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Altered glutamate concentration in major depressive disorder during antidepressant treatment: A glutamate CEST MRI study

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Original Article

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Abstract

Background. Selective serotonin reuptake inhibitors (SSRIs) represent an effective treatment for major depressive disorder (MDD). This study employed glutamate chemical exchange saturation transfer (GluCEST) magnetic resonance imaging (MRI) to compare glutamate-sensitive signals in the prefrontal cortex and hippocampus of MDD patients before and after SSRI treatment.

Methods. The study included 35 unmedicated MDD patients and 39 healthy controls (HCs) who underwent baseline GluCEST imaging, using magnetization transfer ratio asymmetry (MTR_{asym}) values to reflect regional glutamate levels. Twenty MDD patients completed follow-up GluCEST imaging after 8 weeks of SSRI treatment. Depressive symptoms were assessed using the Hamilton Rating Depression Scale (HAMD).

Results. At baseline, the MTR_{asym} values in the left hippocampus and bilateral prefrontal cortex were significantly lower in MDD patients compared to the HCs. Following SSRI treatment, the 20 MDD patients who completed follow-up showed significantly increased MTR_{asym} values in the bilateral hippocampus and bilateral prefrontal cortex relative to baseline. Uncorrected correlation analyses showed that treatment-related differences in MTR_{asym} values in the left hippocampus and left prefrontal cortex were associated with changes in HAMD-17 total score, sleep disturbance, and retardation scores.

Conclusions. GluCEST imaging suggested abnormal glutamate-sensitive signals in the prefrontal cortex and hippocampus of patients with MDD. SSRI treatment was associated with increased GluCEST signals across all regions of interest. The observed associations between regional GluCEST signal changes and symptom changes further suggest a potential role of glutamatergic-related modulation in the therapeutic effects of SSRIs.

Introduction

Major depressive disorder (MDD) is a prevalent psychiatric condition characterized by persistent depressed mood or anhedonia, which imposes significant burdens on both individuals and society (GBD, 2022 Mental Disorders Collaborators, 2022). MDD is highly heterogeneous, with diverse etiologies and considerable individual variation in treatment response, complicating the delivery of precise clinical interventions. This frequently results in worsening symptoms or adverse events. Elucidating the pathological mechanisms of MDD is therefore essential for advancing diagnostic accuracy and personalized treatment. The prefrontal cortex and hippocampus are two key brain regions within the prefrontal–hippocampal circuitry that have been implicated in the pathophysiology of MDD (Geng et al., 2016). These regions are critically involved in emotion regulation, cognitive control, stress responsivity, and memory processing, all of which are closely related to the core symptoms of depression. Consistent with their functional relevance, multiple structural and functional magnetic resonance imaging (MRI) studies have reported volumetric and functional abnormalities in the prefrontal cortex and hippocampus in patients with MDD (Chan et al., 2016; Krug et al., 2022; Wei et al., 2017; Wise et al., 2017). In particular, the prefrontal cortex plays a central role in the top-down regulation of emotion and executive function (Pizzagalli & Roberts, 2022), whereas the hippocampus is closely associated with stress-related neuroplasticity, contextual memory, and illness burden (Tartt et al., 2022). Neurochemical studies further suggest that glutamatergic dysregulation contributes to MDD pathophysiology, with relatively consistent evidence of altered glutamatergic metabolites in

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frontal regions (Moriguchi et al., 2019; Onaolapo & Onaolapo, 2021) and accumulating findings implicating hippocampal-related abnormalities (Zeng et al., 2023). Based on this evidence, the present study focused on the prefrontal cortex and hippocampus as regions of interest and used glutamate chemical exchange saturation transfer (GluCEST) imaging to assess glutamatergic-related alterations in these regions and their associations with clinical symptoms and treatment response (Figure 1).

