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Neuroimaging evidence of white matter inflammation in newly diagnosed Systemic Lupus Erythematosus

Amy E. Ramage^{1,2}, Peter T. Fox^{1,2,3,4,5,6}, Robin L. Brey³, Shalini Narayana^{1,5}, Matthew D. Cykowski^{1,7}, Mohammad Naqibuddin⁹, Margaret Sampredo⁹, Stephen L. Holliday⁶, Crystal Franklin¹, Daniel J. Wallace⁸, Michael H. Weisman⁸, and Michelle Petri⁹

¹University of Texas Health Sciences Center at San Antonio, School of Medicine, Research Imaging Institute

²Department of Psychiatry, San Antonio

³Department of Neurology, San Antonio

⁴Department of Physiology, San Antonio

⁵Department of Radiology San Antonio

⁶VA Heart of Texas Health Care Network, San Antonio

⁷The University of Oklahoma Health Sciences Center, Department of Pathology

⁸Cedars-Sinai Medical Center/David Geffen School of Medicine at UCLA, Los Angeles, CA

⁹Johns Hopkins University School of Medicine, Division of Rheumatology

Abstract

Objective—Systemic lupus erythematosus (SLE) with central nervous system (CNS) involvement is frequent and can have high morbidity. The primary pathophysiology of SLE in the CNS is thought to be inflammation secondary to autoantibody-mediated vasculitis. Neuroimaging studies have reported hypometabolism (impending cell failure) and atrophy (late-stage pathology), but not inflammation. We used a validated index of SLE-related disease activity as a regressor for positron emission tomographic (PET) images of glucose uptake to detect the presence and regional distribution of inflammation (hypermetabolism) and tissue failure, apoptosis or atrophy (hypometabolism).

Methods—Eighty-five newly diagnosed SLE patients without focal neurological symptoms were studied. Disease activity was quantified using the SELENA SLE Disease Activity Index (SS). ¹⁸Fluoro-deoxy-glucose (FDG) PET images were analyzed by visual inspection and as group statistical parametric images using the SS score as the analysis regressor.

Results—SS-correlated increases in glucose uptake were found throughout the white matter, most marked in heavily myelinated tracts. SS-correlated decreases were found in frontal and parietal cortex, in a pattern similar to that seen by visual inspection and in prior reports of hypometabolism.

Conclusion—We interpret the SS-correlated increases in glucose consumption as potential evidence of inflammation, in keeping with prior reports of hypermetabolism in inflammatory disorders. To our knowledge, this is the first imaging evidence of SLE-induced CNS inflammation in an SLE inception cohort. The dissociation between ¹⁸FDG uptake characteristics, spatial

distribution, and correlation with disease activity argues that glucose hyper- and hypometabolism reflect fundamentally different aspects of the pathophysiology of CNS SLE.

Keywords

systemic lupus erythematosus; positron emission tomography; glucose metabolism; SLEDAI; inflammation

When systemic lupus erythematosus (SLE) patients exhibit central nervous system (CNS) signs or symptoms, the prognosis is poorer, the mortality higher (1), and the quality of life is reduced (2). The increased mortality and poor quality of life accompanying CNS involvement highlights the importance of detecting SLE-mediated effects on the brain as early as possible. The best estimate for the prevalence rate of SLE in the United States is approximately 350,000 (3) with CNS involvement in as many as 80% (2, 4, 5). Within the first two years of disease, approximately 20% of patients report neuropsychiatric (NP) symptoms that are attributed to SLE (2). However, many patients (28–40%) report at least one neuropsychiatric episode before or within the first year of diagnosis (2).

The primary pathophysiology of SLE is inflammation secondary to autoantibody-mediated effects on tissue, degeneration of small vessels and vasculopathy (6). Inflammation is initiated by circulating autoantibodies generating inflammatory mediators and ends with cell dysfunction, apoptosis and tissue loss (1, 6, 7). Neuroimaging studies in SLE have supplied ample evidence of chronic changes indicative of late-stage pathology. PET studies have reported decreased blood flow (hypoperfusion) and decreased glucose metabolism (hypometabolism), chiefly in frontal and parietal grey matter. T1- and T2-weighted MRI studies have reported white matter volume loss and small punctate lesions. Diffusion tensor MRI and magnetization transfer imaging (MTI) studies show reduced myelination, even in SLE patients with no clear structural damage (8). No neuroimaging methods used to date have detected the inciting pathology, i.e., inflammation.

