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Neurotransmitters and Neurometabolites in Late-Life Depression: A Preliminary Magnetic Resonance Spectroscopy Study at 7T

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Abstract

Background: Magnetic resonance spectroscopy (MRS) methods have quantified changes in levels of neurotransmitters and other neurometabolites in patients with major depression across the lifespan. 7T field strengths and greater have not been a major focus of study in patients with late-life depression (LLD).

Methods: Nine LLD patients who met DSM-IV criteria for a current major depressive episode and nine non-depressed, healthy, age-matched controls underwent clinical and neuropsychological assessment and single-voxel 7T ^{1}H-MRS at baseline and after 10–12 weeks of antidepressant

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Conflict of Interest

The authors have no competing interests to declare.

treatment (Citalopram; patients only). Spectra were acquired from two brain regions implicated in both depressive symptoms and neuropsychological deficits in LLD, the anterior (ACC) and posterior cingulate (PCC). Levels of γ-aminobutyric acid (GABA), glutamate (Glu), glutathione (GSH), N-acetylaspartylglutamate (NAAG), N-acetylaspartate (NAA), and *myo*-inositol (mI) were quantified relative to total creatine (tCr) using linear-combination modeling.

Results: Baseline Glu/tCr levels were not significantly different between groups. Decreased Glu/tCr levels levels after Citalopram treatment was observed in a subset of LLD patients, although the group difference was not statistically significant. Exploratory analyses showed that LLD patients had lower NAA levels in the PCC relative to controls. Higher levels of ml in the LLD patients relative to the controls and decreases after Citalopram treatment had large effect sizes but were not statistically significant. Further, decreases in PCC Glu/tCr and increases in ACC GSH/tCr were associated with improvement in depressive symptoms.

Limitations: Sample size.

Conclusions: These preliminary results suggest a role of neurochemicals and neurometabolites in the neurobiology of LLD and antidepressant treatment response.

Keywords

magnetic resonance spectroscopy; depression; late-life; Citalopram

Introduction

Depression in late life is associated with greater variability in antidepressant treatment response and greater rate of relapse compared to younger depressed patients (Dew et al., 1997). Further, depression in late life is associated with an increase in the rate of all-cause dementia (Alzheimer's and vascular dementia; (Diniz et al., 2013). The neurobiological mechanisms underlying heterogeneity in treatment response and increased dementia risk are not well understood. Positron Emission Tomography (PET) studies have shown increased cerebral glucose metabolism in LLD patients relative to controls, which correlated with greater depressive symptom severity. The regional extent of hypermetabolism in LLD is much greater than that observed in mid-life depressed patients who show decreases in metabolism or no change in these regions and overlaps with areas of hypometabolism in individuals at genetic risk for Alzheimer's disease (AD), as well as AD patients (Reiman et al., 1996; Smith et al., 2009, 1992). Antidepressant treatment with Citalopram, a selective serotonin reuptake inhibitor (SSRI), decreased metabolism in neural networks that were hypermetabolic prior to treatment that were correlated with improvement in (depression and anxiety) and cognition (Smith et al., 2002, 2009, 2011; Diaconescu et al., 2011). Understanding the mechanisms that underlie these metabolic alterations may inform the development of more effective treatments for depressive symptoms and neuropsychological deficits. Cerebral glucose metabolism is a final common pathway of synaptic activity. Astrocytes and glutamate signaling play an important role in the coupling between neuronal function and glucose metabolism (Magistretti, 2006). MRS and preclinical studies suggest that higher glutamate concentrations and decreases with antidepressant treatment may be

a neurobiological mechanism that might contribute to the glucose metabolism changes (Binesh et al., 2004; Golembiowska K. Dziubina, 2000).

Magnetic resonance spectroscopy (MRS) is a non-invasive method for quantifying the levels of endogenous metabolites. MRS-detectable molecules that have been implicated in neuropsychiatric and neurodegenerative disease include the major excitatory and inhibitory neurotransmitters in the brain, glutamate (Glu) and γ-aminobutyric acid (GABA), N-acetylaspartylglutamate (NAAG; a modulator of glutamatergic neurotransmission), N-acetylaspartate (NAA; a measure of neuronal integrity), the primary antioxidant glutathione (GSH), and *myo*-inositol (ml), which is a potential marker of phospholipid metabolism, gliosis, or neuroinflammation (Rae, 2014). MRS methods are used to detect a broad variety of low-molecular-weight compounds, including neurotransmitters, antioxidants, and compounds reflecting neuronal loss or inflammation; they therefore provide complementary information to that provided by target-specific PET molecular imaging methods. Field strengths of 7T and greater have the advantage of increased spectral resolution and signal-to-noise ratio (SNR) compared to commonly used clinical MRI scanners, resulting in greater sensitivity for the quantification of low-concentration compounds, and improved separation of overlapping resonances (e.g. glutamate and glutamine, or NAA and NAAG).

MRS has been applied to the study of depression across the lifespan, as reviewed previously (Moriguchi et al., 2019; Maddock and Buonocore, 2012; Mathias et al., 2017; Reddy-Thootkur et al., 2020; Yksel and Öngür, 2010). The majority of studies were performed at 3T field strength. The most consistent findings in mid-life depression patients relative to controls are lower levels of Glx (glutamate + glutamine; reported as a composite due to low spectral resolution) and of GABA in frontal, cingulate and occipital cortices (Reddy-Thootkur et al., 2020; Arnone et al., 2015; Godfrey et al., 2018; Luykx et al., 2012; Moriguchi et al., 2019; Yksel and Öngür, 2010, Bhagwagar et al., 2007; Sanacora et al., 1999). Studies of glutamate and glutamine at higher field strength (7T) have shown, similarly, mixed results, including an increase, decrease or no change in frontal cortex and anterior cingulate (Godlewska et al., 2018). MRS studies of the effects of antidepressant treatment (selective serotonin reuptake inhibitors; SSRIs) have shown either decreases or no change in GABA and Glx (Brian P. Brennan et al., 2017; Sanacora et al., 2002; Taylor et al., 2012).

