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ORIGINAL RESEARCH

Cortical thickness reductions associate with abnormal resting-state functional connectivity in non-neuropsychiatric systemic lupus erythematosus

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Abstract To detect the abnormal cortical thickness and disrupted brain resting-state functional connectivity (RSFC) in patients with systemic lupus erythematosus (SLE) without neuropsychiatric symptoms (non-NPSLE). Using T1-weighted 3D brain structural data, we first determined the regions with abnormal cortical thickness in a cohort of 33 adult female non-NPSLE patients. By taking brain regions with significantly reduced cortical thickness as the seeds, we calculated their RSFC based on the resting-fMRI data and detected the relationship between the RSFC and cortical thickness in the non-NPSLE patients. Compared to the controls, the non-NPSLE patients showed significantly cortical thinning in the left fusiform gyrus (FUS.L), left lingual gyrus (LING.L), right lingual gyrus (LING.R) and left superior frontal cortex (SFC.L). As for the RSFC, statistical analyses indicated that the abnormal cortical thickness in LING.L is associated with increased RSFC in the left posterior cingulate cortex (PCC.L), and cortical thinning in SFC.L associated with decreased

Chen Niu and Xiangliang Tan contributed equally to this work.

Highlights:
1. We found cortical thinning in FUS.L, LING.L, LING.R and SFC.L in non-NPSLE patients.
2. Observed lower frontal-cerebellar RSFC in non-NPSLE patients compared to healthy controls.
3. Decreased cortical thickness in LING.L positively correlated with the connectivity of LING.L-PCC.L in non-NPSLE.
4. Cortical thinning in SFC.L positively correlated with connectivity of SFC.L-CRBL 6.L in non-NPSLE.

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RSFC in left cerebellum 6 (CRBL 6.L) in non-NPSLE patients. In addition, in non-NPSLE patients, the decreased cortical thickness in LING.L was correlated to the increased RSFC in PCC.L, and decreased cortical thickness in SFC.L was correlated to the decreased RSFC in CRBL 6.L. Our findings suggest that the cortical abnormalities may affect brain intrinsic connectivity in non-NPSLE patients.

Keywords Fronto-cerebellar · Functional connectivity · Surface-based morphometry (SBM) · non-NPSLE

Abbreviations

SLE	Systemic lupus erythematosus
NPSLE	Neuropsychiatric systemic lupus erythematosus
non-NPSLE	Non-neuropsychiatric systemic lupus erythematosus
RSFC	Resting-state functional connectivity
SBM	Surface-based morphometry
ACR	American College of Rheumatology
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC/ACR	Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index
GM/WM	Gray matter/white matter
CSF	Cerebrospinal fluid
R-fMRI	Resting-state fMRI
T-fMRI	Task-fMRI

Introduction

Systemic lupus erythematosus (SLE) is a mainly female inflammatory autoimmune disorder that can affect the central or peripheral nervous system resulting in neuropsychiatric SLE (NPSLE) (Kaul et al. 2016). SLE may cause global alterations in vascular reactivity and indirectly affect brain function (Difrancesco et al. 2007; Mak et al. 2012). Previous studies reported brain structural and functional changes in SLE in the absence of overt neuropsychiatric manifestation (non-NPSLE) (Lin et al. 2011; Mak et al. 2012; Xu et al. 2015). Evidence showed that brain structural abnormalities may influence the properties of brain function (Appenzeller et al. 2007; Zhang et al. 2016). Appenzeller et al. (2007) conducted a voxel-based morphometry analysis in SLE patients and found that SLE patients with severe cognitive impairment had a greater decreased gray matter volume in the frontal, occipital and cerebellum than controls. In a review paper, Rykhlevskaia et al. (2008) suggested that the integration of structural and functional information could reformulate the links between brain structural abnormalities and further functional consequences. Accumulated evidence also showed that local brain structural abnormalities may influence the properties of brain function in major depression disorder (Horn et al. 2010; Van Tol et al. 2014), nonmedicated bipolar disorder (Wang et al. 2016) and psychopathy (Ly et al. 2012). However, it is still unclear how the local structural abnormalities relate to the intrinsic functional properties in SLE patients even without neurophychiatric symptoms and whether abnormal local structure can be served as a marker of functional deficits. Therefore, in this study, we used a multi-modal imaging approach to detect abnormal cortical thickness and the corresponding altered brain functional properties in non-NPSLE patients.

The Surface-based morphometry (SBM) analysis is widely used to study brain structural morphology for providing more precise information about cortical thickness (Hutton et al. 2009). Recent studies suggested the measurement of cortical thickness can be effectively to detect neurobiological changes in diversity diseases (Lüsebrink et al. 2013), such as autism (Ecker et al. 2013) and psychopathy patients (Martina et al. 2012). The SBM method is also used to study brain cortical thickness in SLE patients for understanding neuropsychiatric mechanism of SLE-related brain. For example, Jung et al. (2010) used the SBM method to compare cortical thickness among NPSLE, non-NPSLE and healthy controls, and found decreased cortical thickness in the left postcentral, supramaginal, rostralmiddle frontal, precuneus gyri and right inferior parietal in NPSLE patients compared to healthy controls, but detected no significant cortical thickness difference between non-NPSLE and controls.

Recently, a number of studies also used resting-state fMRI (R-fMRI) and task-fMRI (T-fMRI) to detect cognitive dysfunctions in SLE (Difrancesco et al. 2013; Du Boisgueheneuc et al. 2006; Lin et al. 2011; Mak et al. 2012; Ren et al. 2012). Lin et al. (2011) used R-fMRI to analyze brain regional homogeneity (ReHo) in non-NPSLE patients and found decreased ReHo value in cerebellum and in areas of the default mode network (DMN) in non-NPSLE patients compared to healthy controls. Shapiralichter et al. (2013) used a free-recall paradigm T-fMRI to study memory of non-NPSLE and found increased activation in anterior medial prefrontal cortex, suggesting that non-NPSLE manifested memory impairment compared to controls. Based on R-fMRI data, Hou et al. (2013) analyzed resting-state functional connectivity (RSFC) in SLE patients and found increased frontal-parietal RSFC in SLE compared with controls. However, very few studies have taken brain structure and functional analyses together to reveal abnormal cortical structure and RSFC in non-NPSLE.

Several multimodal imaging studies (Ly et al. 2012; Späti et al. 2015) have combined cortical thickness with RSFC to evaluate brain structure-functional relationship and it may potentially aid in clinical diagnose (Zhang et al. 2016). For

example, Ly et al. (2012) investigated cortical thickness and RSFC abnormalities in a group of criminal psychopathy, detected that cortical thinning in the left insula and dorsal anterior cingulate cortex could influence RSFC between them. Späti et al. (2015) used a multimodal imaging method to study the relationship between cortical thickness and RSFC in major depressive disorder (MDD), and revealed that cortical thinning in the right anterior PFC may impair the ability of supragenual ACC in depressed patients during a major depressive episode. By now, there are very few studies using multimodal imaging methods to detect relationship of brain structure and function in non-NPSLE patients.

