Alterations in BOLD response and metabolite concentrations support decreased glial enzyme activity in major depression: a quantitative JPRESS and fMRI study.

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Introduction

MRI has become an accepted tool of investigating brain alterations underlying psychiatric disorders such as major depressive disorder (MDD). Converging evidences exist for increased cortical activity in the pregenual portion of the anterior cingulate cortex (pgACC), mainly derived from functional MRI (fMRI) studies [1,2]. Hereby, the pgACC is characterized by high neuronal activity at rest and deactivations during cognitive tasks. Functionally, this region is also related to subjective evaluation of internal states by attributing hedonic values and maintenance of emotional states. Further insights exist for structural abnormalities [3] and decreased concentrations of glutamate as measured by magnetic resonance spectroscopy (MRS) [4]. This sets investigations of the causes of MDD in the position to specify these findings not only in the anatomical but also in the functional dimension. However, combining functional and metabolic measurements in a conjoint study are needed to change the focus of investigation from a descriptive to a causal level. Hence, ***in this work*** parameters specifying metabolic alterations inside the pgACC, assessed by quantitative in-vivo 2D j-resolved magnetic resonance spectroscopy (JPRESS), were recorded in line with functional parameters measured by fMRI during emotional stimulation and subjective evaluation of the emotional state in healthy volunteers and MDD patients. Given previous reports of altered Glx levels and neuronal hyperactivation in MDD patients, we hypothesized an altered excitation/inhibition balance. Thus, changed GABA, glutamate and glutamine levels would be specifically related to reduced deactivation, represented by signal decreases during an emotional task, in the patient group. Further this relation was expected to be specified for altered subjective evaluation of emotional intensities and corresponding clinical markers of anhedonia. The presented data corroborate these hypotheses. In addition, our in vivo data support a decreased activity of glial SLC1A2 and SLC1A3, enzymes that are mediating the Glu reuptake from the synaptic cleft, as well as glial glutamine synthetase, which catalyses the transformation of glutamate into glutamine.

Materials and Methods

All MRI/MRS data were recorded on a Philips Achieva 3T scanner using an eight-channel Philips SENSE head array for fMRI measurements and a birdcage transmit-receive head coil for MRS measurements. An adapted PRESS-localized 2D *J*-resolved MR spectroscopy sequence (JPRESS) was applied to assess concentrations of 19 metabolites including GABA, glutamine (Gln) and glutamate (Glu) in the pcACC at rest. This approach allows for significant reduction of spectral overlap by spreading multiplet resonances along two frequency axes and therefore enables GABA and Gln quantification at 3T at all. In addition, a maximum echo sampling scheme avoids the distortion of metabolite signals of interest by the tail of the water signal [5]. The acquisition time of one JPRESS measurement was 16 min. Quantification of 19 brain metabolites was performed using ProFit [6]. In contrast to former quantification methods ProFit can access the full information content of 2D J-resolved spectra by fitting a linear combination of simulated 2D basis spectra to it. Negative bold responses in our regions of interest, the pcACC, were obtained in fMRI during passive emotional picture viewing (PV), subjective evaluation of elicited emotions (PJ – picture judgement) and anticipation periods (EX - expectancy) by the corresponding contrasts against rest. This slow event related fMRI paradigm has previously proven to elicit reliable signal decreases in the pgACC [7]. Experimental parameters included T_E = 35ms, FOV = 22 cm, voxel size = 2.75 x 2.75 x 4 mm^3, 32 slices, SENSE acceleration factor R = 2.0, T_R = 3000 ms and θ = 82°. Data analysis was performed using SPM2. MRS and fMRI measurements were performed in 24 healthy subjects and 16 MDD patients in two consecutive measurement sessions each.