Prior studies in LLD patients relative to controls have revealed higher Glx, lower NAA in frontal cortex, increased GSH in the anterior cingulate and increased myo-inositol in basal ganglia and medial temporal lobe (Binesh, et al., 2004, Chen et al., 2009; Duffy et al., 2015; Venkatraman et al., 2009). Lower hippocampal Glx levels were associated with poorer working memory performance and higher hippocampal Glx levels with more severe depressive symptoms and earlier age at onset (Jayaweera et al., 2015). These studies were performed at field strengths of 3T or lower. The application of MRS to evaluate the effects of antidepressant treatment in LLD patients have not been a focus of study.

The purpose of the present study was to measure neurotransmitter and neurometabolite levels in the anterior (ACC) and posterior cingulate (PCC) of patients with LLD prior to and after 10–12 weeks of treatment with the SSRI, Citalopram, using 7T ^{1}H-MRS. These two

regions were chosen for study, rather than the dorsal-lateral prefrontal cortex, for example, because prior MRS and PET glucose metabolism studies have shown disease- and treatment-related changes in the ACC and PCC (A.O. et al., 2011; Arnone et al., 2015; Luykx et al., 2012; Maddock and Buonocore, 2012; Smith et al., 2009; Yksel and Öngür, 2010). Three primary hypotheses were tested: 1) prior to antidepressant treatment, LLD patients would have higher Glu levels relative to controls; 2) Glu levels in LLD patients would decrease with antidepressant treatment and 3) decreases in Glu would be associated with improved depressive symptoms and cognition (executive function and memory). Exploratory analyses characterized baseline diagnostic and prospective treatment-related alterations in levels of GABA, GSH, NAAG, NAA, and mI, as well as their associations with changes in depressive symptoms and cognition.

Materials and Methods

Participant Screening and Selection

Participants were recruited with advertisements in the community and from the Johns Hopkins University Alzheimer's Disease Research Center (2P50AG005146). All potential participants underwent psychiatric and cognitive screening, including the Structured Clinical Interview for DSM-IV by a clinical psychologist (NG), clinical dementia rating scale (CDR), Mini Mental State Examination (MMSE; First et al., 1995; Morris, 1993; Folstein et al., 1975). Potential participants also underwent a physical and neurological examination, had laboratory testing performed (including complete blood count and blood chemistries) and had toxicology screening performed (psychotropic drugs and drugs of abuse).

Inclusion criteria for the controls was no DSM-IV diagnosis of a psychiatric disorder and a CDR score of 0 (normal control). Inclusion criteria for the LLD patients was DSM-IV diagnosis of major depressive disorder (non-bipolar, non-psychotic), age at onset of first depressive episode after age 55, and no antidepressant treatment in the past year. Chronic health conditions such as hypertension and diabetes had to be well-controlled in all participants. Exclusionary criteria were contraindications for MR imaging (pacemakers, aneurism clamps and metal), a history of or active neurological or Axis I psychiatric disorders (except for a diagnosis of current major depressive episode, non-bipolar, non-psychotic, in the LLD patients), and not medically stable. Participants were excluded from participating with a positive toxicology screen for psychotropic drugs or medications with central nervous system effects (e.g. antihistamines, cold medications) or if they used such medications within two weeks before enrollment. The Institutional Review Board and the Radiation Research Committee of the Johns Hopkins University School of Medicine approved the study protocol and consent forms (Protocol Number NA_00021615). Participants received transcribed and verbal descriptions of the research study and written informed consent was obtained.

Citalopram Treatment

After the baseline study procedures were completed, LLD patients began treatment with Citalopram (Celexa; 10mg oral dose per day) for one week to minimize side effects. Then, the dose was increased to 20 mg. If significant clinical improvement was not observed at

the 20mg dosage after three weeks of treatment based on an improvement rating of 3 or greater on the Clinical Global Impression Scale (CGI; National Institute (National Institute of Mental Health, 1976), the dose was increased to 30 mg and then if necessary, to 40 mg. All patients were followed clinically on a weekly basis. Clinical ratings for depressive symptoms included the (Hamilton Depression Rating Scale-24 item [HDRS]; (Hamilton, 1960) and Beck Depression Inventory [BDI]; (Beck et al., 1996).

Neuropsychological Testing

Neuropsychological assessments were performed at baseline and repeated after 10–12 weeks of treatment in patients and after an equivalent period in controls. The neuropsychological test battery included measures of executive function, attention, auditory-verbal and visual-spatial memory and decision making (data not shown). Four measures were chosen *a priori* to represent two domains affected in LLD patients (executive function and memory) using tests that are sensitive to detecting deficits in LLD patients and that show improvement with antidepressant treatment. The executive function tests were the Delis-Kaplan Executive Function System [DKEFS] letter and category fluency (Delis, Kaplan, Kramer, 2001). The memory tests included a test of auditory-verbal memory (California Verbal Learning Test; CVLT) and a test of visual-spatial memory (Brief Visual Memory Test-Revised; BVMT-R; (Benedict, 1997; Delis et al., 1987). Alternate forms of the tests were used. The CVLT variable analyzed was the total number of words recalled without perseverations and intrusions over the first five trials. Similarly, the BVMT-R variable analyzed was the number of shapes and their location recalled over three learning trials.