With the aim to detect the relationship between abnormal cortical thickness and RSFC in non-NPSLE patients, we used a multi-modal neuroimaging approach, combining brain structural MRI with R-fMRI data, to characterize whether abnormal cortical thickness could be related to disrupted brain functional connectivity in non-NPSLE patients. Previous studies (Difrancesco et al. 2013; Mak et al. 2016) found abnormal structure or function in the lingual gyrus and the superior frontal cortex in SLE patients. We hypothesized that non-NPSLE patients may show abnormal cortical thickness or related impaired functions in the lingual gyrus and the superior frontal cortex (Appenzeller et al. 2007; Jung et al. 2010; Mak et al. 2016). In order to test these hypotheses, we calculated the cortical thickness and RSFC for the non-NPSLE and the healthy controls using vertex-wise SBM and RSFC approaches.

Materials and methods

Subjects

Initially, a total of 39 female non-NPSLE patients were recruited from the Development of Rheumatology in Nanfang Hospital, Southern Medical University, Guangzhou, China. Of them, 6 patients were excluded from the further study, including one patient less than 18 years old, two patients with obvious focal brain atrophy, and three patients with infarcts. Finally, the remaining 33 non-NPSLE patients (aged 29.27 ± 9.07 years old) were included for further analyses. The inclusion criteria for the patients were as follows: (1) 18–50 years old, (2) fulfilling four or more criteria to the 1997 revised American College of Rheumatology (ACR) (Hochberg 1997), and (3) without neuropsychiatric syndromes involvement (Liang et al. 1999). The structural images for all non-NPSLE patients were checked by a dermatologist (K. H.) and a rheumatologist (Q. H.) separately. The exclusion criteria were (1) patients with neuropsychiatric syndromes involvement of central nervous system and peripheral nervous system in their history proposed by the ACR, such as obviously disorganized behaviors, psychiatric disorders, conscious disturbances, and neurological symptoms, (2) severe claustrophobia, pacemaker, metal implant, or orthodontic braces that unable undergo MRI scan, (3) a history of substance abuse, such as drug abuse and alcohol abuse, (4) previous clinical conditions, such as a history of stroke, diabetes mellitus, arterial hypertension, and malignancy, or brain neurological disorders, such as Parkinson's disease, head trauma, or seizures that would influence brain structure, function and cerebral atrophy, and (5) any physical illness or pregnant.

The degree of cumulative SLE-related damage for each patient was diagnosed according to the Systemic Lupus International Collaborating Clinics or ACR Damage Index (SLICC/ACR-DI) (Gladman et al. 1997). Disease activity was determined according to the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (Gladman et al. 2000). In addition, we also collected three serum assay indices (C3, C4 and CH50) for each patient. Anti-Sm antibody (Anti-Sm) was tested and used to aid clinical diagnosis. Doses of prednisone were equivalent to those of oral and parenteral corticosteroids.

In addition, we also recruited 32 female healthy subjects with age-matched as the control group (aged 31.44 ± 8.91 years old). The exclusion criteria for the controls were as follows: (1) age < 18 or age > 50 years old, (2) MRI images showed obvious head movement, (3) patients with previous history of neurological or psychiatric illness. The study protocol was approved by the Institute Review Board of Nanfang Hospital of the Southern Medical University. Written informed consent was obtained from each subject prior to this study. Table 1 lists the demographic information for all the patients and the controls.

Data acquisition

All images were obtained on a 3 T Philips Medical Achieva Systems MR scanner with an 8-channel phased-array head coil at the Nanfang Hospital, Southern Medical University, Guangzhou, China. The high-resolution brain structural images were acquired using a T1-weighted 3D turbo field echo (TFE) sequence with the following parameters, repetition time (TR) = 9.0 ms, echo time (TE) = 4.0 ms, flip angle = 8°, field of view (FOV) = 256 × 256 mm^2, data matrix = 256 × 256, slice thickness = 1 mm, voxel size = 1 × 1 × 1 mm^3, and 176 sagittal slices covering the whole brain. The R-fMRI data were obtained using a single-shot gradient-echo EPI sequence (TR = 2000 ms, TE = 35 ms, flip angle = 90°, slice thickness = 3.6 mm with interslice gap = 0.7 mm, 33 interleaved axial slices covering the whole brain, and 240 time points in 8 mins). During the R-fMRI scan, each subject was requested to relax, close eyes and wake, but not thinking about other things. For each subject, we acquired R-fMRI data, high-resolution brain structural images, and diffusion-weighted

Table 1 Demographics and clinical data for the non-NPSLE patients and the healthy controls in this study

	non-NPSLE (n = 33)	HC (n = 32)	t-value	p-value [a]
Age (years old)	29.27 ± 9.07	31.44 ± 8.91	−0.970	0.336
Years of education	11.55 ± 4.20	12.97 ± 3.75	−1.441	0.155
Disease duration (months)	37.12 ± 51.88	NA		
Age at disease onset (years)	26.24 ± 9.75	NA		
SLICC	0.61 ± 0.56	NA		
SLEDAI	9.82 ± 7.26	NA		
C3 (g/l)	0.59 ± 0.29	NA		
C4 (g/l)	0.11 ± 0.08	NA		
CH50 (g/l)	30.98 ± 20.83	NA		
Anti-Sm	52.16 ± 74.30	NA		
Prednisone (mg)	39.39 ± 24.65	NA		

Abbreviations: *SLICC* Systemic lupus erythematosus international collaborating clinics; *SLEDAI* Systemic lupus erythematosus disease activity index; C3, C4, and CH50, three serum assay indices (*C3* Complement component 3; *C4* Complement component 4; *CH50* 50% hemolytic complement activity); *Anti-Sm* Anti-Sm antibody; *NA* Not applicable

[a] The p-value was obtained from two-sample t test analysis

images in the same session. Diffusion-weighted images were used in other analyses. All the brain structural images and R-fMRI data were initially visually inspected by an experienced radiologist (X. T.) to exclude the subjects with abnormal structure such as focal or diffuse brain atrophy, infarcts, and lesions that are not related to SLE.