Recent neuroimaging studies have provided critical evidence supporting the role of glutamatergic metabolic dysfunction in depression. Positron emission tomography (PET) imaging has shown that symptom remission in MDD patients is significantly associated with increased prefrontal metabolic activity (Carlson et al., 2013; Drevets, Bogers, & Raichle, 2002). This suggests that prefrontal hypometabolism may reflect functional alterations related to depressive states, with glutamate/glutamine (Glu/Gln) metabolic dysfunction potentially serving as a key underlying factor. Glx commonly refers to the combined signal or metabolic cycle of glutamate and glutamine. As the primary excitatory neurotransmitter in the cerebral cortex, glutamate is predominantly located in the central nervous system and plays vital roles in learning, memory, and neurotrophic functions. Glutamate metabolism is regulated through the Glu-Gln cycle, in which glutamate released from neurons is taken up by astrocytes, converted to glutamine, and then recycled back to glutamate. Multiple studies have confirmed that excessive glutamate accumulation can cause severe neuronal and brain tissue damage, leading to abnormal glutamate levels in MDD patients (Dai et al., 2025). Hasler et al. measured prefrontal Glx levels in medication-free adult MDD patients and found significantly reduced Glx in the prefrontal cortex (Hasler et al., 2007). More recently, this reduction has been shown to correlate directly with the severity of depressive symptomatology (Gonsalves et al., 2024). However, findings across studies remain inconsistent. Some reports indicate elevated Glx or glutamate in the prefrontal cortex (PFC) and anterior cingulate cortex (ACC) of MDD patients compared to healthy controls (HCs) (Kantrowitz et al., 2021), while others observed increased glutamate concentrations in the midcingulate cortex (MCC) but no significant differences in the dorsolateral prefrontal cortex (DLPFC) (Grimm et al., 2012). This heterogeneity may arise from limitations of conventional magnetic resonance spectroscopy (MRS), which cannot reliably distinguish glutamate from glutamine, thereby complicating precise pathological interpretation.

GluCEST imaging is an emerging quantitative technique that can overcome the limitations of MRS by enabling high-specificity detection of free glutamate concentrations. Prior studies have demonstrated significantly reduced GluCEST signals in the left hippocampus of patients with MDD, and these reductions were positively correlated with the glutamate/glutamine-to-creatine (Glx/Cr) ratio measured by MRS (Zeng et al., 2023). Furthermore, Cai et al. achieved high-resolution glutamate imaging of human subcortical tissues using 7 T GluCEST, reporting considerably higher GluCEST signals in the amygdala than in the hippocampus. The overall contrast in gray matter was 40% higher than in white matter, a distribution pattern that closely matched glutamate receptor PET mapping (Cai et al., 2013). By providing a more direct measure of glutamate rather than the composite Glx signal from

