European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

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Associations of hippocampal metabolism and regional brain grey matter in neuroleptic-naïve ultra-high-risk subjects and first-episode schizophrenia

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Received 13 February 2015; received in revised form 6 May 2015; accepted 13 May 2015

KEYWORDS
Magnetic resonance spectroscopy (MRS);
Prefrontal cortex (PFC);
Psychosis;
Schizophrenia;
Voxel-based morphometry (VBM)

Abstract
Hippocampal pathology has been shown to be central to the pathophysiology of schizophrenia and a putative risk marker for developing psychosis. We applied both ^{1}H MRS (proton magnetic resonance spectroscopy) at 3 Tesla and voxel-based morphometry (VBM) of high-resolution brain structural images in order to study the association of the metabolites glutamate (Glu) and N-acetyl-aspartate (NAA) in the hippocampus with whole-brain morphometry in 31 persons at ultra-high-risk for psychosis (UHR), 18 first-episode schizophrenia patients (Sz), and 42 healthy controls (all subjects being neuroleptic-naïve). Significantly diverging associations emerged for UHR subjects hippocampal glutamate showed positive correlation with the left superior frontal cortex, not seen in Sz or controls, while in first-episode schizophrenia patients a negative correlation was significant between glutamate and a left prefrontal area. For NAA, we observed different associations for left prefrontal and caudate clusters bilaterally for both high-risk and first-episode schizophrenia subjects, diverging from the pattern seen in healthy subjects. Our

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http://dx.doi.org/10.1016/j.euroneuro.2015.05.005
0924-977X/

Please cite this article as: Nenadic, I., et al., Associations of hippocampal metabolism and regional brain grey matter in neuroleptic-naïve ultra-high-risk subjects and first-episode.... European Neuropsychopharmacology (2015), http://dx.doi.org/10.1016/j.euroneuro.2015.05.005

results suggest that associations of hippocampal metabolites in key areas of schizophrenia might vary due to liability to or onset of the disorder.

1. Introduction

The high-risk state for psychosis has become a major paradigm in schizophrenia research that is relevant for both early clinical intervention as well as the study of the biological basis of schizophrenia (Fusar-Poli et al., 2013). Subjects at ultra-high risk (UHR) of developing psychosis show a number of cognitive as well as brain structural and functional changes similar to those seen in schizophrenia (Cooper et al., 2014; Fusar-Poli, 2012; Palaniyappan et al., 2012). These alterations reflect, to differing extent, the contribution of genetic risk or liability, changes seen in the prodrome, and changes at the onset of schizophrenia (Jung et al., 2012).

The hippocampus has been of particular interest for UHR studies, since it is central to the pathophysiology of schizophrenia, especially in the context of glutamatergic dysfunction (Tamminga et al., 2012). Structural changes of the hippocampus have been demonstrated with magnetic resonance imaging (MRI) in both first-episode and chronic populations (Adriano et al., 2012), and multi-modal imaging has revealed multiple abnormal hippocampal markers in UHR subjects (Wood et al., 2010).

Magnetic resonance spectroscopy (MRS) has increasingly been used to assess metabolic changes in UHR subjects and during transition to psychosis, as it provides additional information about specific metabolites, such as glutamate (Glu), or markers of neuronal integrity, such as N-Acetyl-aspartate (NAA). There is some evidence that NAA is decreased in the hippocampus in schizophrenia (Steen et al., 2005), although there have been conflicting results (He et al., 2012), and the influence of several aspects, like chronicity of disease or medication, needs further evaluation. However, the pathophysiological process accompanying changes of Glu and/or NAA in the hippocampus in emerging psychosis might not only include changes in the level of these metabolites, but more importantly also changes in their effects on functional parameters and connectivity with other key regions of schizophrenia pathophysiology, and/or on remote neural network. This has been suggested by a number of recent studies that combined MRS with other structural and/or functional imaging techniques. Kraguljac and colleagues reported that the association between NAA and Glu concentrations in the hippocampus (as seen in healthy controls) was lost in a large sample of schizophrenia patients, indicating a decoupling of these physiologically interrelated metabolites (Kraguljac et al., 2012). In a subsequent study, the same group also identified a correlation between NAA and combined glutamate and glutamine markers with hippocampal volume in unmedicated Sz patients (Kraguljac et al., 2013). Abnormal levels of hippocampal metabolites, however, also appear to influence remote areas, as seen in diverging correlation patterns between hippocampal NAA and prefrontal activation measured with functional MRI (Hutcheson et al., 2012).