MRS Acquisition

MRS acquisition was performed within one week of the neuropsychological assessment, prior to and after 10–12 weeks of Citalopram treatment. The MRS acquisition and analysis methods have been described previously (Oeltzschner et al., 2019) and are briefly summarized. All data were acquired on a 7T Philips Achieva scanner (Philips Healthcare, Best, The Netherlands) with a 32-channel receive and quadrature transmit head coil (Nova Medical, Wilmington, MA). After a high-resolution (0.96 mm isotropic) anatomical T_1-weighted magnetization prepared gradient echo (MP-RAGE) scan, MRS voxels were placed in two brain regions: the ACC and PCC (Figure 1). For both regions, the MRS voxels had dimensions of 28 mm (anterior-posterior) × 20 mm (left-right) × 16 mm (caudal-cranial). Voxels were centered at the midline with the anteriorposterior edge tangential to the corpus callosum. The ACC voxel was placed in the dorsal ACC with the caudal-cranial edge perpendicular to the genu of the corpus callosum, and the PCC voxel was placed in PCC with the caudal-cranial edge perpendicular to the splenium of the corpus callosum. A researcher who was present at all acquisitions monitored reproducibility of voxel placement between pre- and post-treatment scans using anatomical landmarks.

Prior to data acquisition, shimming was performed up to 2^{nd} order using a FASTMAP-based routine, and RF power was optimized on the localized volume. Data were acquired using the Stimulated Echo Acquisition Mode (STEAM) sequence with the following parameters: TR = 3000 ms; 96 averages; 2048 data points; 3 kHz spectral width; VAPOR (Tkac et al., 1999)

water suppression. Four water-unsuppressed averages per voxel were recorded with the same settings. TE was set to the shortest possible value (14 ms in ACC, 15 ms in PCC).

MRS Data processing

Spectroscopic data were analyzed with LCModel v6.3–0D (Provencher, 2001, 1993), using TE-specific simulated basis sets including alanine (Ala), aspartate (Asp), creatine (Cr), GABA, glucose (Glc), glutamate (Glu), glutamine (Gln), GSH, glycerophosphocholine (GPC), glycine (Gly), lactate (Lac), mI, NAA, NAAG, phosphocholine (PCh), phosphocreatine (PCr), phosphoethanolamine (PE), serine (Ser), scyllo-inositol (sI), taurine (Tau), and resonances from lipids (Lip09, Lip13a-d, Lip20). Basis functions for macromolecules and lipids (MM09, MM12, MM14, MM17, MM20, Lip09, Lip13, Lip 20) were internally simulated by LCModel using the default settings. Baseline flexibility was likewise set to internal LCModel defaults (DKNTMN = 0.15). Levels of GABA, Glu, GSH, NAA, NAAG, and mI (estimated with respect to the total creatine signal tCr = Cr + PCr) were used for further analysis. Individual metabolite measures with %SD Cramér-Rao lower bounds (%SD, as determined by LCModel) higher than 15% were excluded. Detection of gross outliers was performed by calculating the mean Cook's distance across both groups (HC, MCI) and regions (ACC, PCC) for each metabolite (Stevens, 1984). Individual data points with more than 5 times the mean Cook's distance were regarded as gross outliers and discarded.

Statistical Analysis

Two sample t-tests were used to compare LLD patients to healthy controls on baseline depressive symptoms, neuropsychological measures and metabolite levels. Paired t-tests were used to assess within-subject change over time in the LLD patients in depressive symptoms, neuropsychological measures and metabolites. Effect sizes were calculated according to published methods (Cohen, 1988). Linear regression models were used to assess the relationship between change in depressive symptoms and neuropsychological measures with change in metabolite levels. The models were adjusted for the baseline depressive symptoms and neuropsychological measures, respectively. The coefficients were scaled so that they could be interpreted as the expected difference in the change outcome measure between two individuals who differed in their change in metabolite levels by 0.1 units.

Results

Nine LLD patients and nine healthy controls were enrolled in the study. The demographic and clinical characteristics for both groups are summarized in Table 1a. Three of the patients had been treated with SSRIs in the past (only one patient with an adequate course of treatment), although not within the past two years. One of the controls and none of the LLD patients were left-handed. All controls and LLD patients had a CDR score of 0 (normal).

The groups did not differ significantly in age or sex distribution or in baseline neuropsychological measures (MMSE, CVLT, BVMT, DKEFS-Category and Letter Fluency). As expected, the LLD group showed significantly higher HDRS t_{16}=−16.9,

$p<0.001$) and BDI scores ($t_{16}=-7.6$, $p<0.001$) at baseline, corresponding to moderate and moderate-to-severe levels of depression, respectively. The mean Citalopram dose was 18 mg ± 7 (range 10–40 mg) at the time of the follow-up MRS scan. Medication side effects were not reported. HDRS ($t_8=7.7$, $p<0.001$) and BDI ($t_8=4.5$, $p<0.001$) scores showed similar improvement with Citalopram treatment (Table 1b). All of the LLD patients met criteria for treatment response (score of 10 or below on the HDRS for two weeks consistently; (Dew et al., 1997). There were no significant changes in the verbal fluency and verbal and visual-spatial memory measures with Citalopram treatment.

There were no significant baseline between-group differences in Glu/tCr levels in the ACC or PCC between the LLD patients and controls (Table 2, Figure 2). PCC NAA/tCr levels were significantly lower in the LLD patients relative to the controls ($t_{16}=2.2$, $p=0.04$). There were no statistically significant between-group differences in the other metabolite measures.