Here, we used PET imaging to detect and localize both brain markers of inflammation (incipient pathology) and tissue failure and apoptosis (late-stage pathology) in persons with newly diagnosed, neurologically asymptomatic SLE. This was done using ^{18}F -fluoro-deoxy-glucose (^{18}F FDG) PET to index both inflammation (detected as increased ^{18}F FDG uptake) and cell failure (detected as decreased ^{18}F FDG uptake). ^{18}F FDG is commonly used to detect grey matter dysfunction and atrophy, because the glucose metabolic rate decreases as tissue fails. ^{18}F FDG, however, can also be used to detect inflammation (e.g., vasculitis (9)) given that inflammatory cells demonstrate increased glucose transporter expression and that cytokines increase the affinity of glucose transporters for deoxyglucose (10). Similar methods to ours have been used to detect early evidence of white matter hypermetabolism in schizophrenia (11) and attention-deficit/hyperactivity disorder (12).

PET data can be analyzed either by visual inspection, or more objectively by using regression methods to quantify covariance of regional ^{18}F FDG uptake with a clinical measure (13). The Safety of Estrogens in Lupus Erythematosus National Assessment modified version of the SLE Disease Activity Index (SELENA SLEDAI, SS) is a clinical measure used regularly in the evaluation of SLE (14). It is an index of disease activity in multiple organs, including the brain. Its score correlates with the presence of punctate white matter lesions in the brain of SLE patients without CNS signs or neuropsychiatric (NP) symptoms (15). The imaging analysis we utilized allows for the use of SS as a pattern vector to determine covariance of ^{18}F FDG uptake with disease activity. We hypothesized that combining the in vivo assessment of inflammation or tissue failure in the brain and the SS would provide a potential window into the CNS pathophysiology in SLE.

Patients and Methods

Patients

SLE patients meeting at least four of the American College of Rheumatology (ACR) revised classification criteria were recruited into the study within 9 months of initial diagnosis. Patients were recruited from: Johns Hopkins University School of Medicine in Baltimore (JHU), University of Texas Health Science Center in San Antonio (UTHSCSA), and Cedars-Sinai Hospital in Los Angeles (CS). Institutional review board approval was obtained at each site and informed consent was obtained from all patients. One hundred fourteen patients were enrolled. Of those, 29 were excluded because: they did not receive a baseline PET image (18); did not have current SS scores (5); or there was evidence of stroke (6). Of the remaining 85 subjects (Entire Study group), 19 had evidence of neuropsychiatric symptoms (NP), and 17 had evidence of hyper-intense white matter lesions or atrophy on MRI, as reported previously (16) (MRI+), consistent with a typical inception SLE cohort. However, to exclude any influence of prior NP symptoms or CNS signs on the imaging findings, we also analyzed the data using patients with no history of NP symptoms and no abnormalities on MRI (n=49, non-NP/MRI-).

Clinical Data

The demographic, medical and neurological/neuropsychiatric information was recorded and American College of Rheumatology NPSLE case definitions were assigned. The Automated Neuropsychological Assessment Metrics Test Battery (17) and a battery of traditional neuropsychological tests (i.e., California Verbal Learning Test (18), Finger Tapping (19), Wisconsin Card Sorting Test (20), Wechsler Adult Intelligence Scales (21) Digits Forward/Backward and Block Design subtests, verbal fluency (22) and the Rey-Osterrieth Complex Figure- copy and delay (23)) were administered to characterize cognitive functioning. A board-certified clinical neuropsychologist (SLH) made the determination of impairment on the neuropsychological tests based on published age-corrected normative data for each test. The Calgary Depression Scale was administered to assess current mood (24).