Cortical thickness

Structural image data preprocessing The brain structural images were processed using FreeSurfer package (http://surfer.nmr.mgh.harvard.edu/), a well-documented automated program and widely used to perform surface-based morphometric (SBM) analysis (Dale et al. 1999). For each subject, we processed brain structural images in the following steps: (1) removing the non-brain tissue based on a deformable template model (Ségonne et al. 2004), (2) transforming the skull-stripping brain volume to Talairach-like space (Ségonne et al. 2004), (3) segmenting brain tissues to GM, WM, cerebrospinal fluid (CSF) (Fischl et al. 2004), (4) performing intensity normalization to remove the effect of bias field (Sled et al. 1998), (5) building a surface tessellation to generate a triangular cortical mesh consisting of about 300,000 vertices in the whole brain surface (Dale et al. 1999), (6) correcting topological deficit of cortical surface (Ségonne et al. 2007), and (7) deforming brain surface to generate optimized models of GM/WM and GM/CSF boundaries (Fischl and Dale 2000). Subsequently, we generated two surfaces, one is the WM surface or the GM/WM interface, and the other is the pial surface or the GM/CSF interface. We measured two shortest distances, from the GM/WM interface to the GM/CSF interface and from the GM/CSF interface to the GM/WM interface, at each vertex. At the given vertex, the cortical thickness was defined as the average value of the above two values.

After cortical surface being reconstructed, the cortical thickness map for each subject was resampled onto the cortical surface and smoothed with a 10-mm full-width at half maximum (FWHM) Gaussian kernel. In the calculations, a spherical transformation was performed to register each subject's cortical surface to a spherical surface. At last, we obtained the inflated WM surface and the normalized cortical folding patterns of gyrus and sulcus for each subject. Based on group-level comparison, we detected the clusters showing significant changed cortical thickness in the non-NPSLE patients compared to the controls.

Resting-state functional connectivity (RSFC)

R-fMRI data preprocessing The functional images were preprocessed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) and DPARSF-A (http://rfmri.org/DPARSF). For each subject, we first discarded the first 10 volumes for magnetization equilibrium and adapting the scanning environment. Then we performed slice timing for the remaining 230 volumes to account for the acquisition time delay between different slices and realigned all images to the first volume for head-motion correction. Afterward, we normalized the functional images to the individual structural images and then to the MNI standard space by using an affine transformation and resampled it to $3 \times 3 \times 3$ mm^3 by using a Gaussian kernel with FWHM of 4 mm. At last, we performed signal linear detrending and band-pass filtering (0.01–0.08 Hz), and regressed out the nuisance covariates including head motion parameters derived from the Friston 24-parameter model, WM signal, and CSF signal within each voxel in whole brain. Due to the

controversy which regressing out global signal has been shown to introduce negative activation in R-fMRI analysis, we have not regressed out the global signal in this study (Fox et al. 2009; Kevin et al. 2009).

In this study, we first estimated 6-parameter head motion and all of subjects satisfied our criteria: translation <2.5 mm in any plane and angular rotation <2.5° in any direction during realignment. Then we applied the Friston 24-parameter model in realignment to estimate the head motion. A previous study showed this is an effective model to decrease the effect of head motion (Yan et al. 2013). We estimated mean framewise displacement (FD) from the head-motion profiles obtained from realignment. Finally, we took the mean FD of head motion as a covariate to regress it out in statistical processing.

RSFC The regions with significantly changed cortical thickness in non-NPSLE patients were selected as seed regions of interest (ROIs). The calculation of RSFC mainly includes two steps. First, first-level or individual-level RSFC measures were computed between each of these seed ROIs and every other voxel in the whole brain after regressing out the effect of age. Briefly, we first resampled the ROIs to $3 \times 3 \times 3$ mm^3 in MNI space. Then we extracted mean time series of each voxel in a given ROI and calculated the Pearson's correlation coefficients between the mean time series of the given ROI and the time series of all voxels throughout the whole brain to generate the RSFC map for each subject. We only focused on positive correlation and discarded negative correlation, because the explanation to negative correlation is ambiguously and would influence test-retest reliability (Achard and Bullmore 2007). Second, in order to improve the normality and second-level general linear model (GLM) analyses, we performed Fisher's r-to–z transformation to convert the correlation coefficient map into a Fisher-z RSFC map for each subject. Finally, second-level or group-level statistical analysis was performed on Fisher-z RSFC maps to determine RSFC difference between the non-NPSLE patients and the controls.

We also calculated correlation between cortical thickness of each seed region and the corresponding RSFC in non-NPSLE patients.

Statistical analyses

Demographics Two-sample t-test was used to calculate significant difference in age and in years of education between the non-NPSLE patients and the controls.

Cortical thickness Group analyses of cortical surface were conducted by resampling each subject's cortical thickness maps to the FreeSurfer average atlas. A standard GLM was used to detect significant differences in cortical thickness between non-NPSLE patients and controls. We regressed out the effect of age. And Monte Carlo simulation cluster analysis with 10,000 permutations and a cluster-wise threshold of $p < 0.05$ was adopted for multiple comparisons correction. In this way, we determined the regions with significant group differences in cortical thickness. For each of these clusters, we also calculated the correlation between the mean cortical thickness and each of the clinical variables (disease duration, age at disease onset, SLICC, SLEDAI, C3, C4, CH50, Anti-Sm, and prednisone) in the patients.

RSFC One-sample t-test was performed on the Fisher-z RSFC maps of the non-NPSLE patients to detect brain regions with significantly different from zero ($p < 0.0005$, FWE correction) by regressing out age and mean FD of head motion. Similar calculation was also performed for the controls. Then we determined the overlapping regions in RSFC of the two groups for group-level comparison (Fig. 1). A two-sample t-test was then used to identify significant difference in RSFC between the two groups by regressing out age and mean FD. Correction for multiple comparisons was performed using cluster-extent thresholding at an uncorrected $p < 0.05$, $\alpha = 0.05$. Cluster extents were using Monte Carlo simulations performed in 3dClustSim program (AFNI https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html). Finally, we estimated correlation between the connections and clinical variables in the non-NPSLE patients.

The whole procedures of this study are described in Fig. 1.

Results

Demographic and clinical variables

Two-sample t-test showed no significant differences in either age ($t = -0.970$, $p = 0.336$) or years of education ($t = -1.441$, $p = 0.155$) between the non-NPSLE patients and the controls (Table 1).

Cortical thickness

Figure 2 shows brain regions with significant difference in cortical thickness between the non-NPSLE patients and the controls. We found that the non-NPSLE patients had uniformly significantly decreased cortical thickness in four regions, three in the left and one in the right hemispheres, which are primarily located in the left fusiform (FUS.L), left superior frontal cortex (SFC.L), left lingual gyrus (LING.L), and right lingual gyrus (LING.R). Table 2 lists the detail information of these regions.

