The World Journal of Biological Psychiatry, 2011; 0: 1–12

ORIGINAL INVESTIGATION

Hippocampal integrity and neurocognition in first-episode schizophrenia: A multidimensional study

ALKOMIET HASAN[1,5,*], THOMAS WOBROCK[1,6,*], PETER FALKAI[1], THOMAS SCHNEIDER-AXMANN[1], BIRGIT GUSE[1], MARTIN BACKENS[3], ULLRICH K. H. ECKER[4], JANINA HEIMES[1], JOSEPH MICHAEL GALEA[5], OLIVER GRUBER[1,#] & HARALD SCHERK[1,2,#]

[1]*Department of Psychiatry and Psychotherapy, Georg August University, Göttingen, Germany,* [2]*AMEOS Klinikum Osnabrück, Osnabrück, Germany,* [3]*Department of Neuroradiology, University of Saarland, Germany,* [4]*School of Psychology, University of Western Australia, Crawley, Australia,* [5]*Institute of Neurology, University College London, London, UK, and* [6]*Centre of Mental Health, Darmstadt-Dieburg Clinics, Groß-Umstadt, Germany*

Abstract

Objectives. Impairments in memory and executive function are key components of schizophrenia. These disturbances have been linked to several subcortical and cortical networks. For example, anatomical and functional changes in the hippocampus have been linked to deficits in these cognitive domains. However, the association between hippocampal morphometry, neurochemistry and function is controversial. Therefore, we aimed to investigate the relationship between hippocampal anomalies and their functional relevance. *Methods.* Fifty-seven first-episode schizophrenia patients (FE-SZ) and 61 healthy control subjects (HC) participated in this study. Hippocampal volumes were investigated using structural magnetic resonance imaging (sMRI) and hippocampal neurochemistry was determined using proton magnetic resonance spectroscopy (1H MRS). Verbal memory was used as a hippocampus-dependent cognitive task whereas working memory and cognitive flexibility assessed frontal lobe function. *Results.* FE-SZ presented smaller volumes of the left hippocampus, with a significant correlation between left hippocampal volume and verbal memory performance (immediate recall). There was also an inverse correlation between neurochemical ratios (NAA/Cho and Cho/Cr) and verbal memory (delayed recognition). Tests of cognitive flexibility and working memory were not correlated with MRI and 1H MRS values. Compared to HC, FE-SZ demonstrated reduced performance in all of the assessed neurocognitive domains. *Conclusions.* These results point to a relationship between verbal memory and hippocampal integrity in schizophrenia patients which might be independent from deficits in other memory domains. Disturbed verbal memory functions in FE-SZ might be linked specifically to hippocampal function.

Key words: *First-episode schizophrenia, MRI, MRS, hippocampus, neurocognition*

Introduction

Cognitive impairments in memory function are key components in schizophrenia and include deficits in declarative memory, working memory and other executive functions (Green 1996; Galderisi et al. 2009; Mesholam-Gately et al. 2009). These impairments are suggested to be a result of disturbed cortical and subcortical networks which underlie these cognitive domains (Hopfinger et al. 2000; Gaffan 2005; Zilles et al. 2009). Within these networks the hippocampus, which is located in the medial temporal lobe, is thought to have a prominent role in the onset of different cognitive dysfunctions (Tamminga et al. 2010). In schizophrenia patients, and their relatives, a link between hippocampal and temporal lobe volume reduction and declarative memory performance has been found, although some studies have failed to affirm this relationship (DeLisi et al. 1991; Torres et al. 1997; Gur et al. 2000; Seidman et al. 2002; Antonova et al. 2004; Thoma et al. 2009).

One functional MRI (fMRI) study showed that schizophrenia patients have impairments in identifying

*Authors contributed equally. #Authors contributed equally.
Correspondence: Dr.med. Alkomiet Hasan, M.D., Department of Psychiatry and Psychotherapy, Georg August University Göttingen, Von-Siebold-Strasse 5, D-37075 Göttingen, Germany. Tel: +49 551 39 13660. Fax: +49 551 39 12721. E-mail: ahasan@gwdg.de

(Received 1 February 2011; accepted 29 August 2011)