In UHR subjects with at-risk mental state (ARMS), a series of recent studies has suggested that hippocampal glutamate changes might lead to a number of structural and functional changes in interconnected networks (Egerton et al., 2012). Hippocampal glutamate was correlated with striatal [18F]-DOPA uptake, an indicator of striatal dopamine turnover, and a putative indicator of transition to psychosis (Stone et al., 2010). Also, the physiological association between hippocampal glutamate and medial temporal brain activation seen in healthy subjects was lost in UHR subjects with ARMS status (Valli et al., 2011). Currently, it is unclear whether the loss of such associations (studied as correlations between two structural/functional markers) is related to liability or to transitional processes towards the onset of psychosis.

Against the background of these findings, we investigated the relation between the metabolic markers glutamate and NAA in the hippocampus with brain structure (i.e. morphometry) for three different groups: UHR subjects identified in an early psychosis programme, patients with first-episode schizophrenia, and healthy controls. We tested the hypothesis that correlations between hippocampal Glu and/or NAA with other key brain regions implicated in previous studies, i.e. the lateral prefrontal cortex, anterior cingulate cortex, thalamus, and the hippocampus itself, would show a group effect indicating that associations are different depending on risk vs. actual onset of schizophrenia. In order to avoid confounding effects of medication, which have been shown in previous MRS studies on Glu (Poels et al., 2014), we only included subjects who were neuroleptic-naïve, i.e. had never been treated with antipsychotics.

2. Experimental procedures

2.1. Subjects

We included in this study a total of 91 subjects: 31 persons at ultra-high-risk (UHR) of developing psychosis, 18 patients with first-onset schizophrenia (Sz), and 42 healthy control subjects. Demographic details are given in Table 1. Groups did not differ in age (ANOVA: $F=0.211$; $p=0.81$) or gender composition (Chi-square-test: $p=0.525$). All study participants provided written informed consent to a study protocol, which had been approved by the Ethics Committee of Jena University Medical School and was in accordance with the Declaration of Helsinki. This is a sub-sample of a cohort used in a previous study of brain structure in UHR and first-episode schizophrenia patients, which focused on different UHR subgroups (Nenadic et al., 2015).

Clinical assessment of UHR subjects included a Comprehensive Assessment of At-Risk Mental Status exam (CAARMS), administered by a trained rater of the department's early psychosis intervention unit. Sz patients met DSM-IV-TR criteria for schizophrenia. Clinical

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Table 1 Clinical and psychopathology criteria of the studied samples: ultra-high-risk subjects for psychosis (UHR), first-episode schizophrenia (fe-Sz), and healthy controls (HC).

	UHR	fe-Sz	HC
n	31	18	42
Age: mean (SD) and range	23.68 yr (3.572) range 18–32	24.28 yr (2.421) range 19–28	23.83 yr (3.099) range 18–34
Gender (female/male)	17/14	7/11	19/23
PANSS total score mean: (SD)	N/A	53.2 (SD 6.3)	N/A
PANSS positive subscale: mean (SD)	N/A	30.4 (SD 4.9)	N/A
PANSS negative subscale: mean (SD)	N/A	29.1 (SD 8.1)	N/A
PANSS mean global subscale: mean (SD)	N/A	44.3 (SD 7.2)	N/A
Duration of untreated psychosis in months (mean and SD)	N/A	4.1 (SD 1.9)	N/A

psychopathology in first-episode schizophrenia patients ($n=18$ data sets) was assessed using the Positive and Negative Syndrome Scale (PANSS). Mean total scores, positive subscale, negative subscale, and global subscale, as well as duration of untreated psychosis are given in Table 1. Healthy volunteers were assessed with a semi-structured interview (health questionnaire) to exclude a current psychiatric disorder or history thereof. Further general exclusion criteria were substance dependence, traumatic brain injury, neurological or major medical conditions.