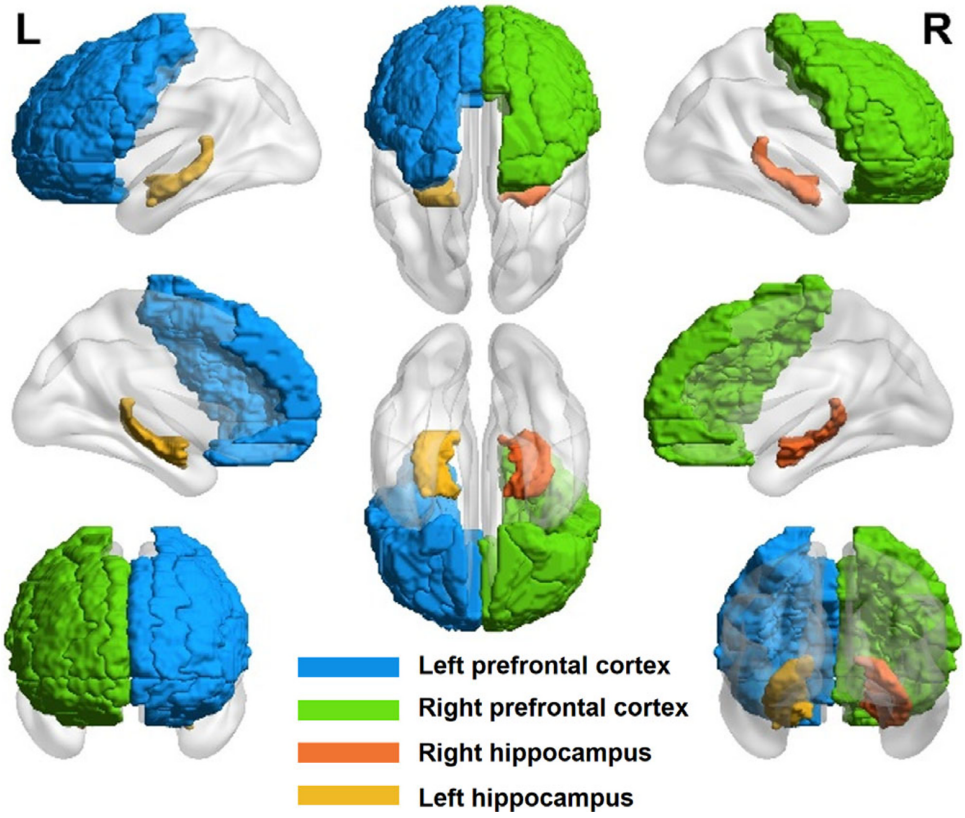


Figure 1. The prefrontal cortex and hippocampus were visualized with the BrainNet Viewer (http://www.nitrc.org/projects/bnv/). The regions of interest (ROIs) denote the areas for data quantification of the prefrontal cortex (left in blue; right in green) and the hippocampus (left in yellow; right in orange). The representative 3D brain maps are presented from multiple anatomical perspectives to show the spatial distribution of the selected structures.

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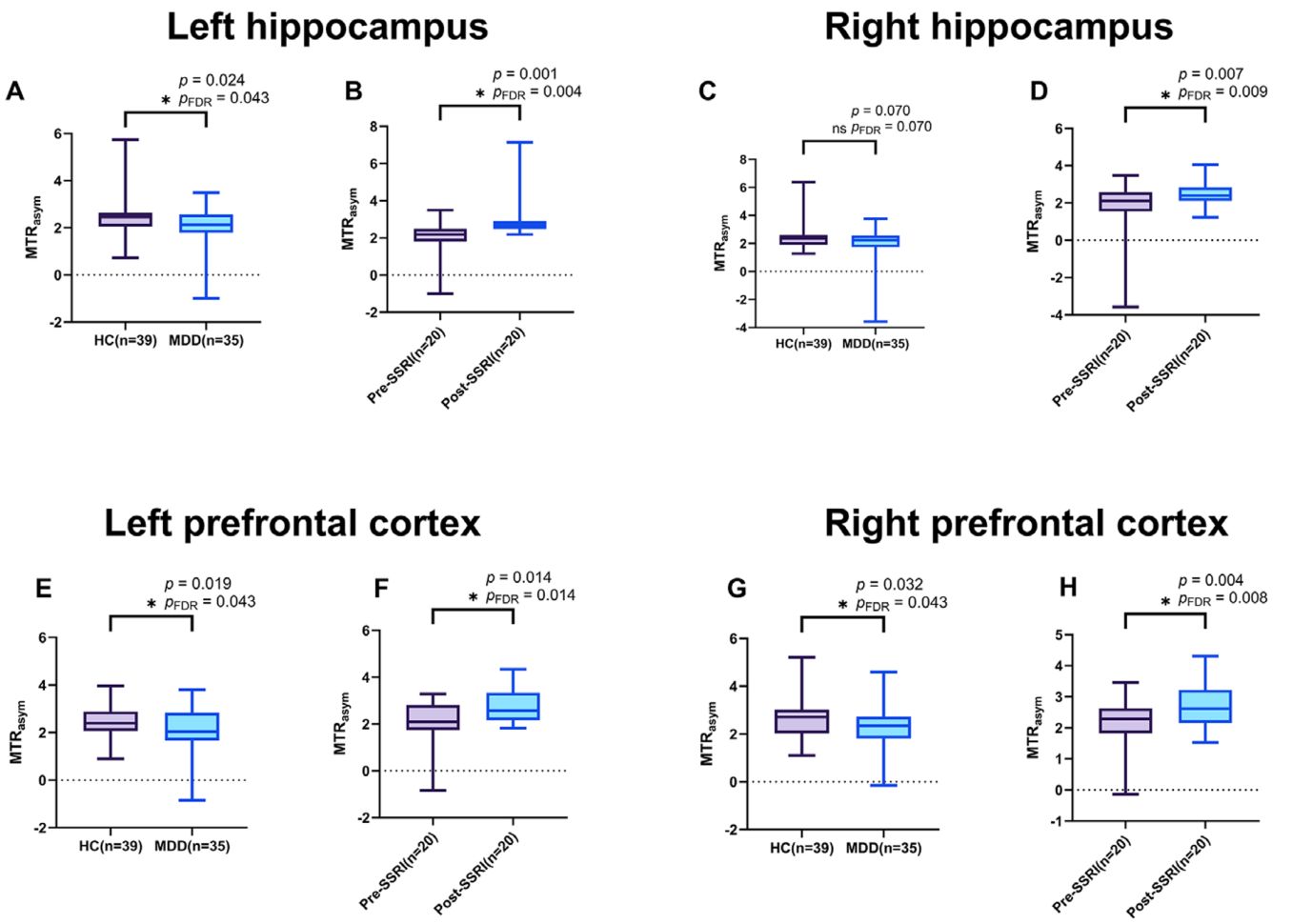