For each cluster listed in Table 2, we first estimated the correlation between the cortical thickness and the clinical variables and then performed Bonferroni correction ($p < 0.0125$)

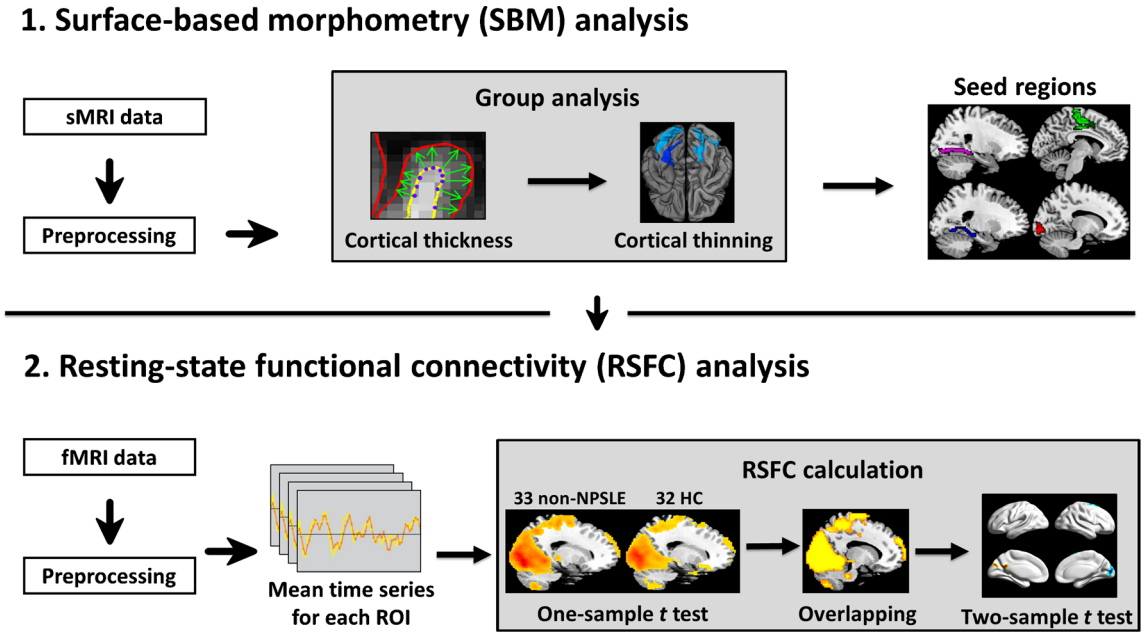

Fig. 1 Flowchart of procedures for analyzing cortical thickness and resting-state functional connectivity (RSFC) in this study

for multiple comparisons. Statistical analysis revealed that the mean cortical thickness in the FUS.L was significantly positively correlated with the age at disease onset in the non-NPSLE patients ($r = 0.515$, $p = 0.002$). However, no significant correlation was found between the cortical thickness and the age at disease onset in any of the other clusters, such as the LING.L ($r = 0.225$, $p = 0.208$), SFC.L ($r = 0.386$, $p = 0.026$), and LING.R ($r = 0.411$, $p = 0.018$), in the non-NPSLE patients (Fig. S1, Supplementary Materials). Similarly, no significant correlation was found between the mean cortical thickness in any of these clusters (FUS.L, LING.L, SFC.L and LING.R) and the disease duration in the patient group.

RSFC

Figure 3 shows brain regions with significant difference in RSFC between the non-NPSLE patients and the controls. The detail information for these regions is listed in Table 3. The RSFC between the seed LING.L and the left posterior cingulum (PCC.L) was significantly increased in the non-NPSLE patients compared to the controls ($t = 2.863$, $p = 0.01$). But the RSFC between the seed SFC.L and the three regions, the left cerebellum 6 (CRBL 6.L) ($t = -3.127$, $p = 0.001$), right superior frontal cortex (SFC.R) ($t = -3.038$, $p = 0.001$), and right calcarine (CAL.R) ($t = -3.052$,

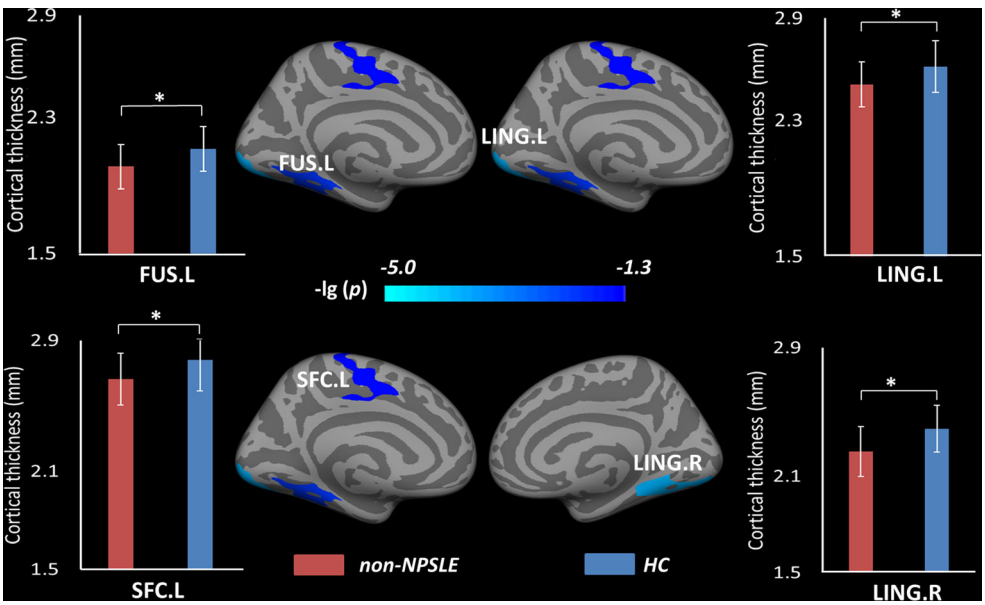

Fig. 2 Vertex-wise analysis of cortical thickness in the non-NPSLE patients compared to the healthy controls. Four regions showed significant between-group difference in cortical thickness ($p < 0.05$, Monte Carlo simulation corrected). Color bar indicates the p-value ($-\lg(p)$). The non-NPSLE patients showed uniformly significantly decreased cortical thickness compared to the controls. These regions are located in the left fusiform gyrus (FUS.L), left lingual gyrus (LING.L), left superior frontal cortex (SFC.L), and right lingual gyrus (LING.R)

Table 2 Significant regions resulted from the vertex-wise comparison of cortical thickness between the SLE patients without neuropsychiatric symptoms (non-NPSLE) and the healthy controls (HC) ($p < 0.05$, Monte Carlo simulation corrected). Peak coordinates were presented in the Talairach-like space. These four regions showed uniformly significantly decreased cortical thickness in the patients after multiple comparisons

	Index	Peak location	Vertex number	Size (mm^2)	Peak Talairach coordinates			Cluster-wise *p*-value
					x	y	z	
Patients < Controls	1	FUS.L	2443	1894.20	−42.0	−56.3	-12.2	1.00E-04
	2	LING.L	2153	1145.95	−29.8	−48.2	-2.3	5.20E-03
	3	SFG.L	2229	892.98	−11.7	−2.8	41.6	2.45E-02
	4	LING.R	2783	1828.21	26.8	−45.3	-3.0	1.00E-04

Abbreviations: *CWP* Cluster-wise *p*-value; *LING.L* Left lingual gurus; *FUS.L* Left fusiform gyrus; *SFC.L* Left superior frontal cortex; *LING.R* Right lingual gyrus; *L* (*R*): left (right) hemisphere

$p = 0.001$), were uniformly decreased in the non-NPSLE patients compared to the controls.

