



## Region-specific glutamate changes in patients with unipolar depression

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### ABSTRACT

The present study aimed to investigate glutamate concentrations in patients with unipolar depression in the midcingulate cortex (MCC) as compared to the left dorsolateral prefrontal cortex (DLPFC). We hypothesized a dissociation of glutamate levels with unchanged levels in DLPFC and abnormally changed levels in MCC as well as differential effects of antidepressant pharmacotherapy. Glutamate was determined using magnetic resonance spectroscopy at 3 T in DLPFC and MCC in fourteen depressed patients and matched healthy volunteers. A follow-up measurement was performed after 4 weeks of antidepressant treatment. The main finding is a region-specific pattern of glutamate concentrations with increased MCC glutamate concentrations and no significant differences in DLPFC glutamate concentrations in unipolar depressive patients compared to healthy controls. Response and non-response to antidepressant pharmacotherapy were predicted by high glutamate at baseline in DLPFC and MCC, respectively. In addition, treatment responders showed a further increase in DLPFC glutamate levels after successful antidepressant treatment. Findings indicate altered region-specific glutamate concentrations in DLPFC and MCC that are predictive of response and non-response, respectively, to antidepressant pharmacotherapy. These findings might serve as a starting point for future studies in which the value of this metabolite pattern for treatment response prediction should be investigated.

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### 1. Introduction

Glutamate, the major excitatory neurotransmitter of the mammalian brain, influences a variety of behavioral and physiological mechanisms such as neuronal plasticity, learning and memory (Krystal, 2007). Moreover, glutamate is centrally involved in physiological emotion processes and the pathophysiology of mood disorders and, as such, is a target and mediator of several antidepressant interventions. Evidence from numerous studies suggests that glutamatergic neurotransmission plays a critical role in the pathophysiology of mood disorders (Zarate et al., 2002; Sanacora et al., 2008; Mathew et al., 2008; Yüksel and Ongur, 2010). Increased glutamate levels were observed in serum (Kim et al., 1982), plasma (Altamura et al., 1993; Mauri et al., 1998; Mitani et al., 2006) and in post-mortem samples of frontal cortex (Hashimoto et al., 2007) of patients with major depressive disorder

(MDD). Noninvasive in vivo proton magnetic resonance spectroscopy (1H-MRS) studies report an inconsistent picture of glutamate levels in different brain areas in MDD. Sanacora et al. (2004) and Bhagwagar et al. (2007) described significantly elevated glutamate levels in the occipital cortex. A number of recent studies focused on dorsolateral prefrontal cortex (DLPFC) and cingulate cortex, since these regions are implicated in mood regulation and show structural and functional alterations in MDD (Mayberg, 2003; Phillips et al., 2003; Grimm et al., 2008). In the left DLPFC, levels of glutamate were reported to be unchanged (Nery et al., 2009; Merkl et al., 2011) in acute MDD. In contrast, studies consistently report a decrease in glutamate concentrations in the anterior cingulate cortex (ACC) of MDD patients (Auer et al., 2000; Merkl et al., 2011; Luykx et al., 2012). When investigating the cingulate cortex it is crucial to account for the histoarchitectural diversity of this region, which is characterized by different cytological, connective, functional, and receptor fingerprint markers (Palomero-Gallagher et al., 2009). Especially the midcingulate cortex (MCC) differs not only structurally and functionally from the ACC (Vogt et al., 2003), but also in number and distribution of ionotropic glutamate

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receptors of the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) and N-Methyl-D-Aspartate (NMDA) subtype (Palomero-Gallagher et al., 2009).

Antagonizing ionotropic glutamate receptors by pharmacological means leads to clear antidepressant effects as demonstrated in animal experiments using the forced-swim and the learned helplessness model (Meloni et al., 1993; Yilmaz et al., 2002; Tokita et al., 2011). Correspondingly, human studies demonstrated antidepressant effects of glutamate release inhibitors such as lamotrigine and riluzole as well as the NMDA receptor antagonist ketamine (Calabrese et al., 1999; Zarate et al., 2004, 2006). Further evidence comes from studies reporting selective modulation of glutamate levels in DLPFC and ACC during the course of different therapeutic interventions such as electroconvulsive therapy (Merkel et al., 2011) or transcranial magnetic stimulation (Luborzewski et al., 2007). However, while changes in glutamate levels and their modulation by antidepressant treatment have been well described for the ACC and the DLPFC, to date there have been no studies investigating glutamate levels in MCC. This is of special relevance, since previous MRS- studies on the cingulate cortex either investigated the pregenual anterior cingulate cortex (pACC) or an overlap of pACC and subgenual anterior cingulate cortex (sACC). These regions differ functionally as well as in their responsiveness toward a specific antidepressant treatment (Ressler and Mayberg, 2007). A coactivation of sACC and MCC during the processing of valenced information may suggest that these regions engage together in particular cingulate functions (Goldstein et al., 2007). The functional connection and the similar receptor architecture of MCC and sACC highlight the importance of an *in vivo* measurement of glutamate content in MCC, specifically since an MRS investigation of the sACC proves to be difficult due to prevalent magnetic susceptibility artifacts. Therefore, our study aimed to investigate glutamate concentrations in the midcingulate cortex in patients with unipolar depression. As a control region, we focused on the left DLPFC, where studies consistently described reduced density and size of neurons and glial cells (Rajkowska et al., 1999, 2001; Cotter et al., 2001), lower glucose metabolism (Mayberg et al., 1999), reduced activation in cognitive and emotional-evaluative tasks (Mayberg, 2003; Grimm et al., 2008), but unchanged levels of glutamate in unipolar depression (Nery et al., 2009; Merkel et al., 2011). We hypothesized a dissociation of glutamate levels with unchanged levels in DLPFC and abnormally changed levels in MCC. Furthermore, we hypothesized a differential effect of successful antidepressant pharmacotherapy on these brain metabolites.