Comparing metabolites levels in the LLD group at baseline to post-Citalopram treatment revealed lower ACC and PCC Glu/tCr levels, although shy of achieving statistical significance. (Table 3, Figure 3). Likewise, ACC mI/tCr levels showed a notable decrease with treatment, which, while yielding a p value (0.058) slightly above the significance threshold, had a substantial effect size. The other metabolite measures were not significantly affected by treatment.

Exploratory linear-regression modeling (Table 4) detected an association between decreased Glu/tCr in PCC with depressive symptom improvement (BDI score) during Citalopram treatment, as well as an association between increased GSH/tCr in ACC and depressive symptom improvement (BDI score). A 0.1 difference in Glu/tCr decrease was associated with 1.94 (SE: 0.75; $p=0.042$) points improvement (decrease) in depressive symptoms (BDI score). Conversely, a 0.1 increase in GSH/tCr in ACC was associated with a 5.9 (SE: 1.9; $p=0.021$) point improvement (decrease) in depressive symptoms (BDI score).

Discussion

This study is among the first to investigate the neurobiology of LLD using high-field MRS to measure levels of neurometabolites in LLD patients relative to healthy, age-matched, controls. In contrast to the study hypotheses, the LLD patients did not have higher Glu/tCr levels than the controls at baseline. While the lower Glu/tCr levels in the LLD patients after Citalopram treatment were not statistically significant for the group as a whole, the pre- compared to post-treatment plots (Figure 3) did reveal that a sub-group of LLD patients showed reductions of GABA/tCr and Glu/tCr levels with Citalopram treatment. This suggests that the small sample size may have reduced the statistical sensitivity for detecting effects of Citalopram treatment, which is a limitation of the present study. The main limitation of the study, the small sample size, was in part due to the “black box” warning for Citalopram that was issued during the conduct of the study (Vieweg et al., 2012), at which point, study recruitment ended. Statistical testing was performed using parametric testing, which may inflate Type I error rates, but was chosen since a non-parametric version of the regression analysis is not available. Another limitation is the lack of correction for multiple comparisons. Further, it is not possible to conclude

whether the MRS results are attributable to the effect of reduced depressive symptoms or an effect of Citalopram and other neurobiological mechanisms may be involved in the response to Citalopram. The strengths of the study included enrolling a group of well-characterized, late-onset LLD patients who had limited or no previous exposure to antidepressant treatment and monitoring outcomes for both depressive symptoms and neuropsychological outcomes during a prospective treatment trial with the same SSRI. All of the LLD patients were considered treatment responders. Moreover, as a group, the LLD patients did not show evidence of significant neuropsychological impairment at baseline or significant change during Citalopram treatment, although some patients improved. If the patient cohort included LLD patients, who were treatment-resistant and/or who had greater neuropsychological deficits, larger between-group differences and stronger relations between the MRS measures and clinical and neuropsychological outcomes may have been observed.

Exploratory analyses revealed that at baseline, LLD patients had lower PCC NAA/tCr levels relative to the controls. This observation is consistent with previous reports in younger depressed patients (Tan et al., 2016; Li et al., 2016). Lower concentrations of NAA/tCr and higher levels of mI/tCr in the PCC have been observed also in mild cognitive impairment, where declines in PCC NAA/tCr and increases in mI/tCr are greater in individuals who are “amyloid-positive” (Voevodskaya et al., 2019). The PCC shows early hypometabolism and amyloid deposition in mild cognitive impairment. Decreased PCC NAA may reflect a loss of neuronal integrity that could be associated with cognitive decline in LLD (Klunk et al., 2004; Minoshima et al., 1997). The effect size for between-group differences in ml (higher levels were observed in LLD patents relative to controls) were large relative to the other metabolites, but the values did not reach statistical significance. Previous studies have shown increased mI/tCr in the basal ganglia and medial temporal lobe in LLD (Chen et al., 2009; Venkatraman et al., 2009).

Exploratory analyses did not show significant changes in the metabolites after antidepressant treatment in the LLD patients, but showed associations between improvement in depressive symptoms and decrease in Glu/tCr in the PCC and increase in GSH in the ACC. The association between depressive symptom improvement and Glu/tCr is consistent with the study hypotheses regarding the role of glutamate in treatment response in LLD patients.

MRS studies in mid-life depressed patients have shown that SSRIs variably affect GABA and Glx, in some studies, depending on treatment duration (B P Brennan et al., 2017; Sanacora et al., 2002). In mid-life depressed patients, baseline Glx levels were unchanged after one week of Citalopram treatment, but nevertheless correlated, inversely, with depressive symptoms (Taylor et al., 2012). Another study showed significantly reduced hippocampal Glx levels after 8 weeks of Citalopram treatment in mid-life depressed patients (Block et al., 2009). Two studies have shown decreased GABA concentrations in the occipital cortex after SSRI treatment (Bhagwagar et al., 2004; Sanacora et al., 2002).

Preclinical and human MRS studies have shown reductions in GSH with Citalopram treatment (Godlewska et al., 2015; Gupta et al., 2018). However, the role of GSH in depression is not well understood. While lower GSH levels in mid-life depressed patients

have been interpreted as evidence for increased oxidative stress (Godlewska et al., 2015; Shungu et al., 2012), it is conceivable that recovery from depression with SSRI treatment may be associated with less oxidative stress as reflected by increased GSH (Behr et al., 2012).

Similar to the between-group analysis, the effect size for within-group differences in ml/tCr was large relative to the other measures, although with a *p* value slightly above the nominal significance threshold level. Notably, ml/tCr was decreased in the ACC and PCC with Citalopram treatment. There are limited data on the effects of SSRI's on ml/tCr. One study in mid-life depressed patients showed lower mI/tCr levels compared to controls and an increase to normal levels after SSRI treatment (Chen et al., 2014). As increased mI/tCr may reflect abnormalities in metabolism and intracellular cell signaling (Stork and Renshaw, 2005), further investigation of the effects of SSRI's on mI/tCr, particularly in relation to cognitive function and AD pathology may be informative.