The SS was used to document SLE activity. In addition, the Systemic Lupus International Collaborating Clinics American College of Rheumatology Damage Index (SLICC/ACR) was used to record irreversible changes in organ function present for at least 6 months (25).

Image Acquisition

Two PET scans were obtained for each subject in a single scanning session: one transmission scan and one ^{18}F FDG emission scan. The 10-minute transmission scan used a $^{68}\text{Ge}/^{68}\text{Ga}$ rod source and was used for attenuation correction of the emission scan. A 20-minute emission scan was obtained following intravenous administration of 185–370 megabecquerels (~ 5 millicuries) of ^{18}F FDG and a 30-minute uptake period, during which the subject rested with their eyes closed in a darkened room. Images were reconstructed by filtered back projection, using site-specific filters, resulting in a single PET scan with average emission per voxel. All images were re-filtered at the image analysis site (UTHSCSA) with a Gaussian kernel, to a full-width half maximum (FWHM) of 7 mm isotropic and value normalized to a whole-brain mean value of 1,000 PET counts, thus correcting for global differences in glucose metabolism across patients. Because PET counts and ^{18}F FDG uptake are linearly correlated (26) and the data analyses were non-quantitative (visual inspection) or correlation based (voxel-wise analysis), images were not converted to glucose metabolic rate or standard uptake values.

Two, high-resolution, whole-brain MRI scans were obtained for each subject in a single scanning session: one T1-weighted image and one T2-weighted image. T1-weighted image

parameters were: TR = 500 ms; TE = 20 ms; flip angle = 90°. T2-weighted image parameters were: TR = 3400 ms; TE = 20–80 ms; flip angle = 90°, using a dual echo pulse sequence. T1-weighted images from all sites were used for visual assessment of atrophy. T1-weighted images from two sites (UTHSCSA, JHU) were obtained in 3D mode and were suitable for spatial normalization of the PET images (below), as well as for atrophy assessment. T2-weighted images were used to detect white-matter lesions.

Image Spatial Normalization

Spatial normalization (alignment of the PET images to a known anatomical reference) of PET images is a prerequisite for the voxel-wise correlational analysis used here. Because anatomical MRI images were acquired in 3-D at two sites (UTHSCSA and JHU) and in 2-D at one site (CS), spatial normalization steps differed between sites. For UTHSCSA and JHU PET data, a subject's MRI image was used as references for spatial normalization of the PET image. This method is preferred, as the anatomical features used for spatial normalization are more apparent in T1-weighted MRI images than in PET images. PET images were co-registered per subject to their corresponding T1-weighted MRI (non-brain tissue removed), with the anterior commissure as the origin, the mid-sagittal plane as the y-z plane, and in the dimension of the Talairach and Tournoux (1988) atlas using the FSL Linear Image Registration Tool (27). For CS data, PET images were normalized directly to a high-resolution anatomical image (28). Once in standard space, an average PET image was created for each site separately and each subject's normalized PET image was non-linearly aligned to the site-specific average (Automated Image Registration, (29)). After spatial normalization, PET images were isotropically re-sampled at $2 \times 2 \times 2$ mm voxel spacing, sinc interpolated, and smoothed to 15 mm FWHM with Hanning filter.

Voxel-wise Correlational Analysis

Whole brain, voxel-wise analyses were computed for four patient groups: 1) Entire Study ($n = 85$); 2) subjects negative for neuropsychiatric sign/symptoms and MRI signs (NP-/MRI-; $n = 49$); 3) subjects with MRI findings (MRI+; $n = 17$); 4) subjects with neuropsychiatric signs/symptoms (NP+; $n = 19$) – two of the NP+ patients also had MRI abnormalities. For each subject group, correlation images were calculated in two stages. First, voxel-wise correlation images were computed to determine the pattern of ^{18}F FDG uptake to SS score for each subject group within each site. Second, these group-wise images were pooled across sites. This two-stage approach was taken to avoid introducing artifacts into the analysis by merging “raw” images from different PET scanners.

Within group, within-site t-statistic images were computed using the SS score as a regressor, controlled for the effects of age. Images were computed using the FSL general linear model function (randomise, (30)). Monte Carlo permutations (1000 permutations per image) were computed to create a distribution of test statistics under the null hypothesis (no effect of SS), using an exact test for partial correlation.