For each region listed in Table 3, we estimated the correlation between RSFC values and clinical variables. Statistical analysis showed no significant correlation between the RSFC and any of clinical variables in the non-NPSLE patients after Bonferroni correction ($p < 0.0125$).

Figure 3 shows correlation between the cortical thickness of each seed region and the corresponding RSFC. In the non-NPSLE patients, we found that the cortical thickness in LING.L is significantly positively correlated with the RSFC of LING.L-PCC.L ($r = 0.387$, $p = 0.026$), and the cortical thickness in SFC.L is significantly positively correlated with the RSFC of SFC.L-CRBL 6. L ($r = 0.368$, $p = 0.035$).

Discussion

In this study, we analyzed abnormal brain structure and the relationship between cortical thickness changes and abnormal RSFC in the non-NPSLE patients. We found that the non-NPSLE patients showed decreased cortical thickness in four regions compared to the controls, which were located in FUS.L, LING.L, SFC.L, and LING.R. We also detected that the non-NPSLE patients had increased RSFC of LING.L-PCC.L and decreased RSFC of SFC.L-CRBL 6.L compared to the controls.

Cortical thickness

This study found significantly decreased cortical thickness in FUS.L, LING.L and LING.R in the non-NPSLE patients

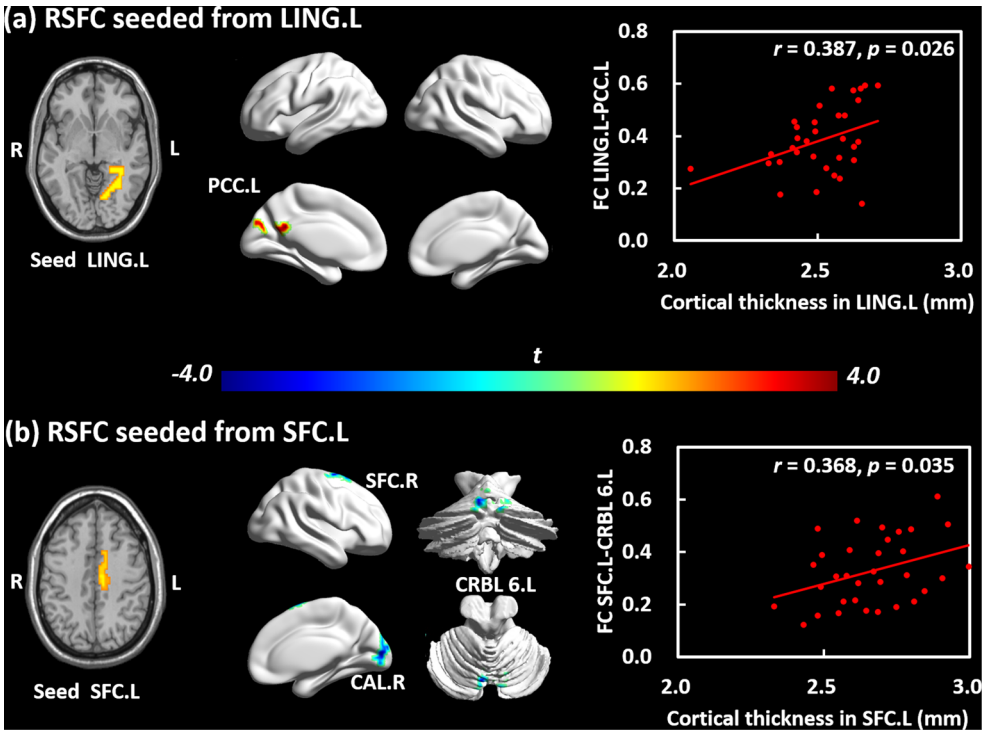

Fig. 3 Group differences in RSFC between the non-NPSLE patients and healthy controls. **a** RSFC seeded from LING.L. The RSFC of LING.L-PCC.L was significantly increased in the patients compared to the controls. The scatter plot shows the positive correlation between the RSFC of LING.L-PCC.L and the cortical thickness in LING.L. **b** RSFC seeded from SFC.L. The RSFC of SFC.L-SFC.R, SFC.L-CAL.R and SFC.L-CRBL 6.L was significantly uniformly decreased in the patients compared to the controls. The scatter plot shows the positive correlation between the RSFC of SFC.L-CRBL 6.L and the cortical thickness in SFC.L. Red dots represent the non-NPSLE patients

Table 3 Significant differences in the resting state functional connectivity (RSFC) between the non-NPSLE patients and the healthy controls (multiple comparisons correction, cluster-extent thresholding at an uncorrected $p < 0.05$, $\alpha = 0.05$). In the calculations, we selected the four regions listed in Table 2 as the seed regions, calculated their RSFC in the whole brain for the non-NPSLE patients and the controls, compared group difference in RSFC to obtain the regions with significant between-group differences in RSFC, and determined the peak coordinates

Seed regions	RSFC regions	Size (No. voxels)	Volume (mm^3)	*t*-value	Peak MNI coordinates		
					x	y	z
Patients > Controls							
LING.L	PCC.L	111	999	2.86	−6	−48	24
Patients < Controls							
SFC.L	CRBL 6.L	53	477	−3.13	−6	−75	-15
	CAL.R	89	801	−3.05	6	-87	9
	SFC.R	51	459	−3.04	18	-3	63

Abbreviations: *LING* Lingual gyrus; *SFC* Superior frontal cortex; *PCC* Posterior cingulum; *CRBL 6* Cerebellum 6; *CAL*, calcarine; *L* (*R*), left (right) hemisphere

compared to the controls (Fig. 2, Table 2). Several studies suggested that the FUS and LING, parts of the visual recognition network, involve in emotional face processing (Fusar-Poli et al. 2009) and visual processing, such as object recognition and visual attention (Caspers et al. 2014). Previous studies showed that abnormal brain activation in FUS and LING may lead to poor object recognition and visual attention abilities in SLE patients (Difrancesco et al. 2013; Mak et al. 2012). The result of abnormal cortical thickness in FUS converges with a previous fMRI study (Mak et al. 2012), finding brain activity in non-NPSLE and significant decreased activation in FUS in non-NPSLE patients which reflected poor color processing and object recognition abilities. Our finding of the decreased cortical thickness in LING also aligns closely with a previous study, which found GM volume reductions in LING.L in SLE patients (Mak et al. 2016). This suggested that decreased LING.L GM volume may be associated with neuropsychological and behavioral dysfunctions in SLE. In addition, our result of structural abnormality in LING.L also converges with an fMRI study, which showed decreased LING activation responding to a goal-directed task in SLE patients (Mak et al. 2012), suggesting the dysfunction of visual attention ability in SLE patients. Thus, our results of the abnormal FUS and LING may reflect impairment of visual attention and object recognition in SLE patients even in the absence of neurophychiatric symptoms. In addition, we found cortical thickness in the FUS.L was significantly positive correlated with age at disease onset (Fig. S1). This means that, for the cortical thickness in non-NPSLE, the earlier age at disease onset of non-NPSLE, the thinner cortical thickness in FUS.L. This may indicate that the progress of SLE may response to brain's adaptability or reorganization.

