Cortical glutamate is linked to reward related ventral striate activity – A study combining fMRI and MRS at 3 T

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Introduction

Processing of rewarding stimuli is associated with increased firing rate of dopamine neurons in the ventral striatum, a core region of the brain reward system. Psychiatric diseases with dysfunctional reward behavior, like schizophrenia, are associated with abnormal dopaminergic neurotransmission and dysfunctional activation of the ventral striatum [1]. A close interaction between dopamine and glutamate has been proposed to play an important role in reward processing and in the pathophysiology of schizophrenia [2]. In humans, aspects of dopamine function may be reflected by the BOLD activity of the ventral striatum during presentation of rewarding stimuli [1,2], and glutamatergic function may be represented by absolute glutamate concentrations measured by MR spectroscopy [4]. An interaction of dopaminergic and glutamatergic neurotransmission has so far not been imaged in humans.

We hypothesize a correlation between the activity of the ventral striatum (BOLD contrast during reward processing) and glutamate concentration in the anterior cingulate cortex in healthy subjects.

Subjects and Methods

22 healthy subjects (age 9 to 46 y, 10 f) participated in a combined fMRI and MRS experiment using a 3-tesla scanner (MEDSPEC 30/100, Bruker Medical) equipped with a birdcage coil. FMRI was performed using EPI, 36 axial slices without gap, 80 x 80 voxels per slice, T_R = 2.0 s, T_E = 21 ms, inplane resolution 2.5 mm x 2.5 mm, slice thickness = 2.0 mm, flip angle = 70°. In a reward-task similar to Knutson's paradigm [3] participants could win or lose 1 Euro in approx. 160 trials; contrast images of positive anticipation against anticipation of neutral trials were used in the analysis. To ensure that the observed activation was located in the ventral striatum, a voxel mask (296 voxels) from a probabilistic MNI atlas [5] at a threshold of 0.75 probability was applied. MRS was performed in the same session immediately succeeding fMRI. MR spectra were acquired using PRESS optimized for glutamate detection (T_E = 80 ms, T_R = 3 s, n = 128) [4] from the left hippocampus (HC; 2 x 2 x 1.2 cm^3) and the anterior cingulate cortex (AC; 2.5 x 4 x 2 cm^3). The glutamate C4 resonance was quantified [4] with a time domain-frequency domain method using a phantom spectra basis set and prior knowledge for relative frequency, line width and phase. Fitted amplitudes were corrected for relaxation times, coil loading differences, and cerebrospinal fluid content of the voxels analyzed.

Results

In the subjects studied positive anticipation led to robust bilateral activation in the ventral striatum (MNI coordinates, peak voxel at x, y, z = -18, 6, -10; T = 4.48, p < 0.001, corrected). Within the region of interest, multiple regression analysis shows activation in a cluster of 73 voxels on the left side (peak voxel at x, y, z = -18, 16, -6; T = 2.34, p < 0.05, uncorrected) and 23 voxels on the right side (peak voxel at x, y, z = 8, 12, -6; T = 2.12, p < 0.05, uncorrected) to be negatively correlated with the concentration of glutamate in the AC (Fig. 1). The correlation for the BOLD contrast in the peak voxels in all subjects is shown in Fig. 2. No significant positive correlations were observed and no correlation was found for glutamate in the hippocampus voxel.

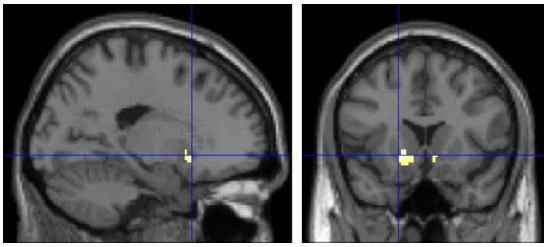

Fig. 1. Two clusters within the ventral striatum where BOLD contrast shows negative correlation with glutamate concentration in the ACC.

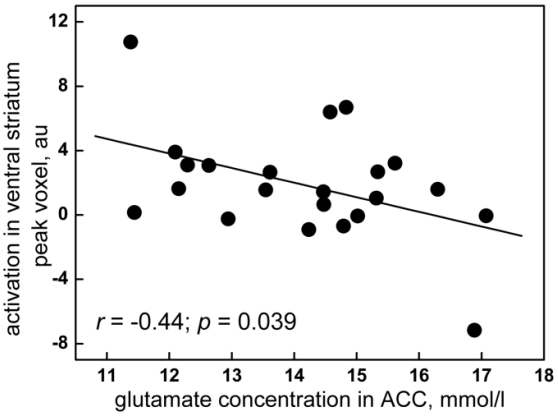

Fig. 2. Correlation between BOLD contrast in the ventral striatum (peak voxels) and glutamate concentration in the ACC.

Discussion

Our findings indicate that frontal glutamate may be related to the activation of the ventral striatum. This association is compatible with a pertinent neuronal model [2], stressing a modulatory effect of cortical glutamate on the dopaminergic activity in the ventral striatum. Thus, our results indirectly visualize an interaction of dopaminergic and glutamatergic neurotransmission which would be highly relevant for schizophrenia research.

References

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