Methods for Exploratory Statistical Parametric Mapping

SPM was used to identify additional brain regions implicated in the response to systemic inflammation. SPM2 (Wellcome Department of Cognitive Neurology, London, UK) executed on a Matlab 6.5 platform was used for voxel-based statistical analysis. Glucose metabolism images were spatially normalized to an FDG template. A mean of each subject's endotoxin and placebo glucose utilization images was used as the source for spatial normalization. Images were smoothed using a Gaussian kernel of 12 mm full-width half-maximum. Comparisons of the endotoxin and placebo conditions (endotoxin minus placebo, and placebo minus endotoxin) were performed using voxel-based paired *t* tests. Brain versus non-brain was determined with an explicit mask of all glucose utilization images proportionally scaled to 0.8. The voxel size was 2.0, 2.0 and 2.0 mm (1 resel = 248 voxels). The search volume was 1,433,520 mm^3, 179,190 voxels, 629.5 resels. The smoothness was full-width half-maximum, 10.6, 12.5 and 14.9 mm = 5.3, 6.3 and 7.4 voxels. A significance threshold of $p \leq .001$ at the uncorrected voxel level was used to increase sensitivity. To confirm SPM findings, the regions that showed significant changes with SPM analysis were assessed with region of interest analysis, using the corresponding region from the automated anatomical labeling template. The confirmatory ROI analysis included condition and region as within-subject factors, and regions were modeled as within-subject factors using random subject effects and structured variance-covariance patterns.

Results of Exploratory Statistical Parametric Mapping Analysis

The regions identified by the exploratory SPM analysis are listed in Supplementary Table 1. Subsequently, ROI analysis was used to confirm the SPM results. There was a main effect of condition (F (1,119) = 9.2, p = .0029) and a condition-by-region interaction (F (7,119) = 3.9, p = .0007). As outlined in Supplementary Table 2, this overall effect was due to 5.5 ± 4.2% lower NGM in the left putamen (F (1, 119) = 20.2, p < .0001; Supplementary Figure 1), 2.6 ± 3.7% lower NGM in the right cuneus (F (1, 119) = 6.4, p = .0013) and 4.4 ± 4.3% higher NGM in the right ventrolateral thalamus (Fig. 3A; F (1, 119) = 5.1, p = .0026). ROI analysis failed to show a statistically significant difference in the other regions identified with SPM. Discrepancies between SPM and ROI results using the AAL template are not unexpected, due to anatomical differences between the regions being compared.

Supplemental Table 1.
Results of Exploratory Statistical Parametric Mapping Analysis

	Cluster Level			Voxel Level				
Higher glucose metabolism (endotoxin minus placebo)								
	$P_{corrected}$	K_e	$P_{uncorr.}$	$P_{corrected}$	*T*	Ze	$P_{uncorr.}$	x, y, z (mm)
Thalamus, right ventral posterior lateral	0.57	45	0.041	0.15	10.8	4.6	0	16,-18,8
Temporal, middle gyrus right	0.13	89	0.007	0.15	7.3	3.9	0	68,-28,-10
Insula, right	0.86	28	0.098	0.19	6.5	3.7	0	38,-22,18
Lingual gyrus, right	0.98	17	0.189	0.23	6.1	3.6	0	16,-62,-4
Lower glucose metabolism (placebo minus endotoxin)								
	$P_{corrected}$	K_e	$P_{uncorr.}$	$P_{corrected}$	*T*	Ze	$P_{uncorr.}$	x,y,z
Cuneus, right	0.94	22	0.138	0.07	13.7	4.9	0	4,-84,30
Frontal, superior gyrus left	0.91	25	0.116	0.61	8.7	4.2	0	-30,32,48
Lingual gyrus, left	0.94	22	0.138	0.86	6.9	3.8	0	-12,-58,2
Parietal, inferior lobule, left	1.0	3	0.592	0.88	5.6	3.5	0	-66,-40,30
Cingulate, right	1.0	9	0.336	0.88	4.8	3.2	0.001	6,8,32
Putamen, left	1.0	2	0.67	0.88	4.6	3.1	0.001	-30,-6,2

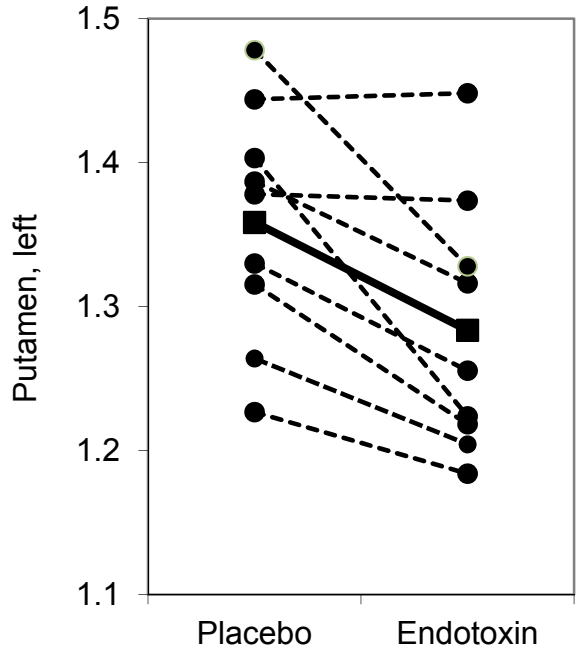
Smoothness: FWHM, 10.6, 12.5, 14.9 mm = 5.3, 6.3, 7.4 voxels. **Search volume**: 1,433,520 mm^2 = 179,190 voxels = 629.5 resels. **Voxel size**: 2.0, 2.0, 2.0 mm (1 resel = 248 voxels).

At the cluster level, *p* values refer to the chance of finding a cluster of this or larger size (k_e), corrected or uncorrected for search volume. At the voxel level, *p* values refer to the chance of finding a voxel with this or greater height (*T* or *Z* statistic), corrected (using a false discovery rate correction) or uncorrected for search volume. The coordinates (x, y, z) denote the location (in mm) in Montreal Neurological Institute (MNI) space of the respective cluster or voxel.

Supplemental Table 2.
Region-of-Interest Analysis of SPM-identified Regions

SPM-identified region	Placebo NGM	Endotoxin NGM	Mean % difference	*F (1, 119)*	Uncorrected *p*
Frontal gyrus, superior left	1.13±0.04	1.11±0.02	-0.8±2.7	1.6	.2
Cuneus, right	1.31±0.08	1.28±0.07	**-2.6±3.7**	6.4	**.013**
Lingual gyrus, right	1.20±0.08	1.19±0.11	-0.8±4.5	0.5	.48
Lingual gyrus, left	1.22±0.08	1.20±0.08	-1.7±4.3	3.1	.08
Parietal gyrus, inferior left	1.38±0.06	1.38±0.08	0.1±5.0	0.0	.89
Putamen, left	1.36±0.03	1.28±0.03	**-5.5±4.2**	20	**<.0001**
Temporal gyrus, middle right	1.27±0.05	1.27±0.05	0.3±2.2	0.0	.97
Thalamus, ventrolateral right	1.07±0.10	1.12±0.08	**4.4±4.3**	5.1	**.026**

The table shows mean values ± standard deviation for normalized glucose metabolism (NGM) in each region in the placebo and endotoxin condition. Mean percent difference = mean of each individual's percent difference between placebo and endotoxin. Regions identified with SPM were considered significant in ROI analysis (in bold) at the uncorrected $p < .05$ level.



Supplemental Figure 1: Within-subject differences in normalized glucose metabolism in the left putamen. Dotted lines represent individual subjects; the solid line represents the mean.