2.2. Magnetic resonance imaging and spectroscopy acquisition

MRS and structural MRI data were acquired on the same day on a 3 T whole-body MR scanner (Magnetom TIM Trio, Siemens Healthcare, Erlangen, Germany) by using a double-resonance ($^{1}H/^{31}P$) transmit/receive volume head coil (Biomedical Rapid GmbH, Germany).

Anatomical T_1-weighted, 3D whole-head MRI data sets were measured with MP-RAGE sequence TR/TE/TI 2300/3.03/900 ms; 192 sagittal 1 mm thick slices, $FOV_{AP \times FH} 256 \times 256$ mm^2, matrix: 256×256 pixels). All structural images passed both a visual inspection checked for artefacts as well as an automated quality check implemented in the VBM8 toolbox (see below).

Subsequently, PRESS single voxel ^{1}H MR spectra (TE/TR: 30/2000 ms, 512 water suppressed and 16 water non-suppressed single acquisitions, manual shim, scan time per region: 19 min) were acquired in the left and right hippocampus. The $30 \times 10 \times 10$ mm^3 MRS voxels were placed along the axis of the hippocampus, thus covering most of its volume (see Figure 1). Spectra were post-processed and quantified with LCModel (Provencher, 1993). Absolute concentrations of glutamate and NAA were calculated in mmol/l by using the intensity of the non-suppressed water intensity as internal reference (Gussew et al., 2012). Since metabolites and tissue water have different T1- and T2-relaxation properties and occupy different volume fractions in grey matter, white matter (GM and WM) and CSF, the extracted metabolic concentrations were individually corrected by taking into account the individual compositions of GM, WM and CSF in the spectroscopic voxels. The later were determined from the MP-RAGE volumes, which were at first segmented by using fully automatic routines included in the image analysis suite *FreeSurfer* (V 4.5.0, http://surfer.nmr.mgh.harvard.edu; (Dale et al., 1999)) and when co-registered with spectroscopic voxels. A detailed description of applied absolute quantitation method is given in our recent publication (Gussew et al., 2012). The overall four values of glutamate and NAA concentrations of the left and right hippocampus were used as variables for subsequent analysis (for sample spectrum, see Figure 1).

2.3. Voxel-based morphometry (VBM) analysis

We used the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/vbm8), which is integrated in the SPM8 software package (Statistical Parametric Mapping, Institute of Neurology, London, UK) and runs under Matlab (Mathworks, USA). VBM8 includes a fully automated processing pipeline, incorporating the DARTEL algorithm for high-resolution normalisation. The spatially registered GM maps were modulated for non-linear effects only. This modulation step preserves actual GM values locally, while still accounting for the individual differences in brain size. Finally, modulated GM maps were smoothed with a Gaussian kernel (12 mm full width at half-maximum, FWHM) and subsequently used for statistical assessment at each voxel across the entire brain. All pre-processed images successfully passed the internal quality assurance protocol.

2.4. Statistics

First, we performed a multivariate ANOVA for the four metabolite variables (Glu and NAA, for each hemisphere). Second, in order to assess laterality effects, we additionally considered a repeated measures analysis of variance (ANOVA) with group (UHR; Sz; HC) as between-subject factor, and hemisphere (left; right) and metabolite (Glu; NAA) as within-subject factors.

VBM statistics were carried out within the general linear model (GLM) framework of SPM software. Four separate GLMs were set up, defining group as a factor and one of the four metabolic parameters as another, to test an interaction between group factor and metabolite variable. In each of the four GLMs, we applied a height threshold of $p<0.001$ (uncorrected) with a whole-brain analysis, based on the anatomical hypotheses in hippocampal, lateral prefrontal, thalamic, and striatal areas (derived from the studies cited above), as well as an exploratory analysis for the rest of the brain grey matter.