Across-site images were computed by applying an un-weighted Z analysis (31) to the three within-site images for each group using MatLab® routines. In this method, t-score images derived from FSL randomise were normalized to z-score image maps. The z-score images for each site were combined and normalized to create a single z-score image representing the combined results across sites. Using this method, the null hypothesis may be rejected within the aggregate data even when the results may not be significant for any site alone. The Z image was then converted to a two-tailed probability map and a significance threshold of $z > 3$ (representing a $p < 0.002$) for clusters > 10 voxels (80 mm^3) was applied. Supra-threshold clusters are reported for both SS-correlated increases (SS+) and decreases (SS-) in ^{18}F FDG uptake. The peak coordinates for each significant cluster were labeled for specific

anatomical location using the Talairach Daemon (www.talairach.org/) and tissue type (white/grey) was verified by visual inspection.

Blinded-Reader Interpretation

Three experienced readers concurrently rated all PET and MRI images, achieving consensus for each reading. Images for each modality were read in independent sessions so that for PET, readers were blinded to results from MRI. Readers were also blinded to patient diagnosis (normal controls were included as foils) and study site. Images were normalized to the cerebellum mean count. Readers saw the PET images in 3 color spectra: 1) spectrum mode using a range of 15% to 85% of the cerebellum mean 2) grey scale mode using a range of 15% to 85%, and 3) spectrum mode using the full width. All three viewing modes were rated on a 4-point scale: 0 = normal; 1 = mildly abnormal; 2 = moderately abnormal; 3 = severely abnormal. MRI results were previously published (14) and are used here only for grouping PET data (e.g., MRI+ and MRI-) for analysis.

Results

Patient Demographics—This was an inception cohort in which all patients were enrolled within nine months of first diagnosis. Patients showed mild to moderate SLE activity (SS mean = 4, s.d. = 4.5), little irreversible tissue damage (SLICC/ACR mean = 0.7, s.d. = 1.16), were not depressed (Calgary mean = 5, s.d. = 4), and performed within normal limits on the ANAM (mean average throughput $z = 0.02$, s.d. = 0.71) compared to age-matched normal subjects. Twenty-four of the patients performed more than two standard deviations below that of an age-matched normative control group on at least one of the traditional neuropsychological tests, but only three patients performed this poorly on two or more of the tests.

Eighty-five SLE patients were scanned across the three sites (20–69 years old, TABLE 1). Nine subjects were in an active, mild-moderate disease flare (i.e., current worsening symptoms as characterized by the SS). The characteristic clinical indication of SLE was arthritis (21/85 of our subjects), rash (27/85) or positive serologies (low complement or DNA, 33/85). NPSLE manifestations were evident in 19 of the subjects, including complaints of anxiety, mood disorder, psychosis, mononeuropathy or headache (NP+ group). In most these patients, symptoms had been present for as many as 10 years prior to SLE diagnosis. Of the components of the SS pertaining to the CNS in the NP+ group, only cranial neuropathy (1) and psychosis (1) were reported. Seventeen subjects had MRI abnormalities (MRI+ group, 12 with atrophy, 5 with hyper-intense white matter lesions). The remaining 49 subjects had no evidence of either NP symptoms or abnormal MRI findings (non-NP/MRI- group).

Voxel-wise Correlational Analysis

SELENA SLEDAI-Related Increases—Disease-activity-related increases in ^{18}F FDG uptake were much greater in extent in white matter than in grey matter (FIGURE 1). In the Entire Study group, SS-related increases were present in frontal, parietal and occipital centrum semiovale, subcortical temporal and limbic white matter, cerebellar white matter and in brain-stem tracts (TABLE 2, FIGURE 2). In the NP+ and MRI+ groups, the SS-related hypermetabolic regions were more extensive in frontal and sub-cortical white matter, particularly evident in the corpus callosum. In contrast, in the non-NP/MRI- group, the SS+ ^{18}F FDG uptake was limited to focal white matter abnormalities in subgyral frontal lobe, anterior cingulate (limbic), and corpus callosum (sub-cortical).