In addition, we found cortical thinning in SFC.L in the non-NPSLE patients compared to the controls (Fig. 2, Table 2). The SFC is believed to involve in high-level cognition mediation and executive function process (Du Boisgueheneuc et al. 2006). This result converges with several previous studies in SLE patients (Difrancesco et al. 2013; Mak et al. 2012) . Mak et al. (2012) performed an event-related fMRI experiment in non-NPSLE patients and detected increased activation in the SFC.L during feedback evaluation event in Wisconsin Card Sorting Test (WCST) compared to healthy controls. They suggested impaired executive control functions in non-NPSLE patients. And DiFrancesco et al. (2013) studied brain activity in childhood-onset SLE (cSLE) patients responding to a cognitive task and found increased SFC activation in cSLE patients, suggesting dysfunction of SFC in cSLE patients compared to controls. We also noted that Mak et al. (2016) found increased GM volume in the SFC.L in SLE patients compared to controls, which seems not consistent with our result of cortical thinning in SFC.L in the non-NPSLE patients. This inconsistency may be resulted from different samples, Mak et al. recruited both male and female as subjects while we only included female subjects, or from different analysis methods (VBM and SBM). VBM takes cortical thickness, cortical surface area and cortical folding together to calculate GM changes and these factors may reduce the sensitivity of detecting significant GM abnormalities (Hester et al. 2009; Voets et al. 2008). Mak et al. (2012) also found significant SFC activation in newly-diagnosed SLE patients during a cognitive-shifting task compared to healthy controls. Taking previous findings together (Hester et al. 2009; Mak et al. 2012; Voets et al. 2008), our result of decreased cortical thickness in SFC may suggest executive control dysfunctions in SLE patients even in the absence of neurophychiatric symptoms.

RSFC

To investigate the functional alterations that were associated with decreased cortical thickness, RSFC analysis was performed in non-NPSLE and the healthy controls. In non-

NPSLE patients, the decreased cortical thickness in LING.L was correlated to the increased RSFC in PCC.L, and decreased cortical thickness in SFC.L was correlated to the decreased RSFC in CRBL 6.L (Fig. 3, Table 3). However, it remains unclear whether the structural abnormalities influence functional properties in non-NPSLE patients. The PCC has been identified a key component of the DMN (Greicius et al. 2003) which is believed involving in cognitive functions (Leech and Sharp 2014), including memory retrieval (Maddock et al. 2001), working memory and attention (Leech and Sharp 2014), self-related cognitive activity especially for episodic memory retrieval (Sestieri et al. 2011; Vannini et al. 2011). We found the abnormal RSFC of LING-PCC was associated to the functional abnormalities in PCC, a hub region of DMN. This result is consistent with several previous studies (Difrancesco et al. 2013; Mak et al. 2012). DiFrancesco et al. (2013) studied three cognitive functions, visuoconstructional ability (VCA), working memory, and attention in cSLE patients by using fMRI tasks and found that the increased activation in PCC in cSLE patients was negatively correlated with neuropsychological testing scores. And Mak et al. (2012) evaluated executive function in SLE patients by using WCST and found abnormal PCC activation in SLE patients. In addition, Lin et al. (2011) found decreased ReHo values in regions located in the DMN in non-NPSLE patients. Taken together, the LING is part of the visual recognition network, involved in visual attention (Caspers et al. 2014). PCC may be significantly activated when percept information from attention task and is involved in regulating the focus of attention (Leech and Sharp 2014). Moreover, we found positive correlation between the cortical thickness in LING.L and the RSFC in LING.L-PCC.L. This suggested that the degree of cortical thickness in LING.L may influence the functional coupling with the PCC.L which was reported associated with impaired visual attention in non-NPSLE patients.

Studies indicated that the cerebellum mainly involves in executive control function (Habas et al. 2009). Our result of the decreased RSFC in SFC.L-CRBL 6.L in the non-NPSLE patients is consistent with a recent study (Lin et al. 2011), which found decreased ReHo values in the cerebellum in non-NPSLE patients, suggesting the executive control function may be impaired in non-NPSLE patients. Mounting evidence showed that this circuit may be involved in higher-order cognitive function (Herting et al. 2011) especially for working memory processing (Bellebaum and Daum 2007). Therefore, our result of decreased RSFC in SFC.L-CRBL 6.L indicated the disrupted fronto-cerebellar circuit which may associate with working memory deficits in SLE patients without neurophychiatric symptoms. In non-NPSLE patients, we found that the thinner cortical thickness in SFC.L, the lower LING.L-CRBL 6.L intrinsic functional connectivity. This result indicated that the abnormal fronto-cerebellar circuit may be modulated by the decreased cortical thickness in in non-NPSLE patients. Because SFC and CRBL are highly connected (Herting et al. 2011), this finding may suggest a specific link between cortical thinning in SFC.L and impaired fronto-cerebellar circuit in non-NPSLE patients.

Limitations

This study has several limitations. A potential limitation of this study was that the non-NPSLE patients in this study still took medicine before MRI scans, which may bias the detected cortical thickness or RSFC in the patients. Previous studies found that medication use may affect fMRI signals (Mak et al. 2012) and brain structure changes (Navari and Dazzan 2009). Therefore, follow-up analysis should be performed to determine whether the differences in cortical thickness and RSFC could be due to medication use by separating the SLE patients with and without medicine use in the future. Another limitation was that we cannot make a prediction of which non-NPSLE patients or when non-NPSLE patients evolve into NPSLE patients because this is a cross section study instead of longitudinal study. We also cannot infer if the abnormal structure and disrupted connectivity are resulted from the non-NPSLE or non-NPSLE caused these abnormalities. Further longitudinal studies are necessary to clarify these concerns. In addition, we did not perform specific behavioral or cognitive tests which was a major drawback of this study. In the future, we will record the behavioral scores and include task-fMRI into our design, including the goal-directed task (Mak et al. 2012) and Wisconsin Card Sorting Test (WCST), to further detect the link of structural or functional differences with behavioral deficits in non-NPSLE patients.