3. Results

3.1. Hippocampal Glu and NAA levels

For the studied four metabolic markers, group effect (ANOVA) reached significance for NAA in the right hippocampus ($F=3.16$; $p=0.047$), whereas post-hoc Tamhane's T2 test revealed a trend ($p=0.059$) for the healthy control vs. UHR comparison. For the additional repeated measures ANOVA, we found no effect for either hemisphere ($F=0.084$; $p=0.773$) or a group by hemisphere interaction

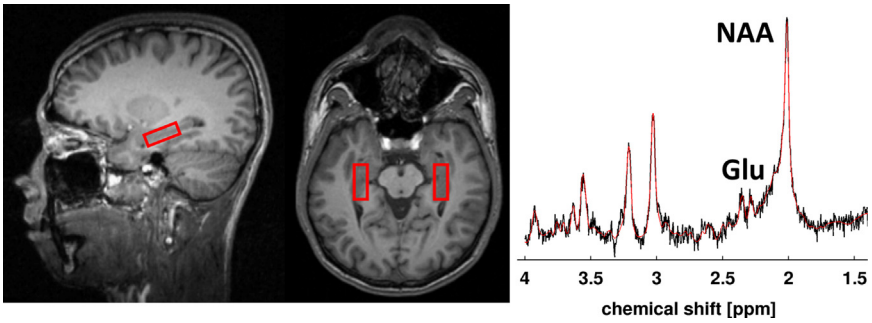

Figure 1 Anatomical location of the hippocampal single voxel for magnetic resonance spectroscopy (MRS) acquisition (left side of images, red box), and sample spectrum with glutamate (Glu) and N-acetyl aspartate (NAA) peaks (right side of image). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2 Mean (and SD) metabolite levels (mmol/l) for glutamate (Glu) and N-acetyl aspartate (NAA) in ultra-high-risk subjects for psychosis (UHR), first-episode schizophrenia patients (fe-Sz), and healthy controls (HC).

	UHR	fe-Sz	HC
Glu right hippocampus	9.827 (1.884)	10.014 (3.152)	10.303 (2.076)
Glu left hippocampus	9.886 (1.846)	10.095 (2.53)	9.878 (2.628)
NAA right hippocampus	9.712 (1.862)	10.424 (1.651)	10.670 (1.418)
NAA left hippocampus	10.254 (2.150)	10.744 (1.702)	10.459 (2.203)

(F=1.088; p=0.341). Mean Glu and NAA levels are given in Table 2.

3.2. Glutamate and brain structural effects

For the VBM analysis with right hippocampal glutamate levels, we found one significant cluster in the left superior frontal gyrus with an interaction effect, extending towards the right superior frontal cortex and the supplementary motor area (SMA) region. The correlation plot indicated a positive correlation with this cluster for UHR subjects, which was not observed in either Sz patients nor in healthy controls (see Figure 2A).

For the VBM analysis with left hippocampal glutamate levels, we also found only one significant cluster, located in the anterior left lateral prefrontal cortex; however, in this cluster the first-episode schizophrenia group showed a negative correlation, while both the UHR and healthy control groups showed positive correlations with grey matter (see Figure 2B)

3.3. NAA and brain structural effects

For the VBM analysis with right hippocampal NAA levels (interaction of NAA level with group) (see Figure 2C), we found three clusters. However, apart from one cluster in the right cingulate cortex (located on the grey/white matter border), for which UHR subjects showed a negative correlation and both Sz and controls revealed a positive correlation, there was no cluster in one of the hypothesised regions. The other two clusters were located in the right uncus/medial temporal pole (bordering on the amygdala) and left cerebellum.

For VBM analysis with left hippocampal NAA levels (see Figure 2D), we found group by metabolite interaction effects in the caudate bilaterally, as well as for a left superior prefrontal gyrus cluster. The strongest effect, located in the right caudate, showed a pattern of positive correlations in both UHR and first-episode schizophrenia groups, but a negative correlation in the healthy control group.