SELENA SLEDAI-Correlated Decreases—Disease-activity-correlated decreases in ^{18}F FDG uptake were quite limited in extent and were chiefly in grey matter (TABLE 2). For example, in the Entire Study group, SS- ^{18}F FDG uptake was limited to a small cluster in the middle frontal gyrus. Interestingly, the majority of SS- uptake was in the frontal and temporal regions and was seen in the non-NP/MRI- and NP+ groups (FIGURE 2). In many cases, the local maximum for a SS- cluster was in white matter, but the extent of the cluster was in grey matter.

Visual Interpretation of PET Images

Decreases in glucose uptake in cortical grey matter were readily apparent to visual inspection in 36 (of 85) subjects. Blinded reader scoring for the normal subject images included as foils was grade 0. For the SLE patients, the scores were: grade 0 = 50 subjects (FIGURE 3, A); grade 1 = 24 subjects (FIGURE 3, B); grade 2 = 8 subjects (FIGURE 3, C); grade 3 = 3 subjects (2 non-NP/MRI-, 1 NP+ [anxiety and psychosis two years prior to PET scanning]). Visually detected abnormalities were limited to frontal and parietal cortex. No raters reported white-matter hypermetabolism; however, this is expected given that white matter does not utilize glucose as extensively as grey matter and therefore is difficult to assess by *visual* inspection in ^{18}F FDG PET and are only detectable with group-wise regression analyses, as described above. The PET scores did not correlate with SS ($r = 0.171$); that is, patients with more severe PET ratings did not have higher disease activity scores. Following completion of the entire study, an unblinded reading (focused on subjects with greatest disease activity (highest SS index)) was performed to determine if hypermetabolism was visually detectable when specifically sought for; it was not.

Discussion

Widespread regional increases and decreases in brain glucose uptake were found in an inception cohort of SLE patients. While decreases in brain glucose metabolism (32) and perfusion (33) have been reported previously in SLE, to our knowledge this is the first report of regional hypermetabolism. Although both hyper- and hypometabolism were detected, the two phenomena differed markedly in their severity, in their spatial distribution, and in their correlation with systemic disease activity. Decreases in glucose consumption were quite marked, being readily apparent to visual inspection, even on single-subject images (FIGURE 3). Hypometabolism was most marked in frontal and parietal cortex, which replicated prior reports. Increases in glucose uptake were undetectable by visual inspection of per-subject images and only detected by group-wise regression analysis. SS-correlated increases in ^{18}F FDG uptake were diffusely present in white matter, being particularly dramatic in heavily myelinated tracts, including the centrum semiovale, corpus callosum and internal capsule (FIGURE 2). Hypometabolism was minimally correlated with systemic disease activity (SS), while hypermetabolism was highly correlated with SS. This triple dissociation (severity, spatial distribution and correlation with systemic disease activity) argues strongly that glucose hyper- and hypometabolism reflect fundamentally different aspects of the pathophysiology of CNS SLE.

White matter inflammation

We interpret the observed SS-correlated white-matter hypermetabolism as evidence of acute inflammation. In the CNS, evidence of inflammation has been found in SLE through post-mortem histological examinations, which demonstrate vasculitis, microinfarcts and perivascular microglia surrounding small blood vessels (34). Antigens and autoantibodies, known to be elevated in SLE (35) in the CSF, generate the inflammatory mediators interferon-alpha, IP-10 (CXCL10), interleukin-6 and -8, and MCP-1 (e.g., (36)) which amplify inflammation and activate microglia (37). As noted above, inflammation increases

glucose transporter expression, while cytokines increase the affinity of glucose transporters for deoxyglucose (10). Thus, increased uptake of ^{18}F FDG would be expected in the presence of inflammation. That the glucose hypermetabolism was specifically elicited by correlation with systemic disease activity suggests that CNS inflammatory activity levels are influenced by systemic activity, even in the non-NP/MRI- group. Perhaps the most striking aspect of this finding is its spatial distribution: the CNS inflammatory activity detected by glucose hypermetabolism was seen virtually entirely in white matter, but diffusely so.