Figure 2. Baseline group differences and longitudinal changes in GluCEST values. (a, c, e, g) Baseline GluCEST values in the bilateral prefrontal cortices and hippocampi in the MDD group compared to the HC group. (b, d, f, h) Longitudinal changes in GluCEST values in the bilateral prefrontal cortices and hippocampi within the MDD group before and after SSRI treatment. Significance was defined as $p_{FDR} < 0.05$. MTR_{asym}, magnetization transfer ratio asymmetry; MDD, major depressive disorder; HCs, healthy controls; SSRI, selective serotonin reuptake inhibitor; p_{FDR}, false discovery rate-corrected *p*-value.

MRS, GluCEST imaging offers a superior approach for investigating glutamatergic dysfunction in MDD (Figure 2).

Selective serotonin reuptake inhibitors (SSRIs) are first-line pharmacological treatments for depression. Their primary mechanism of action involves inhibiting the presynaptic reuptake of serotonin at the serotonin transporter, which increases serotonin levels at the postsynaptic membrane and modulates neural activity (Edinoff et al., 2021). Beyond serotonergic modulation, SSRIs are also thought to influence glutamatergic transmission through indirect mechanisms, potentially restoring glutamate homeostasis to alleviate depressive symptoms and cognitive deficits (Woo et al., 2015). Although MRS studies have provided initial evidence of SSRI-induced changes in glutamatergic metabolites (Tao et al., 2025), no research to date has utilized GluCEST imaging to examine the effects of SSRI treatment on the glutamate system.

This study tested two main hypotheses: first, that patients with MDD would exhibit significant abnormalities in glutamate signals within the prefrontal cortex and hippocampus compared to HCs; and second, that SSRI treatment would modulate these glutamatergic signals. We further examined whether treatment-related changes in GluCEST signals were associated with changes in depressive symptoms. We employed GluCEST imaging to test these hypotheses. This approach was intended to clarify the role of the glutamatergic system in the pathophysiology of MDD and the therapeutic mechanism of antidepressant action.

Methods

Study participants

A total of 74 volunteers were enrolled in this study, comprising 35 patients with MDD and 39 HCs, frequency-matched for age and sex. The MDD group was recruited from the outpatient clinics of Beijing Anding Hospital, which is a tertiary medical institution affiliated with Capital Medical University, while the healthy control group was recruited through advertisements. The inclusion criteria for the MDD group were: (1) Han Chinese ethnicity and right-handed; (2) age between 18 and 60 years; (3) either antidepressant-naïve or having received antidepressant medication for no more than 7 days within the 2 weeks before enrollment; and (4) meeting the diagnostic criteria for MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Exclusion criteria for MDD participants included: (1) a significant comorbid DSM-IV Axis I diagnosis other than depression;

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(2) history of alcohol dependence; (3) pregnancy or lactation; (4) contraindications for MRI; and (5) presence of psychotic symptoms. Inclusion criteria for the HC group were: (1) Han Chinese ethnicity and right-handed; (2) age between 18 and 60 years; (3) no personal history of mental illness; and (4) absence of major chronic physical diseases. Exclusion criteria for HCs consisted of: (1) a family history of mental illness in first-degree relatives; (2) history of alcohol dependence; (3) pregnancy or lactation; and (4) contraindications for MRI. HC participants were screened at enrollment by clinicians through history taking, inquiry about previous psychiatric history, and clinical assessment, together with evaluation using the Mini-International Neuropsychiatric Interview (MINI), to exclude individuals with a personal history of mental illness or clinically significant depressive or anxiety symptoms. During screening, HC participants were also confirmed not to be taking any current psychotropic or nonpsychotropic medications.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Specifically, the study protocol was approved by the Research Ethics Committee of Beijing Anding Hospital, Capital Medical University (approval code: 2022-14-202221FS-2). All participants provided written informed consent.

Clinical assessments

All participants were evaluated using the Hamilton Depression Rating Scale (HAMD), which was administered by board-certified psychiatrists to assess the severity of depressive symptoms (Hamilton, 1967). The 17-item HAMD (HAMD-17) yields several subscale scores, encompassing domains such as retardation, cognitive impairment, anxiety/somatization, sleep disturbance, and weight change (Xue et al., 2023; Zhao et al., 2019). The detailed contents of the HAMD-17 subscales are provided in the Supplementary Material Information.