ISSN 1562-2975 print/ISSN 1814-1412 online © 2011 Informa Healthcare
DOI: 10.3109/15622975.2011.620002

novel items and show a reduced activation of the right anterior hippocampus, but did not present deficits in detecting old items. Therefore, the authors concluded that smaller hippocampal volumes did not lead to a global deficit of hippocampal function in schizophrenia (Weiss et al. 2004). In a recent fMRI study, positive symptoms and memory deficits were linked to dysfunctional hippocampal hyperactivity, whereas other studies have shown contradictory results concerning declarative memory and hippocampal activation (Kubicki et al. 2003; Ragland et al. 2004; Zierhut et al. 2010). A small study with chronic schizophrenia patients revealed an atypical relationship between regional hippocampal volumes and episodic memory abilities. This relationship consisted of a positive correlation between verbal episodic memory and posterior hippocampus volume, and a negative correlation between memory performance and anterior hippocampus volume (Thoma et al. 2009). Finally, the physiological suppression of hippocampal activity and the functional integrity of the physiological frontal-hippocampal connectivity during working memory tasks were shown to be disturbed in schizophrenia patients and linked to psychotic symptoms (Henseler et al. 2009; 2010).

However, disturbances in hippocampal integrity, plasticity and function are a common finding in schizophrenia patients. Yet, the relationship between structural and neurochemical changes and their functional consequences, e.g. cognitive performance, is still unclear.

One consistent and often replicated finding in magnetic resonance imaging (MRI) studies in schizophrenia patients is a reduction of the left hippocampal volume, whereas a bilateral hippocampal volume reduction is less frequently reported (Harrison 2004; Steen et al. 2006; Tamminga et al. 2010). This volume reduction can be already detected at the beginning of the disease and progresses within the disease course (Szeszko et al. 2003; Velakoulis et al. 2006). In vivo measurements of cortical neurochemistry using proton magnetic resonance spectroscopy (1H MRS) revealed a reduction of *N*-acetylaspartate (NAA) in the hippocampus of schizophrenia patients (Steen et al. 2005), pointing to a disturbed neuronal integrity and synaptic abundance (Maier et al. 1995; Yildiz-Yesiloglu and Ankerst 2006). One recent study found a coexistent neurochemical and structural deficit in the hippocampus of these patients, which might emphasize the role of the hippocampus in the pathogenesis of schizophrenia (Klar et al. 2010).

The present study was designed to investigate the link between memory function and hippocampal anatomy and neurochemistry in first-episode schizophrenia patients. We aimed to bridge the gap between hippocampal anomaly and its functional relevance and explore hippocampal functions and integrity in vivo with a multidimensional approach.

According to the literature, we hypothesized that schizophrenia patients would have a reduced volume of the left hippocampus and would present neurochemistry changes in this brain region. Compared to healthy subjects, we hypothesized that schizophrenia patients would exhibit an overall impairment in different neurocognitive tests. Furthermore, we sought to determine if the hypothesized decrease in hippocampal volume and the neurochemical deficits in schizophrenia might be associated with the performance of hippocampal dependent memory (e.g., episodic verbal memory). To specify the link between hippocampal volumes and verbal memory, other cognitive functions, which are less associated with hippocampal function, were assessed. To reduce the effects of disease course, and long lasting antipsychotic medication on hippocampal volume and neurocognitive function (Velakoulis et al. 2006; Mesholam-Gately et al. 2009), we compared well characterized first–episode schizophrenia patients with minimal exposure to antipsychotics with healthy control subjects.

Methods

Subjects

Fifty-seven patients suffering from schizophrenia (all paranoid subtype, first-episode) and 61 healthy controls participated in the study. For further analysis, subjects were subgrouped according to their participation in the different parts of the study. This resulted in varying sample sizes (Table I). A clinical psychiatrist, blinded to the aims of the study, and a member of the study group (TW and HS) made a consensus diagnosis according to the German version of the Structural Clinical Interview for DSM-IV (Wittchen et al. 1997). Patients with organic central nervous system disorder (e.g., epilepsy, traumatic brain injury, infectious, toxic or cerebrovascular disease), mental retardation, or inadequate knowledge of the German language were not included in the study. At the time of the study, most patients received a stable medication, including typical and atypical neuroleptics. Each patient underwent a detailed biographic interview (Bassett et al. 1993), an assessment of psychopathology (Positive and Negative Syndrome Scale) (Kay et al. 1987), disease severity (Clinical Global Impressions) (Guy 1976) and social functioning (Global Assessment of Functioning) (Endicott et al. 1976). Additionally, the duration of illness (DUI), counted from the beginning of initial prodromal symptoms, the duration of psychosis (DUP), counted

Table I. Demographic and clinical data of all control subjects and first-episode schizophrenia patients, split into the different parts of the study.