White matter structural lesions and atrophy

Structural neuroimaging has provided ample evidence of white-matter damage in SLE. Punctate white-matter lesions and volume loss are common in periventricular and subcortical brain regions in SLE (38). Diffusion tensor imaging (DTI) in SLE has shown loss of white matter tissue integrity in limbic regions as well as the insula, thalamus, corpus callosum, and parietal and frontal white matter (8), (39). These findings are more common in NPSLE and in the chronic state of disease (40).

Some structural MRI studies of white matter integrity in SLE have suggested inflammatory changes. Appenzeller and colleagues used proton (hydrogen-1) magnetic resonance spectroscopy (MRS) to detect impaired axonal integrity in occipito-parietal white matter prior to the appearance of focal white-matter lesions or cortical atrophy, inferring that atrophy is the consequence of a prior inflammatory process in SLE (41). Similarly, Bosma and colleagues used magnetization transfer ratio (MTR) to detect subtle, diffuse white-matter changes in SLE patients with neuropsychiatric symptoms as well as in SLE patients without NP symptoms during a symptomatic flare, but not in SLE patients without NP symptoms and not in disease flare, strongly suggesting that a flare may be required to cause white-matter damage (42). Collectively, these findings suggest that white-matter inflammation is a primary or early pathology in SLE, while punctate lesions and diffuse volume loss develop over time.

Grey matter hypofunction, apoptosis and atrophy

Numerous functional imaging studies have demonstrated grey matter functional decline in SLE. ^{18}F FDG PET, H_2^{15}O PET, and technetium-99m hexamethylpropylene amine oxime-single-photon-emission computed tomography (HMPAO-SPECT) have consistently shown cortical grey matter hypometabolism and hypoperfusion, in the same fronto-parietal distribution observed here (43). In view of the evidence suggesting that the incipient pathology in SLE is white-matter inflammation followed by white-matter lesions and volume loss (above), the grey matter specificity of the chronic hypometabolism and hypoperfusion begs an explanation. One potential explanation is that grey matter functional decline is a form of disconnection-induced diaschisis in which diffuse loss of white matter structural integrity causes diffuse cortical functional decline in regions remote from but connected to other regions via these white matter tracts (44). In the functional imaging literature, diaschisis is most commonly associated with a focal, mixed-tissue (grey and white matter) lesion in one region causing a remote functional decline in a connected region. For example, a left frontal-lobe stroke will cause right cerebellar diaschisis (45). Small ischemic white-matter lesions, however, can also produce extensive cortical diaschisis in the area to which the lesioned fibers project (46). Similarly, decline in white matter integrity observed with normal aging results in decreased metabolism of glucose in cortical grey matter and accounts for age-related cognitive decline (47). In SLE then, the diffuse grey-matter hypometabolism may indicate the extensive nature of the white-matter pathology, rather than indicting primary grey matter pathology.

The behavioral consequences of diaschisis are not well known. Remote diaschisis (e.g., cerebral-cerebellar) has been reported to resolve over time but is not well correlated with behavioral recovery. Regions showing diaschisis do not always show later atrophy (46). Whether diaschisis due to undercutting white matter lesions is associated with grey matter volume loss is unknown. In our prior report, we found that volume loss on MRI (by visual inspection) was present in approximately 25% of SLE subjects within 9 months of diagnosis (16). By visual analysis, however, it was impossible to determine whether the tissue loss was limited to white-matter volume loss or included cortical thinning. Measuring cortical thickness with high-resolution structural MRI (T1-weighted) would best answer this question.