MR image acquisition

All MRI scans were performed on a Siemens 3T Prisma MR scanner with a 64-channel head coil. Participants were instructed to remain still and minimize head movement throughout the scanning procedure.

High-resolution structural images were obtained using a three-dimensional magnetization-prepared rapid gradient echo (3D-MPRAGE) sequence to acquire T1-weighted images (T1WI) in the sagittal plane. The acquisition parameters were as follows: repetition time (TR) = 2530 ms, echo time (TE) = 4.21 ms, flip angle = 7°, voxel size = 1.0 mm × 1.0 mm × 1.0 mm, field of view (FOV) = 256 mm × 256 mm, slice thickness = 1 mm, and 192 contiguous slices.

GluCEST imaging data were acquired using a SPACE-CEST sequence (Zhang et al., 2020). The CEST parameters included a saturation power of 3 μT, applied as ten 100-ms Gaussian-shaped pulses with 10-ms inter-pulse intervals (Liu et al., 2019, 2021). A separate B1 field map was acquired with the following parameters: TR = 3500 ms, TE = 17 ms, voxel size = 1.4 mm × 1.4 mm × 2.8 mm, FOV = 212 mm × 212 mm, slice thickness = 2.79 mm, slice number = 648. For B0 field mapping, a dual-echo gradient recalled echo (GRE) sequence was used with the parameters: TR = 30 ms, TE = 4.92 ms, voxel size = 1.4 mm × 1.4 mm × 2.8 mm, FOV = 212 mm × 212 mm, slice thickness = 2.79 mm, slice number = 288. CEST saturation was applied at nine frequency offsets relative to the water resonance: control (no RF saturation), ±2.5 ppm, ±3.0 ppm, ±4.0 ppm, and ± 4.5 ppm.

Data processing

Before image analysis, all MR images were independently reviewed for quality control by two experienced radiologists who were blinded to clinical information. Images with poor quality due to obvious head motion, metal artifacts, or visible structural brain abnormalities were excluded from further analysis. GluCEST data were analyzed using custom scripts and toolboxes within the MATLAB environment. Structural image segmentation was performed with FreeSurfer 6.0 to derive regions of interest (ROIs) for the prefrontal cortex and hippocampus. Within MATLAB, the FLIRT tool from FSL (version 6.0; FMRIB, University of Oxford) was first used to register the GluCEST data to the 3.0 ppm reference image for motion correction. Custom scripts were then applied to co-register the GluCEST data with the structural images and to compute whole-brain quantitative parameter maps. GluCEST images were quantified using Magnetization Transfer Ratio Asymmetry (MTR_{asym}), which served as the primary GluCEST metric in this study. Following established methods (Heo et al., 2017; Zhou et al., 2003), the Glu-weighted MTR_{asym} was calculated by setting the intrinsic frequency offset ($\Delta\omega$) between the amine and bulk water proton pools to 3.0 ppm.

Subsequently, the recon-all command in FreeSurfer was executed to perform automated segmentation of the structural images. This comprehensive pipeline processes data through a sequence of steps, which include motion correction, intensity nonuniformity normalization, Talairach transformation, skull stripping, and nonlinear volume registration. The resulting segmentation outputs were then spatially co-registered with the high-resolution structural images to ensure dimensional consistency among the segmentations, the GluCEST quantitative parameter maps, and the original anatomical scans. Using the FreeSurfer anatomical atlas (https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/AnatomicalROI/FreeSurferColorLUT) as a reference, templates for the prefrontal cortex and hippocampus were extracted. The average glutamate-sensitive signals for each region were quantified by calculating the mean value of the quantitative parameters across the bilateral prefrontal and hippocampal areas.

Statistical analysis

Statistical analyses were performed using SPSS software (version 26.0). Continuous data are presented as mean ± standard deviation. A two-tailed P-value <0.05 was considered statistically significant. Group differences for continuous variables were assessed using two-sample t-tests or Mann–Whitney U tests, depending on whether the data met assumptions of normality.

Analysis of covariance (ANCOVA), with age, sex, and years of education as covariates, was used to compare baseline measures between the MDD and HC groups. Within the MDD group, changes from pre- to post-treatment were evaluated using Wilcoxon signed-rank tests. A post hoc sensitivity analysis was performed using G*Power 3.1 for the longitudinal within-subject comparisons (Faul, Erdfelder, Lang, & Buchner, 2007). With a total sample size of 20, a two-tailed α of 0.05, and 80% power, the minimum detectable effect size was dz = 0.66.

