Metabotropic Glutamate Receptor 5 and Glutamate Involvement in Major Depressive Disorder: A Multimodal Imaging Study

Supplemental Information

FreeSurfer Segmentation

The processing of the structural magnetic resonance images (MRI) was conducted using the publically available FreeSurfer package (http://surfer.nmr.mgh.harvard.edu), version 5.3. The "recon-all" pipeline includes modeling participant's cortical data on an inflated, common surface using inflation based on averaged group folding patterns and spherical registration, as previously described (1-3). All MRI images underwent motion correction, brain extraction, and intensity normalization, followed by Talairach transformation, signal intensity correction, automated topological correction, and tessellation of the boundary between gray and white matter. Following the parcellation of the gray matter, and reconstruction of the pial and white matter surfaces, the volume of region of interest were extracted based on the AAL atlas. Visual inspections for quality assurance were completed; no manual interventions were necessary. All image processing, parcellation, and quality control procedures were conducted while blinded to participants' demographic and clinical characteristics. The volumes of each ROI were compared between groups using *t*-tests. There were no significant differences between groups following correction for multiple comparisons (Table S1).

Magnetic Resonance Spectroscopy

Tissue composition within the MRS voxel was assessed. There were significant differences between MDD and HC in the MRS voxel content of gray matter, white matter, or cerebrospinal fluid (all p values > 0.2).

For validation, we conducted Monte-Carlo analyses on individual spectra to derive within-subject uncertainties. The results were as follows: Glu/Cr mean error = 0.081 +/- 0.055, CI = (0.065, 0.097); Gln/Cr mean error = 0.070 +/- 0.046, CI = (0.057, 0.083); Myoinositol/Cr mean error = 0.050 +/- 0.031, CI = (0.041, 0.059); Scylloinositol/Cr mean error = 0.0078 +/- 0.0036, CI = (0.0068, 0.0088); NAA/Cr mean error = 0.033 +/- 0.018, CI = (0.028, 0.038); Glx/Cr mean error = 0.129 +/- 0.028, CI = (0.107, 0.152); Cho/Cr mean error = 0.011 +/- 0.006, CI = (0.010, 0.013).

Table S1. Volumes of regions of interest

ROIs	HC Mean	HC SEM	MDD Mean	MDD SEM	*p*	FDR
Amygdala	3,411	86	3,332	77	0.50	0.58
Anterior Insula	8,527	174	8,146	175	0.13	0.42
Caudate	7,663	186	7,401	192	0.33	0.55
Anterior Cingulate	8,196	215	7,320	207	0.01	0.07
Posterior Cingulate	1,616	74	1,702	96	0.47	0.58
Frontal Cortex	84,385	1,761	81,257	1,873	0.23	0.49
Hippocampus	8,302	158	7,909	158	0.08	0.36
Occipital Cortex	26,549	559	26,053	708	0.58	0.58
Parietal Cortex	20,716	471	19,929	388	0.21	0.49
Posterior Insula	4,017	106	3,930	104	0.56	0.58
Putamen	10,579	205	10,351	237	0.47	0.58
Temporal Cortex	64,189	1,315	62,455	1,197	0.34	0.55
Thalamus	14,395	285	13,354	272	0.01	0.07

HC = healthy control; MDD = major depressive episode; SEM = standard error of means; Volume unit is mm^3.

Supplemental References

1. Dale AM, Fischl B, Sereno MI (1999): Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage*. 9:179-194.
2. Fischl B, Dale AM (2000): Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences of the United States of America*. 97:11050-11055.
3. Fischl B, Sereno MI, Dale AM (1999): Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. *Neuroimage*. 9:195-207.