4. Discussion

In this study, we tested the hypothesis of diverging associations of hippocampal metabolic markers (glutamate and NAA) with brain grey matter. We demonstrate that these associations occur in key regions relevant to the pathophysiology of schizophrenia, i.e. striatum and prefrontal cortices, and exhibit different behaviour for the UHR, first-episode schizophrenia, and healthy control groups. While in some areas correlations are similar between UHR and first-episode schizophrenia, only effects in the UHR group were found in other areas. More specifically, UHR and first-episode schizophrenia groups showed similar correlations in the caudate nucleus (Figure 2D), but clearly diverging / opposite effects in the superior right frontal cortex and SMA (Figure 2A), left anterior prefrontal cortex (Figure 2B), and right anterior cingulated cortex (Figure 2C). This supports the notion that the investigated hippocampal metabolic markers might impact brain structure differently, possibly due to different effects of (genetic) liability vs. changes occurring at (or shortly after) the onset of psychosis. However, since we used a correlation analysis, we cannot infer on causal relationships, nor on the direction of effects (i.e. whether metabolite changes affect brain structural changes or vice versa). Our study adds to the recent literature that has linked hippocampal metabolism to

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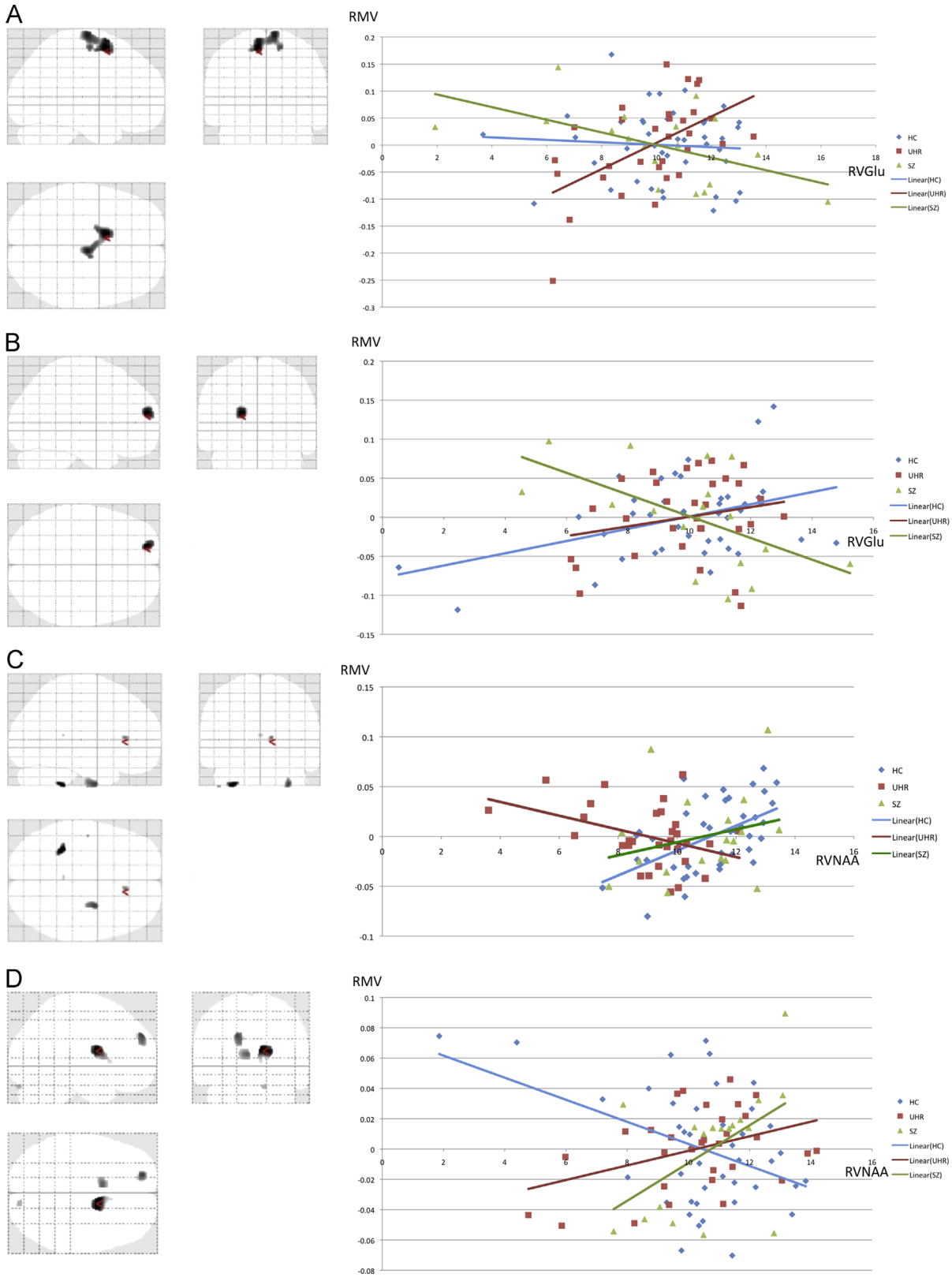