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The relationships between the pretreatment-to-posttreatment changes in GluCEST signals within the prefrontal and hippocampal regions and changes in the HAMD-17 total score and its five subscale factors were examined using partial correlation analyses, controlling for age, sex, and years of education. False discovery rate (FDR) correction was adopted to control for multiple comparisons in the ROI-based GluCEST analyses. FDR correction was applied separately to baseline between-group comparisons, longitudinal pretreatment-to-posttreatment comparisons, and exploratory partial correlation analyses. The significance level was set at an FDR-corrected $p < 0.05$.

Results

Demographic and clinical information

Demographic and clinical characteristics of the study participants are summarized in Table 1. The final sample consisted of 35 patients with MDD and 39 HCs. No significant differences were observed between the groups in terms of age, sex, or educational level (all $p \geq 0.05$).

Baseline comparison of prefrontal and hippocampal GluCEST measurements

At baseline, the MTR_{asym} values in the left hippocampus and bilateral prefrontal cortex were significantly lower in the MDD group than in the HC group ($F = 5.344$, $p = 0.024$, $p_{FDR} = 0.043$; $F = 5.785$, $p = 0.019$, $p_{FDR} = 0.043$; $F = 4.767$, $p = 0.032$, $p_{FDR} = 0.043$, respectively). In contrast, no significant between-group difference was observed in the right hippocampus ($F = 3.386$, $p = 0.070$, $p_{FDR} = 0.070$).

Table 1. Sample characteristics

Sample characteristics	MDD (n = 35)	HCs (n = 39)	p-value
Demographic			
Age (years)	28.714 ± 6.138	27.384 ± 5.575	0.332
Sex (female/male)	26/9	21/18	0.068
Education (years)	16.571 ± 1.501	15.850 ± 3.074	0.637
Clinical			
Age at onset (years)	23.743 ± 6.679	-	-
Duration of illness (months)	60.914 ± 72.352	-	-
First-episode/recurrent episodes	14/21	-	-
HAMD-17 total score	20.771 ± 3.3797	-	-
HAMD-17 Factor 1	6.914 ± 1.853	-	-
HAMD-17 Factor 2	0.543 ± 0.852	-	-
HAMD-17 Factor 3	3.600 ± 1.459	-	-
HAMD-17 Factor 4	6.486 ± 1.687	-	-
HAMD-17 Factor 5	3.229 ± 1.716	-	-
Medication, n			
Antidepressants	35	-	-
Benzodiazepine anxiolytics	11	-	-
Hypnotics	7	-	-

HCs, healthy controls; MDD, major depressive disorder; HAMD-17, 17-item Hamilton Depression Rating Scale. Data are presented as mean ± standard deviation for continuous variables and number for categorical variables. Continuous variables were compared using Student's t-test or the Mann–Whitney U test, and categorical variables were compared using the Chi-square test.

Longitudinal changes in prefrontal and hippocampal GluCEST measurements after treatment

Among the 20 MDD patients who completed follow-up, MTR_{asym} values in the bilateral hippocampus and bilateral prefrontal cortex were significantly higher after SSRI treatment compared to pretreatment levels ($Z = -3.285$, $p = 0.001$, $p_{FDR} = 0.004$; $Z = -2.688$, $p = 0.007$, $p_{FDR} = 0.009$; $Z = -2.464$, $p = 0.014$, $p_{FDR} = 0.014$; $Z = -2.912$, $p = 0.004$, $p_{FDR} = 0.008$, respectively).

Correlation between regional GluCEST changes and HAMD-17 scores

Partial correlation analyses, controlling for age, sex, and years of education showed that the pretreatment-to-posttreatment change in left hippocampal MTR_{asym} values was positively correlated with the change in HAMD-17 total scores ($r = 0.543$, $p = 0.024$, $p_{FDR} = 0.321$). In addition, the pretreatment-to-posttreatment change in left prefrontal cortex MTR_{asym} values was positively correlated with the change in HAMD-17 Factor 5 (sleep disturbance) scores ($r = 0.499$, $p = 0.041$, $p_{FDR} = 0.332$). Similarly, the change in left hippocampal MTR_{asym} values was positively correlated with the change in HAMD-17 Factor 4 (retardation) scores ($r = 0.535$, $p = 0.027$, $p_{FDR} = 0.321$). These associations were significant at the uncorrected level only.

