					
	Cuneus R (1350)					
	Lingual L (891)					
R calcarine	Calcarine R (1161)	18	−57	15	2.92	1,458

AAL, automated anatomical labeling, which is a digital atlas of the human brain. Localization of the cerebral region the AAL area was done by using database from xjview (<http://www.alivelearn.net/xjview>).

and the increase in the ratio correlated significantly both with cognitive score derived from a battery of tests and with time since diagnosis. It was concluded that myelin injury reflected by elevated Ch/Cr could be involved in disease progression and that Ch/Cr changes might represent an initial step in a sequence of neuropathologic events that produce cognitive impairment. Results from this study demonstrate that, in addition to white matter injury, resting state functional alterations are evident in distributed areas of the gray matter intrinsic network. By comparing the results reported here and in other studies, it is notable that the progressive and chronic impact of SLE is predominantly reflected in white matter injury, whereas temporal effects from disease activity was demonstrated by regional functional alterations in gray matter.

The most important finding reported here is direct evidence for changes in resting state cerebral function in gray matter in SLE patients before onset of neuropsychiatric complications. ReHo values were significantly reduced in multiple brain areas compared to healthy controls, and activity was increased in only two regions. Because the low-frequency fluctuation (LFF) BOLD signal has been suggested to reflect spontaneous neuronal activity [Logothetis et al., 2001], ReHo measures the similarity or coherence of

TABLE III. Association between regional ReHo value, disease severity and GC dosage

Location	Correlation with SLEDAI	Correlation with GC dosage
	<i>R</i>	<i>R</i>
Decreased ReHo in SLE		
L cerebellum posterior lobe	0.477**	0.257
L precuneus	0.198	0.193
L inferior frontal gyrus	0.138	−0.031
R cerebellum posterior lobe	0.223	0.237
R limbic lobe	−0.092	−0.019
R cingulate gyrus	−0.145	−0.233
Vermis	0.11	0.204
Increased ReHo In SLE		
Calcarine and R cuneus	−0.197	−0.236
R calcarine	−0.056	0.025
Previous proposed areas		
L ACC	0.482**	0.278

P < 0.01; ACC, anterior cingulate cortex; other previously proposed area without significant correlation was not presented in the table.

LFF within a given area on the basis of hemodynamic properties. Changes in ReHo values could therefore reflect alterations in the coherence of spontaneous neuronal activity, and abnormal ReHo is possibly relevant to changes of temporal aspects of spontaneous neural activity in specific brain regions [Wu et al., 2009]. Decreased or increased ReHo in SLE suggests that neural function in certain regions is less or more synchronized compared to normal controls. However, it is not known whether ReHo might simply indicate SLE-induced changes in blood flow, and this will require further investigation.

The predominant cerebral areas with altered ReHo values lay within the posterior cingulate cortex and adjacent precuneus, brain regions that are regarded as areas of the default mode network [Raichle et al., 2001]. Activity in the default mode network has been shown to correlate inversely with overt task performance [Fox et al., 2005] and has been suggested to be relevant to mental disorders including Alzheimer disease, autism, and schizophrenia [Buckner et al., 2008]. Altered ReHo values in these areas could suggest that activity in the intrinsic default mode network is also attenuated in SLE. Other regions showing altered ReHo values, such as the calcarine and cuneus, are primarily regarded as specialized regions for primary visual processing. Nevertheless, a recent study on cognitive working load has argued that the calcarine gyrus is part of the cognitive reserve network [Stern et al., 2005], and it could be argued that impairment of this network is an underlying mechanism of cognitive dysfunction in NP-SLE patients. Further investigations will be required to address this possibility.

We also report that SLE is accompanied by significantly changed ReHo values in the bilateral crus I and II of the neocerebellum. To best of our knowledge, the cerebellum has not previously been implicated in NP-SLE. In recent research on the role of the cerebellum in nonmotor systems, referred as intrinsic connectivity networks, the neocerebellum (in particular, crus I and II) was found to participate in the right and left executive control networks [Habas et al., 2009]. This is consistent with our findings and with several neuropsychiatric complications of NP-SLE.

Notably, correlation analysis between regional ReHo values and SLEDAI scores or GC dosages revealed that mean ReHo values in both neocerebellum and left ACC correlated positively with disease activity, whereas no area correlated with GC dosage. This indicates that (1) functional activity in the areas highlighted in this study is not significantly influenced by GC dosage and (2) neural activity in neocerebellum and ACC is increased in proportion to SLE disease activity. This latter finding could suggest that the neocerebellum, as part of an executive control network, could play an important role in the pathogenesis of NP-SLE. Overall, the cerebral functional alterations identified in this study appear to be influenced by the temporal effect of SLE activity rather than by GC administration. However, it is worth noting that GC dosage was previ-

ously found to correlate with brain structural changes [Appenzeller et al., 2007b], and the potential influence of GC on cerebral function of patients with SLE should still be investigated further.

Our study has several limitations. First, disease duration was not consistent in the cohort of SLE patients (4.98 ± 4.18 years). Functional deficits are likely to precede the presentation of either structural or neuropsychological abnormalities; it is possible that the extent of brain functional alterations is highly variable within the group. Second, it was not possible to identify a sufficient number of SLE patients with active CNS involvement to serve as a positive reference controls. This was, in part, due to the diversity of neuropsychiatric symptoms displayed by SLE with overt CNS involvement, making it difficult to accumulate a group of NP-SLE patients with comparable neuropsychological presentations. Third, although all the SLE subjects studied failed to meet criteria for CNS involvement, some of the non-NP-SLE patients could have displayed subclinical deficits that would have been revealed by a comprehensive battery of cognitive tests. Because systematic cognitive testing was not performed this study is unable to draw conclusions regarding a potential association between specific impairments of cognitive performance and attenuated cerebral function as revealed by fMRI of regional brain activity.

CONCLUSION

Previous neuroimaging studies focusing on NP-SLE demonstrated cerebral abnormalities associated with CNS complications of SLE [Emmer et al., 2008; Rocca et al., 2006]. MRS studies demonstrated injury to white-matter microstructure in non-NP-SLE patients [Filley et al., 2009; Kozora et al., 2005]. However, changes in resting state gray matter activity in non-NP-SLE patients have not previously been studied using fMRI. This study expands our understanding of SLE-associated changes in brain function in two important ways. First, our findings demonstrate that CNS functional alterations can be observed in SLE in the absence of changes in cerebral structure or overt neuropsychiatric complications. Second, this study provides evidence that alterations may not be limited to focal changes within the domains of specific tasks, but are instead likely to be expressed at the level of intrinsic networks involving multiple brain areas. Furthermore, altered ReHo in neocerebellum correlated with disease activity, suggesting that cerebellum could play a role in the pathogenesis of NP-SLE.

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