In conclusion, using a multi-modal imaging approach, we detected uniformly decreased cortical thickness in FUS.L, LING.L, SFC.L and LING.R in non-NPSLE patients. The RSFC results showed abnormal cortical thickness in LING.L is associated with increased RSFC in the PCC.L, and cortical thinning in SFC.L associated with decreased RSFC in SFC.R and CRBL 6.L in non-NPSLE patients. Our findings suggest that the cortical abnormalities may affect brain intrinsic connectivity in non-NPSLE before evolution to NPSLE. And the findings may provide a better understanding of the basis of brain structure and function in non-NPSLE patients and offer our understanding to the pathogenic mechanisms of NPSLE.

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Compliance with ethical standards

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Conflict of interests The authors declare that they have no competing financial interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

Achard, S., & Bullmore, E. (2007). Efficiency and cost of economical brain functional networks. *PLoS Comput Biol, 3*(2), e17.

Appenzeller, S., Bonilha, L., Rio, P. A., Li, L. M., Costallat, L. T. L., & Cendes, F. (2007). Longitudinal analysis of gray and white matter loss in patients with systemic lupus erythematosus. *NeuroImage, 34*(2), 694–701.

Bellebaum, C., & Daum, I. (2007). Cerebellar involvement in executive control. *Cerebellum, 6*(3), 184–192.

Caspers, J., Zilles, K., Amunts, K., Laird, A. R., Fox, P. T., & Eickhoff, S. B. (2014). Functional characterization and differential coactivation patterns of two cytoarchitectonic visual areas on the human posterior fusiform gyrus. *Hum Brain Mapp, 35*(6), 2754–2767.

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis: I. Segmentation and surface reconstruction. *NeuroImage, 9*(2), 179–194.

Difrancesco, M. W., Holland, S. K., Ris, M. D., Adler, C. M., Nelson, S., Delbello, M. P., Altaye, M., & Brunner, H. I. (2007). Functional magnetic resonance imaging assessment of cognitive function in childhood-onset systemic lupus erythematosus: A pilot study. *Arthritis Rheum, 56*(12), 4151–4163.

Difrancesco, M. W., Gitelman, D. R., Klein-Gitelman, M. S., Sagcal-Gironella, A. C. P., Zelko, F., Beebe, D., Parrish, T., Hummel, J., Ying, J., & Brunner, H. I. (2013). Functional neuronal network activity differs with cognitive dysfunction in childhood-onset systemic lupus erythematosus. *Arthritis Research & Therapy, 15*(2), R40. doi:10.1186/ar4197.

Du Boisgueheneuc, F., Levy, R., Volle, E., Seassau, M., Duffau, H., Kinkingnehun, S., Samson, Y., Zhang, S., & Dubois, B. (2006). Functions of the left superior frontal gyrus in humans: A lesion study. *Brain, 129*(12), 3315–3328.

Ecker, C., Ginestet, C., Feng, Y., Johnston, P., Lombardo, M. V., Lai, M. C., Suckling, J., Palaniyappan, L., Daly, E., & Murphy, C. M. (2013). Brain surface anatomy in adults with autism: The relationship between surface area, cortical thickness, and autistic symptoms. *JAMA Psychiatry, 70*(1), 59–70.

Fischl, B., & Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A, 97*(20), 11050–11055.

Fischl, B., Van Der Kouwe, A., Destrieux, C., Halgren, E., Ségonne, F., Salat, D. H., Busa, E., Seidman, L. J., Goldstein, J., & Kennedy, D. (2004). Automatically parcellating the human cerebral cortex. *Cereb Cortex, 14*(1), 11–22.

Fox, M. D., Zhang, D., Snyder, A. Z., & Raichle, M. E. (2009). The global signal and observed anticorrelated resting state brain networks. *J Neurophysiol, 101*(6), 3270–3283.

Fusar-Poli, P., Placentino, A., Carletti, F., Landi, P., & Abbamonte, M. (2009). Functional atlas of emotional faces processing: A voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. *J Psychiatry Neurosci, 34*(6), 418–432.

Gladman, D. D., Urowitz, M. B., Goldsmith, C. H., Fortin, P., Ginzler, E., Gordon, C., Hanly, J. G., Isenberg, D. A., Kalunian, K., & Nived, O. (1997). The reliability of the systemic lupus International Collaborating Clinics/American College of Rheumatology damage index in patients with systemic lupus erythematosus. *Arthritis Rheum, 40*(5), 809–813.

Gladman, D. D., Urowitz, M. B., Kagal, A., & Hallett, D. (2000). Accurately describing changes in disease activity in systemic lupus erythematosus. *J Rheumatol, 27*(2), 377–379.

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *Proc Natl Acad Sci U S A, 100*(1), 253–258.

Habas, C., Kamdar, N., Nguyen, D., Prater, K., Beckmann, C. F., Menon, V., & Greicius, M. D. (2009). Distinct cerebellar contributions to intrinsic connectivity networks. *J Neurosci, 29*(26), 8586–8594.

Herting, M. M., Fair, D., & Nagel, B. J. (2011). Altered fronto-cerebellar connectivity in alcohol-naive youth with a family history of alcoholism. *NeuroImage, 54*(4), 2582–2589.

Hester, R., Nestor, L., & Garavan, H. (2009). Impaired error awareness and anterior cingulate cortex hypoactivity in chronic cannabis users. *Neuropsychopharmacology, 34*(11), 2450–2458.

Hochberg, M. C. (1997). Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum, 40*(9), 1725.

Horn, D. I., Yu, C., Steiner, J., Buchmann, J., Kaufmann, J., Osoba, A., Eckert, U., Zierhut, K. C., Schiltz, K., & He, H. (2010). Glutamatergic and resting-state functional connectivity correlates of severity in major depression – The role of Pregenual anterior cingulate cortex and anterior insula. *Front Syst Neurosci, 4*(33). doi:10.3389/fnsys.2010.00033.

Hou, J., Lin, Y., Zhang, W., Song, L., Wu, W., Wang, J., Zhou, D., Zou, Q., Fang, Y., & He, M. (2013). Abnormalities of frontal-parietal resting-state functional connectivity are related to disease activity in patients with systemic lupus erythematosus. *PLoS One, 8*(9), e74530. doi:10.1371/journal.pone.0074530.

Hutton, C., Draganski, B., Ashburner, J., & Weiskopf, N. (2009). A comparison between voxel-based cortical thickness and voxel-based morphometry in normal aging. *NeuroImage, 48*(2), 371–380.

Jung, R. E., Segall, J. M., Grazioplene, R. G., Qualls, C., Sibbitt Jr., W. L., & Roldan, C. A. (2010). Cortical thickness and subcortical gray matter reductions in neuropsychiatric systemic lupus erythematosus. *PLoS One, 5*(3), e9302.

Kaul, A., Gordon, C., Crow, M. K., Touma, Z., Urowitz, M. B., Van Vollenhoven, R., Ruiz-Irastorza, G., & Hughes, G. (2016). Systemic lupus erythematosus. *Nat Rev Dis Primers, 2*, 16039. doi:10.1038/nrdp.2016.39.