Discussion

The present study found that patients with MDD showed significantly lower MTR_{asym} values in the left hippocampus and bilateral prefrontal cortex than healthy controls at baseline. After SSRI treatment, MTR_{asym} values in these regions increased significantly, suggesting treatment-related changes in glutamatergic function. Exploratory analyses further suggested that pretreatment-to-posttreatment changes in MTR_{asym} were associated with changes in overall depressive symptoms and some symptom dimensions, although these associations should be interpreted with caution (Figure 3).

This baseline reduction in regional MTR_{asym} is consistent with accumulating evidence that glutamatergic dysregulation plays an important role in the pathophysiology of MDD (Zeng et al., 2023). Previous proton magnetic resonance spectroscopy (^{1}H-MRS) studies have reported reduced glutamate or glutamate-glutamine complex levels in prefrontal and limbic regions of individuals with depression (Hasler et al., 2007; Moriguchi et al., 2019). One possible explanation is that the reduced glutamatergic signal may be related to impaired glutamate homeostasis and maladaptive neuroplastic changes (Cui et al., 2024; Rajkowska & Stockmeier, 2013). Previous neurobiological models have suggested that astrocytic dysfunction and disturbances in the glutamate–glutamine cycle may contribute to these abnormalities. Astrocytes play a key role in synaptic glutamate clearance and glutamine recycling. Dysfunction in these processes may therefore affect excitatory regulation within the prefrontal–hippocampal network. However, these mechanisms were not directly assessed in the present study and thus require further investigation. Some previous studies, particularly those focusing on the hippocampus, have also reported negative or even contrasting findings(Block et al., 2009; Hermens et al., 2015). These

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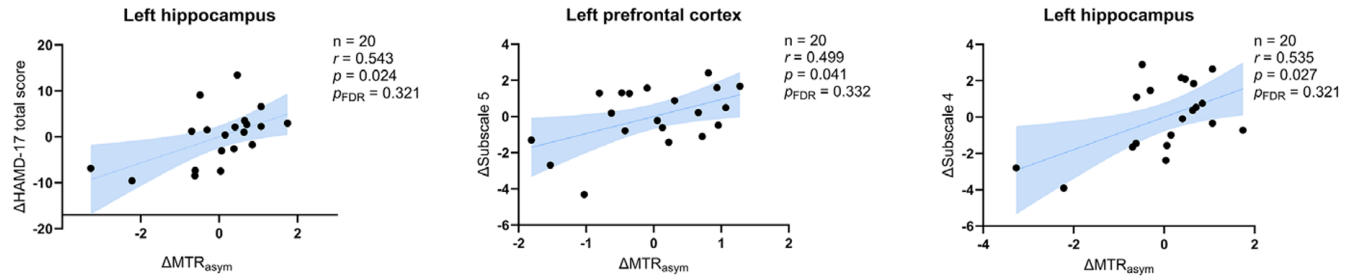


Figure 3. Exploratory associations between changes in GluCEST values and changes in HAMD-17 scores. (a) Scatter plot showing the nominal association between the change in left hippocampal MTR_{asym} values and the change in HAMD-17 total scores. (b) Scatter plot showing the nominal association between the change in left prefrontal cortex MTR_{asym} values and the change in HAMD-17 Factor 5 sleep disturbance scores. (c) Scatter plot showing the nominal association between the change in left hippocampal MTR_{asym} values and the change in HAMD-17 Factor 4 retardation scores. These associations were significant at the uncorrected level but did not survive FDR correction. Δ values were calculated as pretreatment minus posttreatment values. MTR_{asym}, magnetization transfer ratio asymmetry; HAMD-17, 17-item Hamilton Depression Rating Scale; p_{FDR}, false discovery rate-corrected *p*-value.

discrepancies may be related to clinical heterogeneity, including differences in illness stage and prior medication exposure, as well as the methodological limitations of conventional ^{1}H-MRS in assessing deep brain structures (Moriguchi et al., 2019; Yüksel & Öngür, 2010). Our GluCEST findings provide region-specific in vivo evidence of glutamatergic abnormalities in MDD. These baseline regional alterations may also provide a neuroimaging reference for future studies exploring glutamate-modulating treatments and their potential value in treatment monitoring.