Figure 2 Voxel-based morphometry (VBM) analysis of correlations between hippocampal metabolites and grey matter ($p<0.001$, uncorrected): correlation plots depict the association between residualised values for the metabolic marker Glu or NAA, respectively on the *x* axis (abbreviated as RVGlu and RVNAA, respectively) and the residualised modulated volume data (RMV) extracted from the voxel at global maximum (indicated by the red arrow in the maximum intensity projection left of each correlation plot) on the *y* axis. (A) Correlation between right hippocampal glutamate and grey matter. (B) Correlation between left hippocampal glutamate and grey matter. (C) Correlation between right hippocampal N-acetyl aspartate (NAA) and grey matter. (D) Correlation between left hippocampal NAA and grey matter. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

changes in more remote anatomical areas and suggests effects in networks that are relevant to our understanding of disease onset and progression. Two aspects of our study merit particular attention: first, the regional pattern of effects and secondly the diverging direction of correlation across the three groups.

The regions identified in our analyses to correlate with hippocampal metabolites include prefrontal and striatal (caudate) areas, but not the hippocampus itself. Thus, contrary to recent studies in schizophrenia patients (Klar et al., 2010; Kraguljac et al., 2013), we did not find a correlation between either NAA or glutamate with hippocampal grey matter itself. Several factors might contribute to this difference, including medication (in part of the previous studies), our choice of a first-episode sample (vs. chronic patients in other studies), and differences in MRS acquisition parameters. While morphometric studies of the hippocampus suggest that there are effects in both first-episode and chronic samples (Adriano et al., 2012), it is unclear how this translates to the correlation with functional parameters. Associations might exist at different stages of the disorder, and choosing a first-episode sample as in our study might have precluded detection of effects seen in chronic patients. This aspect of stage dependency deserves further study in subsequent investigations, as it relates to an important question regarding the timing and progression: if the structural deficit were related to excess glutamate, the dynamics of this process (especially during the first-episode) and the extent of damage might vary considerably within and across patient cohorts. Studies of metabolites in the thalamus and anterior cingulate cortex do indeed suggest dynamics of changes occurring during the transition to schizophrenia (de la Fuente-Sandoval et al., 2013; de la Fuente-Sandoval et al., 2011), but it is not clear whether this is also the case for the hippocampus, which is already structurally altered at disease onset (Adriano et al., 2012), and for which a recent study has found no change in metabolites, but T2 relaxation times (Wood et al., 2010).

One major finding of our study is that both prefrontal and striatal grey matter is affected by hippocampal Glu and NAA. This effect is different for the three cohorts indicating differential effects at different stages of schizophrenia. These findings add to previous studies linking hippocampal metabolism and functional changes in the prefrontal cortex and striatum, resp. (Hutcheson et al., 2012; Stone et al., 2010) and extend them to show even remote structural effects. The association of hippocampal NAA and (bilateral) caudate grey matter is of particular interest as it provides additional support for the hypothesis of hippocampal pathology affecting the basal ganglia structures central to the dopaminergic system (Egerton et al., 2012). However, the change of sign of this correlation was seen in both of our UHR and first-episode schizophrenia samples, which would suggest that the brain structural effects precede the onset of illness. Although our study is cross-sectional, the divergence of effects across the populations suggests that certain effects (e.g. in the caudate) predate illness onset, while others, such as the prefrontal correlations, only emerge in patients after onset of psychosis.

