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Research report

Hippocampal metabolism and prefrontal brain structure: A combined 1H-MR spectroscopy, neuropsychological, and voxel-based morphometry (VBM) study

Johanna Steinke [a], Christian Gaser [a,b], Kerstin Langbein [a], Maren Dietzek [a], Alexander Gussew [c], Jürgen R. Reichenbach [c], Stefan Smesny [a], Heinrich Sauer [a], Igor Nenadić [a,d,*]

[a] Department of Psychiatry and Psychotherapy, Jena University Hospital, Jena, Germany
[b] Department of Neurology, Jena University Hospital, Jena, Germany
[c] Medical Physics Group, Institute for Diagnostic and Interventional Radiology (IDIR), Jena University Hospital, Jena, Germany
[d] Department of Psychiatry and Psychotherapy, Philipps University Marburg & Marburg University Hospital/UKGM, Marburg, Germany

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ABSTRACT

Hippocampal structural and functional integrity impacts on multiple remote areas of the brain, and this connectivity is central to multiple cognitive functions in healthy and disease. We studied associations of hippocampal metabolic markers N-acetyl aspartate (NAA) and glutamate (Glu and Glx; assessed with 1H magnetic resonance spectroscopy) and brain grey matter (studied with voxel-based morphometry, VBM) in 20 healthy subjects. We found a significant correlation between right hippocampal NAA and left ventrolateral prefrontal cortical grey matter (TFCE, $p < 0.05$, FWE-corrected), as well as verbal fluency markers, and right hippocampal Glx (glutamate/glutamine) and left cerebellar volume. Our studies demonstrate a structure-function correlation that might underlie the interaction of the hippocampus with prefrontal cortex and cerebellum, which might be central to several neurological and psychiatric disorders, including schizophrenia or depression.

1. Introduction

Hippocampal integrity is central to a number of cognitive and emotional functions. Alteration of hippocampal structure and/or function is thus also crucial for a number of pathologies, including mesial sclerosis in epilepsy (Brazdil et al., 2009), but also in depression and schizophrenia (de Diego-Adelino et al., 2013; Kraguljac et al., 2013; Nenadic et al., 2015), post-traumatic stress disorder (O'Doherty et al., 2017), as well as Alzheimer's disease (Wang et al., 2015).

The connectivity of the hippocampus with other brain structures, especially prefrontal cortices, has been a focus of recent research aiming at providing a better understanding of its role in disease (Li et al., 2015; Sigurdsson and Duvarci, 2015). Indeed, the hippocampus shows intricate connections not only to other adjacent medial temporal lobe brain structures, but also features prominent functionally relevant connections to the thalamus (Tsanov and O'Mara, 2015) and prefrontal cortex (Godsil et al., 2013).

Multi-modal imaging is an approach to study such interactions, combining different MR modalities to assess structure and/or function. Examples of this are recent studies, which have linked hippocampal structure and metabolism in epilepsy (Brazdil et al., 2009) and schizophrenia (Hasan et al., 2014; Kraguljac et al., 2013), respectively. In the present study, we used MR spectroscopy (MRS) in healthy subjects to assess hippocampal metabolite levels for N-acetyl aspartate (NAA) as a marker of neuronal viability and glutamate (Glu) (assessed as Glu and Glx), and to correlate those with grey matter structural variation across the brain.

2. Results

Quantitative metabolite levels are given in Table 1.

Right hippocampus NAA concentration correlated significantly with a cluster in the left ventrolateral prefrontal cortex (PFC) at $p < 0.05$ FWE-corrected ($k = 93$ voxels; maximum voxel at −38; 32; −8). Right hippocampus Glx (glutamate and glutamine combined) correlated significantly ($p < 0.05$, FWE-corrected) with two clusters in the left lateral cerebellum ($k = 1984$ voxels, maximum

* Corresponding author at: Department of Psychiatry and Psychotherapy, Philipps University Marburg & Marburg University Hospital/UKGM, Rudolf-Bultmann-Str. 8, 35037 Marburg, Germany.
E-mail address: nenadic@staff.uni-marburg.de (I. Nenadić).

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Table 1
Quantitative levels of metabolites (mean and SD).

Metabolite level (mmol/l)	Left hippocampus mean (SD)	Right hippocampus mean (SD)
N-acetyl aspartate (NAA)	8,89 (2,88)	9,46 (3,03)
Glutamate (Glu)	9,07 (3,14)	9,87 (2,53)
GLX (glutamate + glutamine)	13,73 (5,16)	16,12 (4,46)

at −40; −55; −48; and k = 333, maximum at −45; −78; −27), but this was not significant in the glutamate correlation analysis. Results are shown in Fig. 3.