Temporal evolution

We presume that the regions of decreased SS-correlated ^{18}F FDG uptake in grey matter are indicative of potential tissue failure or diaschisis, but not loss, as a result of impaired white matter function due to inflammation. The cascade of inflammatory antibody/autoantibody release seen in SLE can mediate CNS tissue diaschisis (6). For example, circulating autoantibodies in SLE can bind to neuronal membranes causing transient disruptions in cell function without lethal effects (48). In addition, antibodies may bind to endothelial cells in the vascular wall influencing the blood-brain barrier and allowing inflammatory agents to enter the CNS (49). It is known that indicators of inflammation, i.e., serum autoantibodies and histopathology-confirmed micro-infarcts, are seen in SLE patients without CNS signs or symptoms (34, 50). In fact, the timeline for the presence of serum markers in SLE may be 10 years prior to diagnosis of SLE, and likely 1.5 years prior to any symptoms of the disease (50). Thus, SLE may be a silent disease for a few years prior to diagnosis with the potential of white matter inflammation transiently (7) causing diaschisis in grey matter. The remitting/recurring nature of SLE may allow regions that are frequently exposed to the inflammatory cascade to ultimately fail resulting in apoptosis and atrophy; only a longitudinal study could verify this. Our data lead us to hypothesize that the CNS becomes involved early in the course of SLE, prior to severe systemic medical symptoms, suggesting that SLE manifestations and concomitant systemic inflammation play an important, early role in SLE-related brain pathophysiology.

Future Study

We have shown a strong association between SLE disease activity and increased ^{18}F FDG uptake indicating inflammation in white matter of newly diagnosed SLE patients. Consistent with other studies, we also found decreased ^{18}F FDG uptake in frontal and parietal grey matter that was minimally correlated with disease activity. We propose that inflammation of white matter is the inciting pathology in the CNS and that grey matter tissue failure and subsequent apoptosis or atrophy represent the late-stage pathology. Given the sensitivity of our measure to CNS inflammation in newly diagnosed SLE, future study is necessary to further explore the underlying CNS pathophysiology of SLE using other imaging metrics more sensitive to white matter integrity (e.g., diffusion tensor imaging) and to inflammation (e.g., ^{18}F FDG PK11195 PET to detect microglial activation) very early in the disease progression. These techniques and our methods could also be used to follow the evolution and affect of inflammation on brain tissue during flares and remission, as well as to assess the effectiveness of treatments to reduce inflammation and late-stage damage.

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FIGURE 1.

Breakdown of white and grey matter increased and decreased ^{18}F FDG uptake by patient group (green=non-NP/MRI-, blue=MRI+, and red=NP+) and brain area. Each lobe is differentiated by white and grey matter suprathreshold cluster extent in mm^3 . The NP+ group had the greatest extent of white matter effects. Grey matter effects, both increases and decreases, were seen to a limited extent and primarily in the NP+ and non-NP/MRI- groups except in the cerebellum where all groups showed increased ^{18}F FDG uptake.

FIGURE 2. Increased ^{18}F -FDG uptake associated with SS score for the Entire Study group. Large SS-correlated clusters were observed in the frontal to parietal centrum semiovale (panel A) and bilateral temporal (panel B) white matter. The white arrow indicates the cluster of increased SS-related ^{18}F -FDG uptake that was also present in the non-NP/MRI-group.

FIGURE 3.

Raw PET Image for SLE subjects with PET ratings of 0 (normal, panel A), 1 (mild, panel B), 2 (moderate, panel C) and 3 (severe, panel D) from Visual Inspection. Notice the relative decrease of regions with high ^{18}F FDG uptake (red) and greater regions of low glucose uptake (green to blue). The mild ratings tended to be associated with either bi-frontal or bi-parietal (hypometabolism). Subcortical grey matter regions were spared across all subjects.

TABLE 1

Patient demographic, severity and clinical ratings and medications by group, mean (standard deviation).

SELENA SLEDAI scores were used as the regressor for ^{18}F FDG uptake. Age, gender and race in this sample are representative of the typical SLE population (i.e., higher in young, female, African American and Hispanic groups (1)). The four study groups (Entire Study, non-NP/MRI-, NP+, and MRI+) did not differ significantly for SS ($F(3,170)=1.277$, $p=0.284$), age ($F(3,170)=1.574$, $p=0.198$), PET rating ($F(3,170)=0.389$, $p=0.761$), SLICC/ACR Damage Index ($F(3,170)=1.861$, $p=0.138$), Calgary score ($F(3,170)=0.052$, $p=0.985$) or ANAM average z-throughput ($F(3,170)=0.720$, $p=0.541$).

