Supplemental Data

Resting Glucose Metabolism Validation Studies

1. Validation of hypermetabolic regions previously identified in Group 1

The hippocampus, orbitofrontal cortex (Brodman area (BA) 11), and putamen/globus pallidus (GP) were previously identified as regions with abnormal resting hypermetabolism in SLE-1 compared to 17 healthy control (HC-1) subjects (1). Glucose metabolism in these regions prospectively measured in the 20 SLE-2 subjects also demonstrated significant hypermetabolism in the hippocampus ($p<0.008$), orbitofrontal cortex ($p<0.006$) and putamen/GP ($p<0.004$) compared to the 17 HC-1 subjects plus an additional 8 healthy control subjects (HC-2) (combined; 25 HC-1/2). Metabolism in these regions was not different between the SLE-2 and SLE-1 subjects ($p>0.22$). These results demonstrate prospective validation in the SLE-2 subjects of the hypermetabolic regions previously identified in SLE-1 subjects.

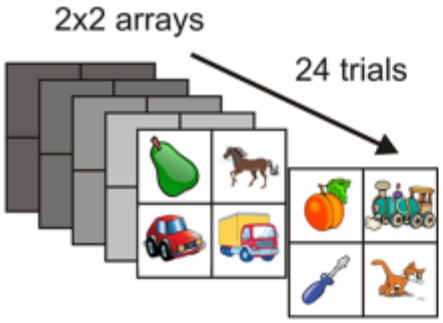
2. Hypermetabolic regions identified in Group 2

A whole brain, voxel-wise approach was used to compare FDG-PET scans in the 20 SLE-2 subjects to the group of 25 HC-1/2. Significant hypermetabolism (**Supplemental Table 1**) was identified in the hippocampus ($p<0.001$), orbitofrontal cortex (BA11) ($p<0.001$), and putamen/GP extending into the thalamus ($p<0.001$); the same hypermetabolic regions previously identified in SLE-1 subjects (1). Four new hypermetabolic regions were also identified, including the sensorimotor cortex (SMC, BA 3/4) ($p<0.001$), occipital lobe (BA 19) ($p<0.001$), temporal lobe (BA 37) ($p<0.001$), and parietal lobe (BA 7/40) ($p<0.001$) (**Supplemental Table 1**).

Glucose metabolism in these regions was then retrospectively measured in the 17 SLE-1 compared to the HC-1/2 subjects; SLE-1 subjects again demonstrated significant hypermetabolism in the hippocampus ($p=0.001$), orbitofrontal cortex ($p<0.03$), putamen/GP ($p<0.001$), and SMC ($p<0.03$), but not in the occipital lobe ($p=0.077$), temporal lobe ($p=0.061$), and parietal lobe ($p=0.61$). Metabolism was not different between the SLE-2 and SLE-1 subjects in any of these hypermetabolic regions ($p>0.08$), except the parietal lobe where SLE-2 had higher metabolism than SLE-1 ($p<0.02$) (**Table 2**). Thus, retrospective

validation of the hypermetabolic regions identified in SLE-2 using an unbiased, voxel wise approach, again demonstrated similar regional hypermetabolism in the 3 regions identified originally in SLE-1 (hippocampus, orbitofrontal cortex, putamen/GP) plus the SMC. These results suggest that hypermetabolism in these regions represents a biologic marker of disease and is not spurious.

To understand why the 4 new regions identified in the SLE-2 group had not been identified in the original analyses with the SLE-1 group, we retrospectively computed and compared metabolism in the 17 SLE-1 patients and the 17 HC-1 in these 4 new regions. We found that 3 of the 4 regions showed a post-hoc trend ($p=0.09$; Temporal Lobe) or non-significant ($p>0.20$; Occipital Lobe and Parietal Lobe) differences between groups; while there was one new region (Sensorimotor Cortex) that showed significantly higher metabolism ($p=0.005$) in the SLE-1 group, it still did not meet the basic voxel-level threshold of $p<0.001$ used in the SPM analysis. By contrast, metabolism in the four new regions was significantly higher in the SLE-2 patients compared to the HC-1/2 control group, exceeding the prespecified SPM threshold. These results demonstrate that the new regions were in fact identified through the addition of the SLE-2 group to the patient mix. That said, the SLE-1 and SLE-2 patients differed in their respective distributions of disease duration (Table 1, Results Section 1.0). We note that SLE-2 included patients with disease duration between 2 and 10 years, whereas SLE-1 patients were selected as having either short (≤2 years) or long (≥10 years) disease duration. The data suggest that the inclusion of patients of intermediate disease duration in SLE-2 facilitated the detection of several new SLE-related areas which had failed to exceed threshold in the dichotomized SLE-1 sample.



Supplemental Figure 1. 2x2 non-spatial and spatial memory task. Subjects observed drawings of objects arranged as 2 × 2 arrays. Immediately after viewing they were asked 1) whether a particular object was present in the array; a question that assesses object memory, or 2) to identify the relationship of one particular object to another in the array; an assessment of spatial memory.

Supplemental Table 1. Brain regions with significant differences in metabolic activity between SLE subjects from Groups 1 (SLE-1) and 2 (SLE-2), and 25 Healthy Controls (HC-1/2).

Brain region	Coordinates[a]						
	x	y	z	Z_{max}[b]	HC (n=25)	SLE Group 2 (n=20)	SLE Group 1 (n=17)
Hippocampus, left	-28	-24	0	3.96 [c]	1.35 (0.07) [d]	1.44 (0.07)***	1.42 (0.06)**
Orbitofrontal Cortex (BA 11), right	30	42	-12	3.48	1.48 (0.07)	1.57 (0.09)***	1.53 (0.09)*
left	-14	48	-18	3.75	1.47 (0.05)	1.54 (0.09)***	1.51 (0.06)**
Putamen/GP/thalamus, right	28	-14	4	4.21 [c]	1.45 (0.07)	1.55 (0.06)***	1.54 (0.08)***
Sensorimotor Cortex (BA 3/4), right	4	-38	74	3.74 [c]	1.47 (0.12)	1.61 (0.12)***	1.58 (0.13)**
left	-4	-38	72	3.65 [c]	1.53 (0.10)	1.66 (0.12)***	1.62 (0.13)*
Occipital Lobe (BA 19), left	-32	-72	6	3.92	1.19 (0.07)	1.31 (0.12)***	1.24 (0.11)
Temporal Lobe (BA 37), right	32	-44	-22	3.73	1.59 (0.08)	1.68 (0.08)***	1.63 (0.09)
Parietal Cortex (BA 7/40), right	50	-58	50	3.68	1.68 (0.08)	1.80 (0.11)***	1.70 (0.11)
left	-48	-52	48	3.73	1.79 (0.07)	1.87 (0.08)***	1.79 (0.10)

[a] Montreal Neurological Institute (MNI) standard space (60)
[b] Significant at $p<0.001$ (peak voxel, uncorrected). [c] Significant at $p<0.05$, corrected for cluster extent.
[d] Mean (SD) regional metabolism
* $p<0.05$, ** $p<0.01$, *** $p<0.001$, Student's T-test of SLE subjects vs. Healthy Control (HC) group BA, Brodmann area; GP, globus pallidus; HC, healthy controls; SLE, systemic lupus erythematosus