Conclusions

In summary, these preliminary results indicate that 7T MRS may elucidate the role of neurotransmitters and neurometabolites in depressive symptoms and cognitive deficits LLD patients. Studies are in progress to further evaluate the relationship between the MRS metabolite measures and PET measures of Alzheimer's disease pathology (beta-amyloid). Understanding the associations between MRS and PET measures may elucidate disease mechanisms and inform the development of biomarkers for diagnosis and prognostication.

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Highlights

- Late-life depressed patients had lower posterior cingulate Nacetyl-aspartate levels
- Improved depressive symptoms correlated with decreased posterior cingulate glutamate
- Improved depressive symptoms correlated with increased anterior cingulate glutathione

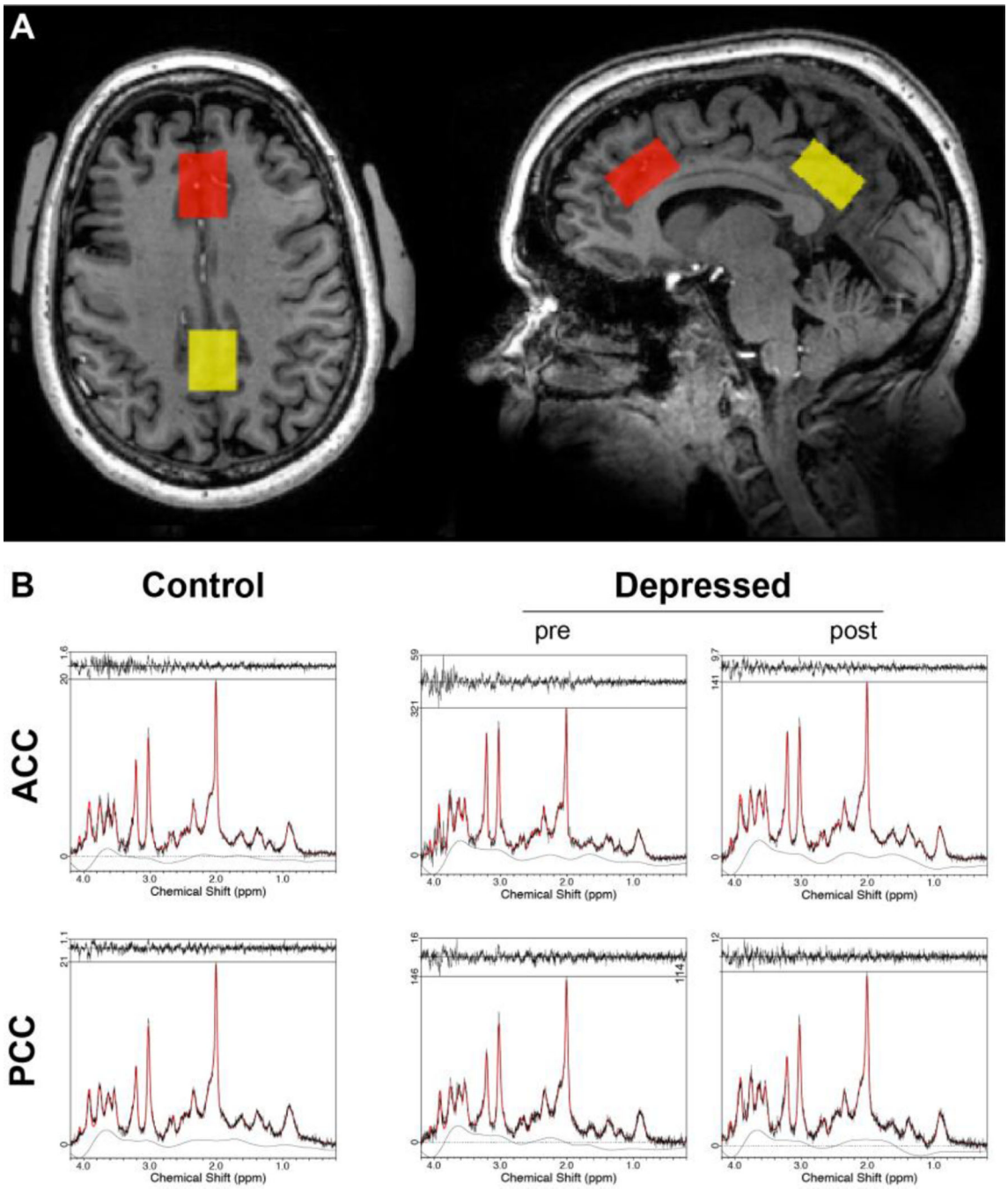

Fig. 1:

A. Example MRS voxel placement in the anterior cingulate (red) and posterior cingulate (yellow) cortices. Voxel dimensions were 28 mm (anterior-posterior) × 20 mm (left-right) × 16 mm (caudal-cranial). The axial image shows signals outside the head originating from padding used to stabilize the subject's head position.

B. Example spectra from the ACC (upper row) and PCC (bottom row) for healthy controls at baseline (left column), and LLD patients pre- (middle column) and post-treatment (right column).