Results and Discussion

For both picture judgement and passive viewing significant negative bold responses (NBR) were found in pgACC in both groups. NBRs were significantly decreased in the patient group (Figure 1a). As opposed to healthy controls there was no difference between picture judgement and passive viewing conditions. For patients with high anhedonia scores, a significant reduction of Gln (Figure 1b) can be reported with no differences in GABA levels. While GABA predicted the amount of NBR´s in healthy subjects [8], this correlation was not present in the patient group. Instead there was a strong correlation between NBRs in the pgACC and related Glu levels (Figure 2a). As predicted patients Anhedonia scores correlated with their subjective ratings of emotional intensity elicited by the stimuli. These intensity rating were significantly correlated with both NBR and Glu levels in the patient group, while there was no corresponding correlation for the controls (Figure 2b). Further analysis revealed that significant correlations of glucose (Glc) with GABA (r=0.775*, p<0.01) and Gln (r=0.686*. p<0.02) that were found in healthy volunteers, are absent in patients. These findings together with the reduced glutamate concentration in MDD patients strongly indicate a diminished conversion of glutamate into glutamine. This step, which is mediated by a glial enzyme - glutamine synthetase - thus represents one observable alteration in the cellular mechanism of depressive patients (Figure 3). Furthermore, the occurring direct correlation of Glu with NBRs as well as the reported emotional intensity might directly relate to an increased amount of Glu in the synaptic cleft, which is caused by a functional deficit in Glu reuptake into astroglia. In the long term this would lead to the death of glutamatergic neurons due to extensive activation (Figure 3). Both hypotheses derived from our data are supported by findings of Choudary et al [9], who found significantly lower concentrations of SLC1A2 and SLC1A3 – glial enzymes that mediate Glu reuptake – as well as glutamine synthethase in tissue extracts of the ACC from suicide victims. Thus, given a specific activation paradigm with predictable signal changes in both patients and controls a region that is known to be involveld in key functions that are disturbed in MDD we could indirectly investigate specific alterations of glial processes involved in the excitation/inhibition balance and thus provide insight into a direct link of so far isolated findings.

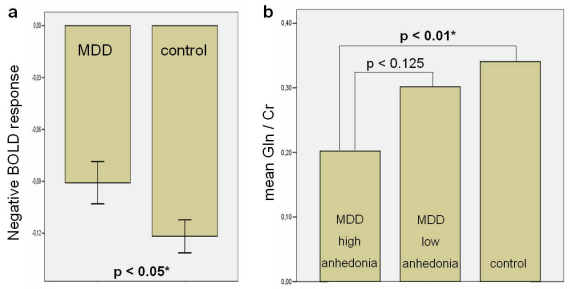

***Figure 1**: Significant decrease of the negative BOLD response in MDD patients compared to controls (a) and the mean Gln concentrations in MDD patients with high anhedonia scores compared to healthy controls (b).*

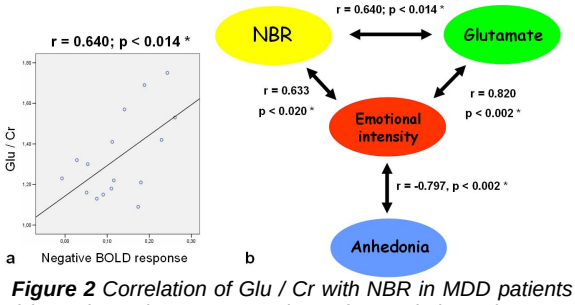

***Figure 2** Correlation of Glu / Cr with NBR in MDD patients (a). Schematic representation of correlations between NBR, Glu, reported emotional intensity and anhedonia score in MDD (b).*

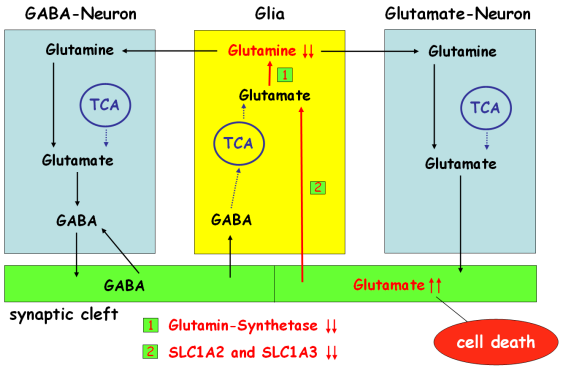

***Figure 3** Schematic representation of the derived hypothesis regarding alterations in glial function in the pcACC of MDD patients.*

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