	Entire Study	Non-NP/MRI-	NP+ ^a	MRI+ ^b
N	85	49	19	17
Age	40 (12)	37 (12)	41 (9)	45 (13)
Gender	75 F	47 F	14 F	14 F
Ethnicity (n)				
African American	10	6	3	1
Asian	4	4	0	0
Hispanic	17	8	3	7
Native American	1	0	1	0
White Non-Hispanic	52	29	12	12
Other	2	2	0	0
SELENA SLEDAI	3.83 (4.53)	3.04 (3.76)	5.37 (6.6)	5.3 (6.6)
SLICC/ACR Damage Index	.65 (1.16)	.53 (1)	1.26 (1.59)	.85 (1.42)
Calgary Depression Scale	4.69 (4.3)	4.91 (4.64)	4.84 (4.85)	4.5 (3.56)
ANAM average z-throughput	.01 (.71)	.11 (.67)	-.12 (.77)	-.10 (.74)
Neuropsychological Tests ^c	21	11	6	4
Medications ^d (% of patients)				
Prednisone	45	32	63	55
Methylprednisone	2	10	0	0
Hydroxychloroquine	81	72	79	95
Acetylsalicylic Acid	8	2	21	10

^aTwo of the NP+ patients had abnormalities in periventricular white matter and one had mild atrophy evidenced on MRI.

^bNone of the MRI+ patients had neuropsychiatric or neurological signs or symptoms.

^cNumber of patients who scored less than 2 standard deviations from a normative control group on the traditional neuropsychological tests.

^dDosages of prednisone qid ranged from 3–60 mg, of methylprednisone ranged from 200–400 mg, of hydroxychloroquine ranged from 200–800, of ASA ranged from 20–400 mg.

TABLE 2
Regions and coordinates (Talairach & Tournoux) for the largest z and cluster size seen in each group.

Location	SLE group	Local Maxima	Cluster size	Standardized Coordinates
		z	mm ³	x y z
<i>INCREASE</i>				
White Matter				
Sub-gyral Frontal	Entire Study	3.7	664	-20 2 30
	non-NP/MRI-	3.41	88	36 28 16
Sub-gyral Temporal	NP+	4.22	480	22 36 -8
	Entire Study	4.89	1952	-32 -12 -10
Anterior Cingulate	NP+	3.61	328	24 -54 14
	non-NP/MRI-	3.87	232	-8 22 -2
Cingulate	NP+	3.99	376	-16 -10 26
	Entire Study	3.87	160	-18 -52 20
Extra-nuclear	NP+	4.25	352	16 -46 6
	non-NP/MRI-	4.5	456	-18 0 22
Corpus Callosum	MRI+	4.09	152	22 -52 6
	Entire Study	3.57	80	12 20 16
	non-NP/MRI-	3.69	136	12 26 10
	NP+	4.65	1880	-10 24 8
<i>DECREASE</i>				
Grey Matter				
Precentral Gyrus	non-NP/MRI-	-3.81	104	-44 -14 52
	NP+	-4.4	120	40 -18 60
Medial Frontal Gyrus	non-NP/MRI-	-3.55	80	-18 10 46
	non-NP/MRI-	-3.91	184	50 -14 50
Precuneus	non-NP/MRI-	-3.54	88	44 -70 34
	non-NP/MRI-	-3.77	480	-46 -6 -2
Superior Temporal Gyrus	non-NP/MRI-	-3.83	192	46 -14 4
Insula	non-NP/MRI-	-3.83	192	46 -14 4

Increased SS-related ^{18}F FDG uptake was seen almost exclusively in white matter whereas decreased SS-related ^{18}F FDG uptake was limited to grey matter (also see FIGURE 2). The non-NP/MRI- group had increased SS-related ^{18}F FDG uptake in all of the 4 same regions seen in the Entire Study group except in temporal white matter. The non-NP/MRI- also had more regions of decreased SS-related ^{18}F FDG uptake in grey matter than any other group.