	Healthy control subjects			First-episode patients			Statistics[1]		
Subjects with neuropsychology	*n*	Mean	SD	*n*	Mean	SD	F/χ^2	df	*P*
Age (years)	52	38.83	12.06	53	28.36	7.82	27.61	1, 101	$<0.0005^*$
Education (years)	52	14.69	2.68	53	12.54	2.77	16.04	1, 101	$<0.0005^*$
Gender (male/female)	52	23/29	–	53	34/19	–	$4.20^{\#}$	1	0.040^*
Hand preference (r/nr)	52	43/9	–	53	44/9	–	$0.00^{\#}$	1	0.97
PANSS total score	–	–	–	53	93.54	17.10	–	–	–
PANSS positive subscore	–	–	–	53	22.28	6.57	–	–	–
PANSS negative subscore	–	–	–	53	22.70	6.62	–	–	–
CPZ daily dose	–	–	–	53	368.11	314.14	–	–	–
Neuroleptics (no/typical/atypical)	–	–	–	53	1/2/50	–	–	–	–
Subjects with MRI data									
Age (years)	53	39.69	12.37	41	28.35	7.05	27.50	1, 92	$<0.0005^*$
Education (years)	51	14.58	2.76	41	12.79	2.77	19.49	1, 90	0.020^*
Gender (male/female)	53	21/32	–	41	28/13	–	$7.61^{\#}$	1	0.006^*
Hand preference (r/nr)	53	42/11	–	41	34/7	–	$0.20^{\#}$	1	0.65
PANSS total score	–	–	–	41	91.34	17.86	–	–	–
PANSS positive subscore	–	–	–	41	21.56	6.45	–	–	–
PANSS negative subscore	–	–	–	41	22.77	6.83	–	–	–
CPZ daily dose	–	–	–	41	320.49	303.49	–	–	–
Neuroleptics (no/typical/atypical)	–	–	–	41	1/2/38	–	–	–	–
Subjects with MRS data									
Age (years)	49	39.56	12.19	46	29.22	7.49	24.39	1, 93	$<0.0005^*$
Education (years)	47	14.69	2.69	46	12.86	2.69	10.67	3, 163	0.002^*
Gender (male/female)	49	19/30	–	46	32/14	–	$9.05^{\#}$	1	0.003^*
Hand Preference (r/nr)	49	39/10	–	46	38/8	–	$0.14^{\#}$	1	0.17
PANSS total score	–	–	–	46	91.91	17.99	–	–	–
PANSS positive subscore	–	–	–	46	21.70	6.01	–	–	–
PANSS negative subscore	–	–	–	46	22.43	7.04	–	–	–
CPZ daily dose	–	–	–	46	290.00	203.30	–	–	–
Neuroleptics (no/typical/atypical)	–	–	–	46	2/2/42	–	–	–	–

Data are presented as mean ± standard deviation unless otherwise indicated.

[1]Values are expressed as χ^2 statistics (indicated by #) for categorical variables and *F* statistics for continuous variables.

F, *F* statistic; df, degrees of freedom; *P*, error probability of first kind; r, right; nr, not right.

$^*P<0.05$.

from the onset of diagnostic/characteristic positive symptoms, and familial risk factors (psychosis in first-degree relatives) were assessed.

Healthy controls were recruited in the same geographical area (as members of the department or via public announcement) and history of neuropsychiatric or other severe organic diseases was excluded in a personal interview with a board-certified psychiatrist. All patients and healthy controls provided informed consent before entering the study, and the study design was approved by the local ethics committee in accordance to the Declaration of Helsinki.