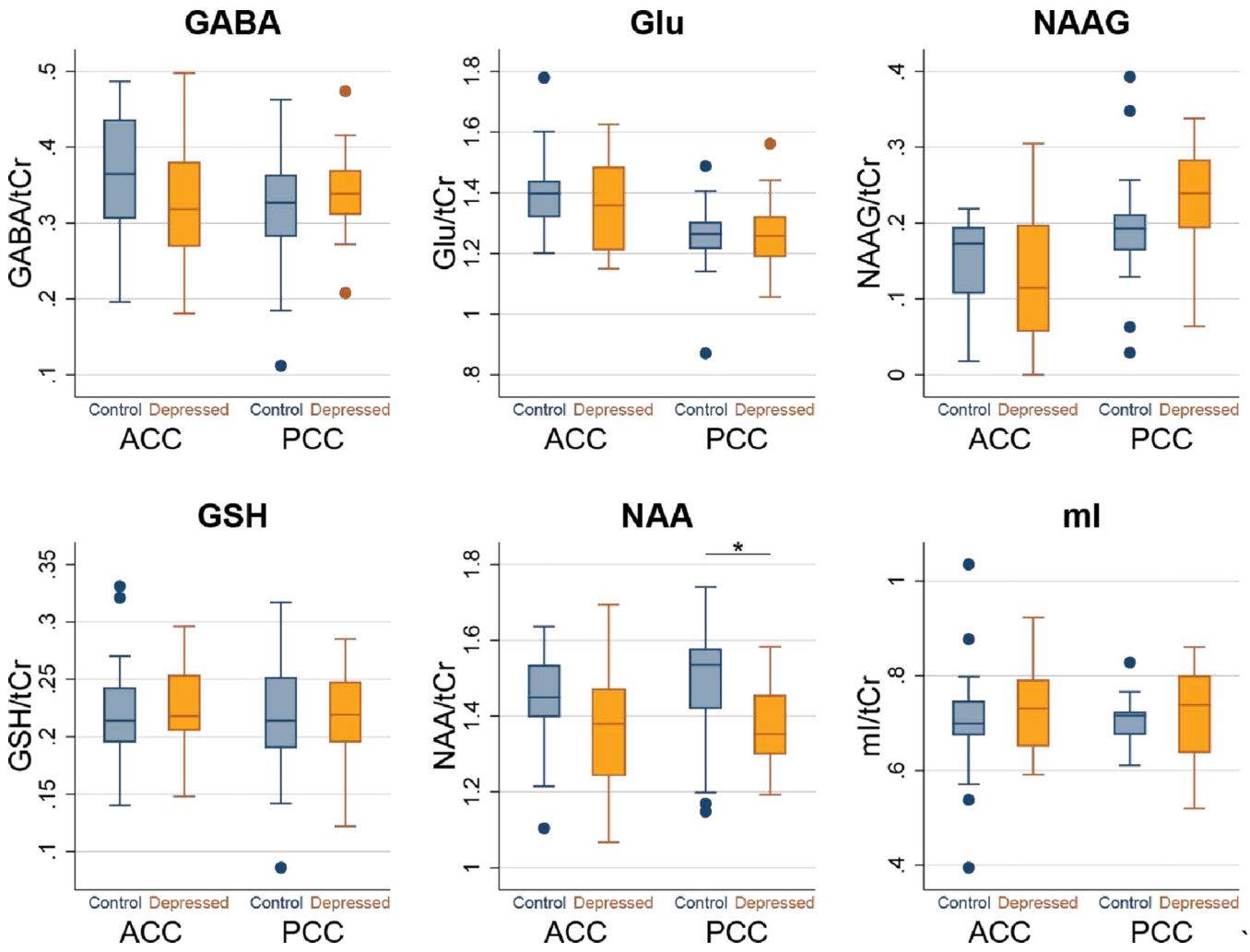

Fig. 2:

Box plots of metabolite levels at baseline from the ACC and PCC in LLD patients and Comparison Healthy Elderly Subjects. Dots represent outliers.

