Brain glutamate and empathy. A proton MRS study at 3 tesla

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Introduction

Empathy is an essential element of human behavior. The multidimensional construct of empathy comprises cognitive aspects (theory of mind, cognitive empathy) that require the ability to imagine or predict another's perspective, intentions or complex emotions, as well as attributions of affective mental states that may involve affective mirroring [1]. Dysfunctions of empathy and mentalizing have been seen as a basal feature of psychopathological syndromes in severe mental disorders like schizophrenia [2] and autism [3]. Whilst brain imaging studies have shown the prefrontal and cingulate cortex activation to be linked to cognitive and affective empathy [4], the role of neurotransmitter systems in empathy is largely unknown. Glutamatergic dysfunction has been suggested in various disorders marked by specific alterations of social reciprocity and empathy, like autism [5] and schizophrenia [6], with research on the genetic underpinnings of these conditions currently focusing on the glutamatergic system [6]. Given the sparse knowledge of the biological underpinnings of empathy, we investigated the relationship between self-rated dimensions of empathy as measured by the Interpersonal Reactivity Index [7], and concentrations of cerebral glutamate determined by 1H-MRS at 3 tesla.

Subjects and Methods

Seventeen healthy individuals (29.7±6.8 y, 12 women) were investigated. Proton MRS at 3 T and glutamate (Glu) quantification were performed using established methods [8]. MR spectra were recorded on a 3-tesla scanner (MEDSPEC 30/100, Bruker Biospin, Germany) from voxels including the left hippocampus (HC, 2x3x2cm^3), the anterior cingulate (ACC, 2.5x4x2cm^3) and the left dorsolateral prefrontal cortex (DLPFC, 2x2x2cm^3). PRESS (T_R=3s) with an echo time of 80 ms, chosen to obtain maximum selectivity for the glutamate C4 resonance, was used. Spectral quantification was carried out using a time domain-frequency domain fitting procedure that includes phantom basis spectra and prior knowledge, and involves background estimation by regularization. In the present spectra, the amplitudes of total choline, total creatine, N-acetylaspartate, Glu and glutamine resonances were fitted. Residual, minor contributions by macromolecules were accomodated in the baseline by the fitting procedure. The fitted metabolite amplitudes were corrected for different coil loadings and relaxation effects [8]. Glu concentrations were corrected for CSF fractions in the voxels by segmenting T_1-weighted images using SPM2.

The Interpersonal Reactivity Index (IRI) assesses aspects of empathic response. We chose three of the five 7-item subscales measuring the core dimensions of empathy, answered on a 5-point Likert scale: 'perspective taking' for cognitive empathy or theory of mind; 'empathic concern' for respondents' feelings of compassion and concern for others; personal distress for self-oriented feelings of anxiety and discomfort in response to the distress of others. Construct validity of the IRI scales was supported in several studies [7]. Statistical analysis was performed using SPSS 12.0®.
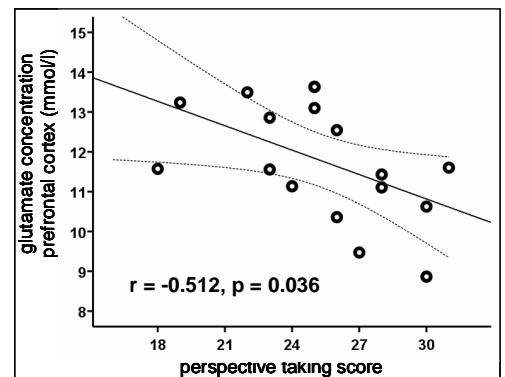
Results

Uncertainties (corresponding to Cramér-Rao lower bounds with added uncertainties from background modelling [9]) for the determination of Glu amounted to 10%–14%. Linear regression analysis showed that Glu concentration in the DLPFC (dependent variable) was predicted by empathy factor 'perspective taking' (T=-2.710, p=0.018) but not by 'empathic concern' (T=1.078, p=0.300) or 'personal distress' (T=-1.313, p=0.212). DLPFC glutamate level and 'perspective taking' score showed a significant negative correlation (Pearson's r=-0.512, p=0.036; **Figure**). Analysis of Glu concentrations in the ACC and HC voxels using empathy factors as predictors did not reveal significant effects.

Discussion

A negative association between left dorsolateral prefrontal concentrations of glutamate with ratings of perspective taking, i.e. cognitive empathy or theory of mind, was observed. No associations were found for the other voxels of interest nor with regard to the other IRI subscales. The association of DLPFC glutamate with perspective taking is compatible with functional brain imaging studies showing a role of the DLPFC in cognitive empathy [1]. Furthermore, lateral prefrontal areas have been implicated in the representation of 'other' as opposed to 'self' [10]. The DLPFC entertains widespread interconnections within the mentalizing network and is involved in executive functioning, maintaining cognitive flexibility and response inhibition.

To our knowledge, this is the first investigation of the neurobiological basis of empathy using MRS. Our data suggest a possible involvement of cerebral glutamate in cognitive empathy and add to findings that glutamate measured in vivo is relevant for human behavior and personality traits [11].

Figure. Glutamate level in DLPFC and perspective taking score determined in 17 healthy subjects.

References

[1] Decety J & Jackson PL, Behav Cogn Neurosci Rev 2004, 3: 71. [2] Brüne M, Schizophrenia Bull 2005, 13: 21. [3] Rogers K et al, J Autism Dev Disord 2007, 4: 709. [4] Brunet-Gouet E & Decety J, Psychiatry Res: Neuroimaging 2006, 148: 75. [5] Page LA et al, Am J Psychiatry 2006, 163: 2189. [6] Coyle JT, Cell Mol Neurobiol 2006, 26: 365. [7] Davis MH, J Personality Soc Psychol 1983, 44: 113. [8] Schubert F et al, Neuroimage 2004, 21: 1762. [9] Elster C et al, Magn Reson Med 2005, 53:1288. [10] Ochsner KN et al, J Cogn Neurosci 2004, 16:1746. [11] Gallinat J et al, Neuroimage 2007, 34: 671.