Our findings are consistent with models of different stages of psychosis involving changes of biomarkers (McGorry, 2013a, 2013b). While this has been shown for structural brain imaging in ultra-high risk or prodromal stages vs. first-episode psychosis (Nenadic et al., 2015; Pantelis et al., 2003), our current data support the notion that the association of neurochemical parameters with brain structure might undergo similar changes in the transition to psychosis. In the model put forward by McGorry et al. (2007), the present study groups would correspond to the transition from stage 1b to stage 2 (Hickie et al., 2013). Clinical staging of schizophrenia is increasingly important in our understanding of the underlying biological changes (McGorry et al., 2014; McGorry, 2013a, 2013b), as it acknowledges the dynamics of biomarkers, and emphasises the differential application of biomarkers in early detection vs. tracking of changes during the disease course.

There are some limitations to be considered. First, while our sample size is similar to the ones used in other MRS or morphometric studies in UHR, confirmation of correlations in subsequent studies would be desirable. Also, metabolic alterations are not only present in the hippocampus, but in other areas as well, such as the thalamus in UHR subgroups (Egerton et al., 2014). Studies using chemical shift imaging are under way, which will allow simultaneous assessment of metabolites across different brain areas and thus investigations whether these are correlated (i.e. more or less specific to a region or rather to the disease stage) or not, and how they might differentially impact on brain structure. Furthermore, there is a lack of information on whether those UHR subjects that show the most widespread structural impact of their metabolic alterations are also the ones that most likely show transition to psychosis. Finally, we also need to consider the limitation that MR spectra were only obtained from one region, i.e. the hippocampus, thus precluding correlation with other volumes of interest in other brain regions, such as the prefrontal cortex or caudate.

In conclusion, our study provides first evidence of a structural impact on different brain regions in relation to hippocampal glutamate and NAA levels, and demonstrates that these associations are different between UHR and first-episode schizophrenia. This suggests that brain metabolic and structural changes might be dynamic markers for the transition from risk stage to frank psychosis and onset of schizophrenia.

Role of funding source

This study was partially supported through Grants of German Research Foundation (Deutsche Forschungsgemeinschaft, DFG, Grant Sm 68/3-1, to St.S.). I.N. was supported by a Junior Scientist Grant of the Friedrich-Schiller-University of Jena. (KST 21007087). GPA is supported by a NHMRC Senior Research Fellowship 1080963.

The funding sources had no influence on data collection, analysis, or interpretation of the report, its writing or the decision to submit the paper.

Contributors

I.N., St.S., H.S., and C.G. designed the study and contributed towards its protocol.

M.D., N.S., and St.S. collected data, where H.S. and I.N. contributed to subject recruitment, and consultation by P.McG. and G.P.A in subject selection.

I.N., C.G., J.R.R., A.G., C.G., and St.S. contributed to establishing of image post-processing routines and processing algorithm.

I.N., R.M, S.B., C.L., and C.G. contributed to data analysis.

I.N. wrote the first draft of the manuscript.

All authors contributed to and have approved the final manuscript.

Conflict of interest

This study was partially supported through grants of German Research Foundation (Deutsche Forschungsgemeinschaft, DFG, Grant Sm 68/3-1, to St.S.). In was supported by a Junior Scientist Grant of the Friedrich-Schiller-University of Jena. (KST 21007087). GPA is supported by a NHMRC Senior Research Fellowship 1080963. Professor McGorry currently receives research support from a National Health and Medical Research Council of Australia and the Colonial Foundation. He has also received grant funding from NARSAD and unrestricted research funding from Astra Zeneca, Eli Lilly, Janssen-Cilag, Pfizer, and Novartis, as well as honoraria for educational activities with Astra Zeneca, Eli Lilly, Janssen-Cilag, Pfizer, Bristol Myer Squibb, Roche and the Lundbeck Institute.

The authors have no other relevant conflicts of interest.

Acknowledgements

The authors would like to thank all study participants for their support.

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Please cite this article as: Nenadic, I., et al., Associations of hippocampal metabolism and regional brain grey matter in neuroleptic-naïve ultra-high-risk subjects and first-episode.... European Neuropsychopharmacology (2015), http://dx.doi.org/10.1016/j.euroneuro.2015.05.005