Following SSRI treatment, we observed a significant increase in MTR_{asym} values in the bilateral hippocampus and bilateral prefrontal cortex, suggesting treatment-related changes in glutamatergic signaling. This finding is broadly consistent with previous ^{1}H-MRS studies reporting that improvement in depressive symptoms after antidepressant interventions may be accompanied by normalization of glutamate- or Glx-related measures in prefrontal regions (Boucherie, Reneman, Ruhé, & Schrantee, 2023; Luborzewski et al., 2007). Together, these observations raise the possibility that regional glutamate-related abnormalities in MDD may be at least partly state-related and potentially reversible with effective treatment.

Although SSRIs primarily target the serotonergic system, converging evidence suggests that their antidepressant effects may also be associated with downstream changes in glutamatergic neurotransmission and neuroplasticity (Bonanno et al., 2005; Musazzi, Treccani, Mallei, & Popoli, 2013; Spurny et al., 2021). At the cellular level, this may involve partial restoration of glutamate homeostasis, improved astrocyte-supported glutamate clearance and recycling, and normalization of excitatory signaling within cortico-limbic circuits. At the synaptic level, antidepressant treatment has been linked to plasticity-related processes, such as synaptic remodeling and functional recovery, of stress-sensitive neuronal networks. In this context, the posttreatment increase in MTR_{asym} observed in our study may reflect broader neurochemical and circuit-level adaptations related to treatment response, rather than a simple direct increase in glutamate content. However, because GluCEST captures macroscopic imaging changes rather than specific cellular or synaptic events, the precise mechanisms underlying this posttreatment increase remain unclear and require further investigation using multimodal approaches.

Sleep disturbance and psychomotor retardation are important clinical dimensions of MDD (Elkjær et al., 2022; Leitner et al., 2025). In our exploratory analyses, pretreatment-to-posttreatment changes in MTR_{asym} in the left prefrontal cortex and left hippocampus were positively correlated with changes in sleep disturbance, psychomotor retardation, and overall depressive symptoms. One possible interpretation is that these associations may reflect the involvement of prefrontal–hippocampal regions in symptom-related processes of depression. The prefrontal cortex is involved in top-down regulation of affective and behavioral responses, whereas the hippocampus is highly sensitive to stress-related plasticity and has also been implicated in sleep-related dysfunction in depression (Duman & Aghajanian, 2012). In this context, treatment-related imaging changes in these regions may accompany improvement in specific symptom domains, although it remains unclear whether these associations are symptom-specific or reflect broader clinical improvement. However, because these correlations did not survive correction for multiple comparisons, they should be considered exploratory and interpreted with caution. Therefore, the present findings do not support symptom-specific mechanistic inferences, and larger longitudinal studies are needed to determine whether regional GluCEST alterations are specifically linked to changes in sleep disturbance and psychomotor retardation, or instead reflect broader clinical improvement.

Several limitations of this study should be noted. First, only 20 of the 35 patients completed follow-up, resulting in a modest longitudinal sample size and potential attrition bias, which may have limited statistical power and generalizability. Although the observed longitudinal changes showed medium-to-large effect sizes (Cohen's d = 0.68–0.89), these findings should still be interpreted cautiously and require replication in larger samples. Second, while GluCEST is a powerful technique, the MTR_{asym} signal serves as an indirect marker of glutamatergic metabolism rather than a direct quantification of absolute glutamate concentration. This signal can be influenced by pH variations, relaxation effects, and other biophysical factors. Consequently, our findings reflect relative metabolic adaptations and should be interpreted without claiming strict mechanistic specificity. Finally, our hypothesis-driven approach was restricted to the hippocampus and prefrontal cortex, and the reliance on a single post-treatment scan without a longitudinal healthy control group prevents us from fully separating treatment-related changes from nonspecific temporal effects or scanner drift. Future large-scale studies incorporating longitudinal healthy controls, multiple follow-up time points, and whole-brain GluCEST imaging are warranted to comprehensively map treatment-related neurochemical changes.

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Conclusions

This study utilized GluCEST imaging and identified region-specific alterations in MTR_{asym} values within the hippocampus and prefrontal cortex of unmedicated patients with MDD. The significant increase in MTR_{asym} values in these regions following SSRI may be associated, at least in part, with changes in glutamatergic signals. By enabling glutamate-sensitive imaging in MDD patients, GluCEST imaging has helped elucidate potential neuropathological mechanisms and provided valuable neurochemical evidence for understanding the pathophysiology of MDD.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S0033291726105571.

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