Kevin, M., Birn, R. M., Handwerker, D. A., Jones, T. B., & Bandettini, P. A. (2009). The impact of global signal regression on resting state correlations: Are anti-correlated networks introduced? *NeuroImage, 44*(3), 893–905.

Leech, R., & Sharp, D. J. (2014). The role of the posterior cingulate cortex in cognition and disease. *Brain, 137*(1), 12–32.

Liang, M., Corzillius, M., Bae, S., Lew, R., Fortin, P., Gordon, C., Isenberg, D., Alarcon, G., Straaton, K., & Denburg, S. (1999). The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum, 42*(4), 599–608.

Lin, Y., Zou, Q. H., Wang, J., Wang, Y., Zhou, D. Q., Zhang, R. H., Zhang, Y. W., Lii, H. T., & Fang, Y. F. (2011). Localization of cerebral functional deficits in patients with non-neuropsychiatric systemic lupus erythematosus. *Hum Brain Mapp, 32*(11), 1847–1855.

Lüsebrink, F., Wollrab, A., & Speck, O. (2013). Cortical thickness determination of the human brain using high resolution 3T and 7T MRI data. *NeuroImage, 70*, 122–131.

Ly, M., Motzkin, J. C., Philippi, C. L., Kirk, G. R., Newman, J. P., Kiehl, K. A., & Koenigs, M. (2012). Cortical thinning in psychopathy. *Am J Psychiatry, 169*(7), 743–749.

Maddock, R. J., Garrett, A. S., & Buonocore, M. H. (2001). Remembering familiar people: The posterior cingulate cortex and autobiographical memory retrieval. *Neuroscience, 104*(3), 667–666.

Mak, A., Ren, T., Fu, E. H., Cheak, A. A., & Ho, R. C. (2012). A prospective functional MRI study for executive function in patients with systemic lupus erythematosus without neuropsychiatric symptoms. *Semin Arthritis Rheum, 41*(6), 849–858.

Mak, A., Ho, R. C.-M., Tng, H.-Y., Koh, H. L., Chong, J. S. X., & Zhou, J. (2016). Early cerebral volume reductions and their associations with reduced lupus disease activity in patients with newly-diagnosed systemic lupus erythematosus. *Sci Report, 6*(22231). doi:10.1038/srep22231.

Martina, L., Motzkin, J. C., Philippi, C. L., Kirk, G. R., Newman, J. P., Kiehl, K. A., & Michael, K. (2012). Cortical thinning in psychopathy. *Am J Psychiatry, 169*(7), 743–749.

Navari, S., & Dazzan, P. (2009). Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings. *Psychol Med, 39*(11), 1763–1777.

Ren, T., Ho, R. C. M., & Mak, A. (2012). Dysfunctional cortico–basal ganglia–thalamic circuit and altered hippocampal–amygdala activity on cognitive set-shifting in non-neuropsychiatric systemic lupus erythematosus. *Arthritis Rheum, 64*(12), 4048–4059.

Rykhlevskaia, E., Gratton, G., & Fabiani, M. (2008). Combining structural and functional neuroimaging data for studying brain connectivity: A review. *Psychophysiology, 45*(2), 173–187.

Ségonne, F., Dale, A., Busa, E., Glessner, M., Salat, D., Hahn, H., & Fischl, B. (2004). A hybrid approach to the skull stripping problem in MRI. *NeuroImage, 22*(3), 1060–1075.

Ségonne, F., Pacheco, J., & Fischl, B. (2007). Geometrically accurate topology-correction of cortical surfaces using nonseparating loops. *IEEE Trans Med Imaging, 26*(4), 518–529.

Sestieri, C., Corbetta, M., Romani, G. L., & Shulman, G. L. (2011). Episodic memory retrieval, parietal cortex, and the default mode network: Functional and topographic analyses. *J Neurosci, 31*(12), 4407–4420.

Shapiralichter, I., Vakil, E., Litinsky, I., Oren, N., Glikmannjohnston, Y., Caspi, D., Hendler, T., & Paran, D. (2013). Learning and memory-related brain activity dynamics are altered in systemic lupus erythematosus: A functional magnetic resonance imaging study. *Lupus, 22*(6), 562–573.

Sled, J. G., Zijdenbos, A. P., & Evans, A. C. (1998). A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Med Imaging, 17*(1), 87–97.

Späti, J., Hänggi, J., Doerig, N., Ernst, J., Sambataro, F., Brakowski, J., Jäncke, L., Grosse Holtforth, M., Seifritz, E., & Spinelli, S. (2015). Prefrontal thinning affects functional connectivity and regional homogeneity of the anterior cingulate cortex in depression. *Neuropsychopharmacology, 40*(7), 1640–1648.

Van Tol, M.-J., Li, M., Metzger, C., Hailla, N., Horn, D., Li, W., Heinze, H., Bogerts, B., Steiner, J., & He, H. (2014). Local cortical thinning links to resting-state disconnectivity in major depressive disorder. *Psychol Med, 44*(10), 2053–2065.

Vannini, P., O'brien, J., O'keefe, K., Pihlajamäki, M., Laviolette, P., & Sperling, R. (2011). What goes down must come up: Role of the posteromedial cortices in encoding and retrieval. *Cereb Cortex, 21*(1), 22–34.

Voets, N. L., Hough, M. G., Douaud, G., Matthews, P. M., James, A., Winmill, L., Webster, P., & Smith, S. (2008). Evidence for abnormalities of cortical development in adolescent-onset schizophrenia. *NeuroImage, 43*(4), 665–675.

Wang, Y., Zhong, S., Jia, Y., Sun, Y., Wang, B., Liu, T., Pan, J., & Huang, L. (2016). Disrupted resting-state functional connectivity in Nonmedicated bipolar disorder. *Radiology, 280*(2), 529–536. doi:10.1148/radiol.2016151641.

Xu, J., Cheng, Y., Lai, A., Lv, Z., Campbell, R. A., Yu, H., Luo, C., Shan, B., Xu, L., & Xu, X. (2015). Autoantibodies affect brain density reduction in Nonneuropsychiatric systemic lupus erythematosus patients. *Journal of Immunology Research, 2015*, 11. doi:10.1155/2015/920718.

Yan, C.-G., Cheung, B., Kelly, C., Colcombe, S., Craddock, R. C., Martino, A. D., Li, Q., Zuo, X.-N., Castellanos, F. X., & Milham, M. P. (2013). A comprehensive assessment of regional variation in the impact of head micromovements on functional connectomics. *NeuroImage, 76*, 183–201.

Zhang, Z., Wang, Y., Shen, Z., Yang, Z., Li, L., Chen, D., Yan, G., Cheng, X., Shen, Y., & Tang, X. (2016). The neurochemical and microstructural changes in the brain of systemic lupus erythematosus patients: A multimodal MRI study. *Sci Report, 6*, 19026. doi:10.1038/srep19026.