## 2. Methods

### 2.1. Participants

Subjects with an acute MDD episode ( $n = 14$ ; 7 females; mean age  $\pm$  SD age,  $38.8 \pm 11.4$  years; age range, 20–53 years; number of episodes  $1.5 \pm .94$ , range 1–4; age of onset  $36.8 \pm 12.81$  years, age range 19–53 years) were recruited from the inpatient department of psychiatry at the Charité Berlin. Diagnoses were established by two independent experienced psychiatrists based on a clinical interview following DSM-IV criteria. Treatment comprised different antidepressants with add-on therapy and dosage being kept constant in all patients: selective serotonin reuptake inhibitors (78%), serotonin-norepinephrine reuptake inhibitors (64%), tricyclic antidepressants (28%), or atypical neuroleptics (57%). Response to antidepressant therapy was defined as a 50% reduction in the Hamilton Depression Rating Scale scores (HDRS; Hamilton, 1960) 17-item version. Psychometric ratings were performed at baseline (T0) and after 4 weeks of antidepressant treatment (T1). Exclusion criteria were major medical illness,

history of seizures, head trauma with loss of consciousness an abnormal clinical laboratory test result, and pregnancy. Specific psychiatric exclusion criteria consisted of atypical forms of depression, suicidal ideation, any additional psychiatric disorder, history of substance abuse or dependence, and electroconvulsive therapy in the preceding 6 months. Healthy subjects without any psychiatric, neurologic, or medical illness were self-referred from online study advertisements ( $n = 14$ ; 7 females; mean  $\pm$  SD age,  $32.3 \pm 6.9$  years; age range, 24–45 years). Participants were entered into the study after a full explanation of the purpose of the study and the study procedures and after written consent was obtained as approved by the local University Ethics Committee of the Charité Berlin.

### 2.2. MR spectroscopy and data processing

MRS data was obtained from voxels of the left DLPFC and MCC (see Fig. 1) in both depressed patients and healthy volunteers. A follow-up MRS in the same voxels was performed after 4 weeks of antidepressant treatment in the group of patients. Levels of glutamate (Glu) were assessed in both regions of interest. MRS was performed on a 3 T scanner (MEDSPEC 30/100, Bruker Biospin, Ettlingen, Germany) using a quadrature birdcage resonator. After automated global shim of the linear,  $xz$ ,  $z^2$  and  $x^2 - y^2$  field components,  $T_1$ -weighted images (MDEFT,  $T_E = 3.8$  ms,  $T_R = 20.53$  ms; 128 contiguous slices, 1.5 mm thick; 1-mm inplane ( $x$ – $y$ ) resolution) were acquired. Following localized shimming, MR spectra were acquired from  $2 \times 2 \times 2$  cm<sup>3</sup> voxels including the left DLPFC, and from  $2.5 \times 4 \times 2$  cm<sup>3</sup> voxels including the MCC. For metabolite quantification (see below) spectra were acquired from equal voxels in the center of metabolite phantoms (.1 M metabolite, pH 7.2, 37 °C). After manual shimming to water linewidths (FWHM) of 7 Hz for the two voxels spectra were acquired with PRESS (point resolved spectroscopy) using Shinnar-LeRoux-optimized 90° and Mao refocusing pulses applied at the water resonance frequency. To obtain one MR spectrum, subspectra (8 for MCC, 16 for DLPFC) of 16 phase cycled scans each were recorded with  $T_R = 3$  s and  $T_E = 80$  ms, giving 128 and 256 averages. Subsequently a water-unsuppressed spectrum (8 averages) was acquired. Fig. 2 shows a typical *in vivo* MR spectrum together with phantom spectra of glutamate and glutamine at approximately physiological concentrations. There is little interference of the C4 resonances around 2.35 ppm of the two neurotransmitter compounds, thus permitting a fairly selective determination of glutamate in the subsequent spectrum fitting procedure. Before further processing, the individual metabolite subspectra were corrected for eddy currents using the water-unsuppressed spectrum, and automatically frequency aligned to correct for frequency shifts during the scan, caused by involuntary subject motion and system instabilities. The resulting spectrum was quantified using a program package that relies on a time domain-frequency domain fitting procedure involving inclusion of phantom basis spectra and prior knowledge, and background estimation by regularization (Schubert et al., 2004; Elster et al., 2005). For the MCC voxel the mean uncertainty for the fitted Glu-amplitude (corresponding to Cramér-Rao lower bounds but with added uncertainties from background modeling) was 11.8%. For the DLPFC voxel this value was moderately higher according to the lower signal-to-noise ratio. The metabolite amplitudes were corrected for differences in coil loading by the phantoms and the individual subject's head and for relaxation effects using relaxation times measured previously (Schubert et al., 2004), assuming equal glutamate relaxation times in the MCC and DLPFC. Metabolite concentrations were corrected for the cerebrospinal fluid in the voxels studied by using the cerebrospinal fluid fractions obtained by segmenting the T1-weighted images with

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