While there were no other significant correlations at corrected thresholds, we did find additional correlations in an exploratory analysis ($p < 0.001$, uncorrected): 1.) For right hippocampal NAA, we found additional positive correlations in the left dorsolateral PFC, right medial PFC, left anterior insula/capsula extrema grey matter, right central sulcus grey matter, and a minor cluster in the right dorsolateral PFC. 2.) For left hippocampal NAA, we found positive correlations in a left orbitofrontal/ventrolateral PFC cluster, left medial PFC, and right central sulcus grey matter, as well as a negative correlation with a small right parietal cluster; or right hippocampal glutamate, we found positive correlations in a left ventrolateral PFC cluster, right medial PFC, right dorsolateral PFC, as well as negative correlation with left amygdala and left posterior cerebellum; for left hippocampal glutamate, we found positive correlations in clusters in the left anterior temporal pole and a smaller cluster in the right medial parietal cortex/precuneus, right middle temporal gyrus, and a negative correlation in a small right caudate cluster. 3.) For right hippocampal Glx, we there was no additional correlation (apart from the two cerebellar clusters significant at corrected thresholds). 4.) Finally, for left hippocampal Glx, there was a negative correlation with the right caudate and a positive with right precuneus, right middle temporal gyrus, and left middle occipital cortex.

Overall, we did not find either positive or negative correlations of hippocampal metabolic parameters with hippocampal grey matter.

Correlation analyses with neuropsychological data showed a significant positive correlation ($p < 0.05$) of right hippocampal NAA with COWT-S ($r = 0.4$, $p = 0.04$). Information score (from WIE/WAIS) showed negative correlations with left hippocampal NAA ($r = -0.49$; $p = 0.02$) and left hippocampal Glx peaks ($r = -0.53$; $p = 0.01$).

3. Discussion

This study demonstrates an association of hippocampal metabolic markers with prefrontal cortex and cerebellar brain structure. Using a multi-modal approach, these findings serve to understand the inter-relations of brain functional and structural interactions. We used NAA and Glx as these are the most studied ^{1}H-MRS parameter for a range of neurological and psychiatric disorders, and have been studied in depth in previous MRS studies (for overview, see (Ramadan et al., 2013)). Three aspects from our findings merit particular attention.

First, the association of NAA, a marker of general neuronal integrity, with left ventrolateral prefrontal cortex volume suggests an interaction of these two brain structures. Their connectivity is central to memory tasks (Takita et al., 2013). This seems to be the case not only for medial PFC regions; recent meta-analyses suggest ventrolateral PFC and medial temporal lobe activation particularly during encoding of episodic memory (Spaniol et al., 2009). Given that our study combines MRS and VBM, it differs from purely functional techniques assessing connectivity, such as analyses of functional connectivity based on fMRI. MRS rather directly captures aspects of metabolites and thus gives evidence additional to BOLD changes tapped in fMRI. In our study, hippocampal NAA was also related to performance on verbal fluency, which is in line with previous fMRI studies (Glikmann-Johnston et al., 2015). Notably, this prefrontal-hippocampal link has multiple implications of disturbed connectivity in psychiatric disorder (Godsil et al., 2013; Li et al., 2015).

Secondly, our glutamatergic findings link hippocampal Glx to cerebellar function. Glutamate has be linked to cognitive functions in multiple MRS studies (Ende, 2015), as it is of central interest to multiple neuropsychiatric disorders (Ramadan et al., 2013). Research on the interaction between the hippocampus and cerebellum and its implications in cognition, however, are by far more scarce. This connection has received more interest in research using fMRI and computational modelling elucidating the interaction and its importance in cognitive processing, such as timing (Yu and Krook-Magnuson, 2015); the recent functional anatomical models stress a bidirectional influence. Recent examples of the cognitive significance of this connection include timing-sensitive prediction of movements (Onuki et al., 2015) and non-motor aspects of navigation (Igloi et al., 2015). Our findings therefore provide additional structure-function evidence of an interaction.

While we only found this association with the Glx sum peak, the lack of significance with Glu might be, in part, due to methodological limitations in isolating the peak, possibly leading to increased variance (Gussew et al., 2012). Also, we need to consider that glutamatergic peaks in MRS might be related to other measures of overall metabolism (Smesny et al., 2015; Squarcina et al., 2017), reminding us of the possibility that MRS possibly not exclusively detects synaptic glutamate but also other non-vesicular forms of this metabolite.

Finally, one negative finding also merits attention: we did not find an association of hippocampal metabolic markers with hippocampal grey matter itself, as suggested by some previous work in schizophrenia (Kraguljac et al., 2013). This might, in part, be attributable to the functional heterogeneity within the hippocampus (Wagner et al., 2016). Increased spatial resolution within the hippocampus would be needed to assess this in further studies.

Our findings suggest further research in several aspects. For example, the limited sample size in our study precluded an in-depth exploration of the effects of age and gender, which have been described for brain metabolites (Jung et al., 2005; Raininko and Mattsson, 2010), but have not been studied in further detail for the association of metabolites and brain structure. While our findings are highly significant, they might only hold for a particular age range and structure-function correlations might differ in children or adolescents.

One methodological limitation of our study relies on the ambiguity of resolving the overlapping resonance patterns in the chemical shift range between 2.1 and 2.4 ppm. Despite being dominated by glutamate signals, the quantitated intensities might be particularly blurred by glutamine and GABA contributions, which might not be fully differentiated even by LCModel quantitation performed with dedicated metabolite model basis set. Therefore, we are working on implementation of more advanced quantitation methods in order to achieve more reliable separation between these metabolites in future studies (Belkić and Belkić, 2016; Belkić and Belkić, 2017).

Future studies might take into account current advances in separating MRS peaks and identify associations with brain structures. For example, separation of glutamate and glutamine as well as addition of gamma-amino-butyric acid (GABA) to such association studies will strengthen our understanding of how specific