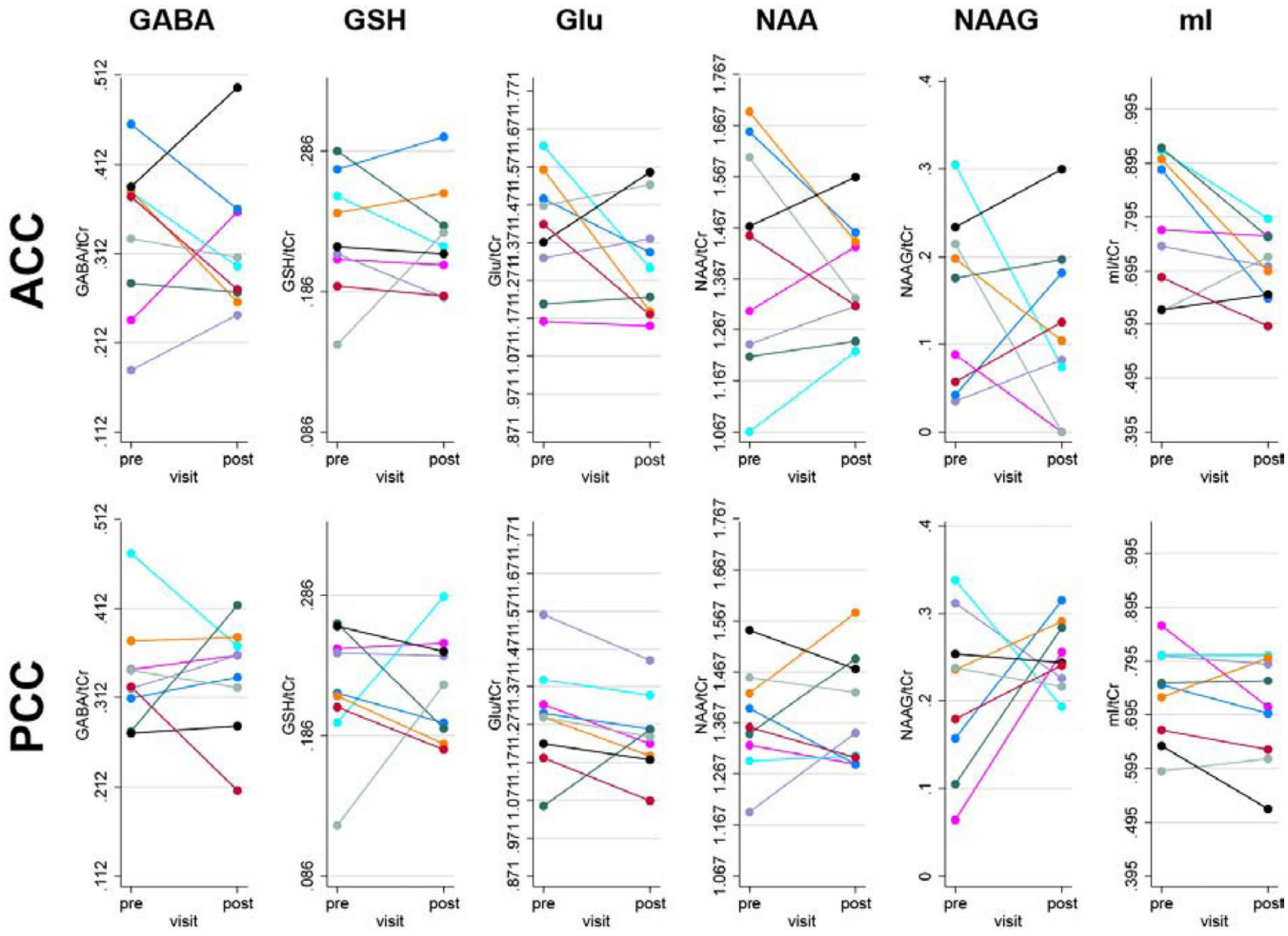

Fig. 3:

Metabolite levels from the ACC (upper row) and PCC (bottom row) in the LLD patients before (pre) and after Citalopram treatment (post). Individual subjects are color-coded.

Table 1a:

Demographic characteristics of patients with Late-Life Depression and Healthy Elderly Control Subjects (mean ± standard deviation)

	Elderly Control Subjects (n = 9)	Patients with Late-Life Depression (n = 9) Baseline
Age	67 ± 7	70 ± 7
Sex (M/F)	5/4	4/5
Years of Education	15 ± 2	16 ± 3
Mini-Mental Status Examination	29 ± 1	29 ± 1
Hamilton Depression Rating Scale	1 ± 2	17 ± 2[a]
Beck Depression Inventory	1.4 ± 2	22 ± 8 [b]
Total California Verbal Learning Test (CVLT) Score (Sum of Trials 1–5)	55 ± 7	54 ± 9
Brief Visuospatial Memory Test, Revised (Sum of Trials 1–5)	19 ± 3	18 ± 9
DKEFS Letter Fluency[*]	41 ± 13	42 ± 7
DKEFS Category Fluency[*]	40 ± 5	40 ± 8

[*] D-KEFS™ = Delis-Kaplan Executive Function System™

[a] Significant difference between healthy controls and LLD patients ($t_{16}=-16.9$, $p<0.001$)

[b] Significant difference between healthy controls and LLD patients ($t_{16}=-7.6$, $p<0.001$)

Table 1b:

The Effects of Citalopram on Depressive Symptoms and Neuropsychological Function in patients with Late-Life Depression (mean ± standard deviation)

	Patients with Late-Life Depression (n = 9) Baseline	**Patients with Late-Life Depression (n = 9) During Citalopram Treatment**
Hamilton Depression Rating Scale	17 ± 2[a]	4 ± 2[a]
Beck Depression Inventory	22 ± 8 [b]	7 ± 3[b]
Mini-Mental Status Examination	29 ± 1	30 ± 1
Total California Verbal Learning Test (CVLT) Score (Sum of Trials 1–5)	54 ± 9	53 ± 10
Brief Visuospatial Memory Test, Re vis d (Sum of Trials 1–5)	18 ± 9	21 ± 7
DKEFS Letter Fluency [*]	42 ± 7	42 ± 9
DKEFS Category Fluency [*]	40 ± 8	40 ± 6

[*] D-KEFS™ = Delis-Kaplan Executive Function System™

[a] Significant difference in the LLD patients before and during Citalopram treatment (t_8=7.7, p<0.001)

[b] Significant difference in the LLD patients before and during Citalopram treatment (t_8=4.5, p<0.001)

Table 2:

Metabolite levels in patients with Late-Life Depression (LLD) and Healthy Elderly Control (HC) subjects

Metabolite [/tCr]	Anterior Cingulate		*t*	df	*p*	Effect Size[1]
	HC Mean (SD)	LLD Mean (SD)				
GABA	0.353 (0.080)	0.334 (0.087)	0.463	16	0.649	0.238
Glu	1.422 (0.163)	1.405 (0.154)	0.237	16	0.816	0.104
GSH	0.225 (0.049)	0.226 (0.043)	−0.026	16	0.980	−0.020
NAA	1.465 (0.128)	1.411 (0.218)	0.639	16	0.532	0.422
NAAG	0.166 (0.052)	0.150 (0.097)	0.423	16	0.678	0.308
mI	0.703 (0.142)	0.785 (0.126)	−1.230	16	0.212	−0.577

Metabolite [/tCr]	Posterior Cingulate		*t*	df	*p*	Effect Size[1]
	HC Mean (SD)	LLD Mean (SD)				
GABA	0.337 (0.081)	0.338 (0.061)	−0.023	16	0.982	−0.012
Glu	1.323 (0.090)	1.290 (0.140)	0.585	16	0.568	0.366
GSH	0.217 (0.052)	0.220 (0.045)	−0.102	16	0.920	−0.058
NAA	**1.510 (0.159)**	**1.370 (0.102)**	**2.209**	**16**	**0.042**	**0.881**
NAAG	0.225 (0.098)	0.209 (0.091)	0.351	16	0.730	0.163
mI	0.670 (0.043)	0.733 (0.088)	−1.024	16	0.321	−1.465

Total creatine (tCr), γ-aminobutyric acid (GABA), glutamate (Glu), glutathione (GSH), N-acetylaspartate (NAA), N-acetylaspartylglutamate (NAAG) and myo-inositol (mI)

[1]Effect size was calculated as the ratio of the between-group difference to the SD of the healthy older adult comparison group.

Statistically significant effects are indicated in boldface.

Table 3:

Metabolite levels in patients with Late-Life Depression at baseline and during Citalopram treatment

Metabolite [/tCr]	Anterior Cingulate		*t*	df	*p*	Effect Size[1]
	Time 1 Mean (SD)	Time 2 Mean (SD)				
GABA	0.334 (0.087)	0.319 (0.079)	0.501	8	0.630	0.200
Glu	1.405 (0.154)	1.318 (0.148)	1.358	8	0.212	0.455
GSH	0.226 (0.043)	0.224 (0.036)	0.162	8	0.875	0.051
NAA	1.411 (0.218)	1.369 (0.112)	0.731	8	0.485	0.243
NAAG	0.150 (0.097)	0.118 (0.097)	0.725	8	0.489	0.244
mI	0.785 (0.126)	0.702 (0.065)	2.214	8	0.058	0.735

Metabolite [/tCr]	Posterior Cingulate		*t*	df	*p*	Effect Size[1]
	Time 1 Mean (SD)	Time 2 Mean (SD)				
GABA	0.338 (0.061)	0.337 (0.062)	0.035	8	0.973	0.013
Glu	1.290 (0.140)	1.244 (0.105)	1.399	8	0.199	0.470
GSH	0.220 (0.047)	0.221 (0.038)	−0.081	8	0.937	−0.017
NAA	1.370 (0.102)	1.388 (0.109)	−0.501	8	0.623	0.168
NAAG	0.209 (0.091)	0.252 (0.039)	−1.072	8	0.315	−0.361
mI	0.733 (0.088)	0.703 (0.099)	1.300	8	0.230	0.429

Total creatine (tCr), γ-aminobutyric acid (GABA), glutamate (Glu), glutathione (GSH), N-acetylaspartate (NAA), N-acetylaspartylglutamate (NAAG) and myo-inositol (mI)

[1]Effect size was calculated as the ratio of the between-time-points difference to the SD of the between-time-points difference.

Table 4a:

Relationships between change in metabolite levels in patients with late-life depression (LLD) and change in depressive symptoms (Beck Depression Inventory): results of linear regression analyses

Anterior Cingulate Metabolite [/tCr]	**β**	**SE**	***p***	**95% CI**
GABA	−0.320	1.128	.786	(−3.080, 2.439)
Glu	−0.282	0.550	.626	(−1.627, 1.063)
GSH	**−5.886**	**1.889**	**.021**	**(−10.509, −1.264)**
NAA	0.704	0.589	.277	(−0.737, 2.146)
NAAG	0.297	0.810	.727	(−1.685, 2.278)
mI	−1.364	0.769	.127	(−3.245, 0.518)
Posterior Cingulate Metabolite [/tCr]	**β**	**SE**	***p***	**95% CI**
GABA	1.163	1.337	.418	(−2.109, 4.344)
Glu	**1.944**	**0.753**	**.042**	**(0.103, 3.786)**
GSH	−2.194	1.648	.231	(−6.225, 1.838)
NAA	0.404	1.008	.702	(−2.063, 2.871)
NAAG	1.096	0.842	.241	(−0.963, 3.155)
mI	−0.337	1.534	.833	(−4.091, 3.417)

Total creatine (tCr), γ-aminobutyric acid (GABA), glutamate (Glu), glutathione (GSH), N-acetylaspartate (NAA), N-acetylaspartylglutamate (NAAG) and myo-inositol (mI) Statistically significant effects are indicated in boldface.

Table 4b:

Relationships between change in metabolite levels in patients with LLD and change in episodic verbal memory (California Verbal Learning Test): results of linear regression analyses

Anterior Cingulate Metabolite [/tCr]	**β**	**SE**	***p***	**95% CI**
GABA	4.924	2.403	.086	(−0.954, 10.803)
Glu	2.570	1.156	.068	(−0.257, 5.398)
GSH	−4.833	7.340	.535	(−22.795, 13.128)
NAA	2.396	1.407	.139	(−1.046, 5.838)
NAAG	−0.918	2.295	.703	(−6.534, 4.697)
mI	3.583	2.328	.175	(−2.113, 9.280)
Posterior Cingulate Metabolite [/tCr]	**β**	**SE**	***p***	**95% CI**
GABA	3.285	3.613	.398	(−5.557, 12.126)
Glu	4.431	2.404	.115	(−1.452, 10.314)
GSH	1.063	5.288	.847	(−11.875, 14.001)
NAA	−1.174	3.478	.747	(−9.684, 7.336)
NAAG	1.372	3.217	.685	(−6.450, 9.244)
mI	−7.187	4.340	.153	(−17.951, 3.578)

Total creatine (tCr), γ-aminobutyric acid (GABA), glutamate (Glu), glutathione (GSH), N-acetylaspartate (NAA), N-acetylaspartylglutamate (NAAG) and myo-inositol (mI)