MRI acquisition and volumetric measurement

As described previously by our study group (Gruber et al. 2008), MRI scanning was performed on a 1.5-Tesla Magnetom Sonata (Siemens, Erlangen). A T1-weighted, MPRAGE sequence of 176 consecutive sagittal slices with a voxel size of 1 mm^3 was acquired. For image processing and analysis the software packages MRIcro, SPM99 as well as IDL applications generated in our imaging lab were used. First, the MR images were realigned in parallel to the AC–PC plane and the origin was set to the anterior commissure. One rater (JH), who was blind to the diagnosis, conducted hippocampal morphometry manually and these results were controlled for accuracy by double tracing of 15 scans. Additionally, a second rater (HS) computed hippocampal morphometry in 15 scans, too. The "region of interest" tool implemented in the software MRIcro was used to draw hippocampal contours in the sagittal view, starting from lateral to medial. After having completed the drawing for all sagittal slices in which the hippocampus was visible, the correctness of the contours was controlled in the coronal and horizontal views. Subsequently, both the hippocampal volumes as marked by the two-dimensional drawings and the

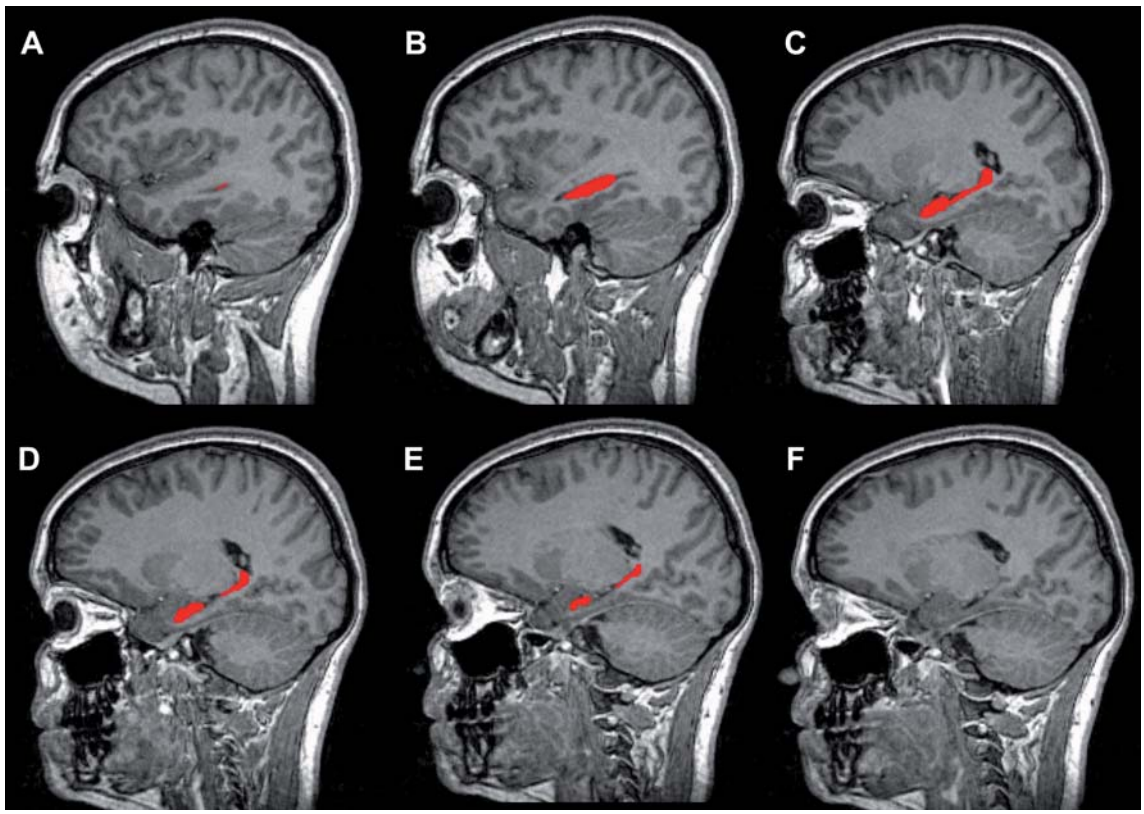

Figure 1. All three orthogonal views (MR images in radiological convention) in one subject with the traced left hippocampus (white).

grey matter volumes were determined using an automatic algorithm programmed in MATLAB and SPM99. Because we were interested in specific effects on the size of the hippocampus independent from total brain volumes, statistical analysis was performed on relative hippocampal volumes as expressed by the quotient of absolute hippocampal and total grey matter volume (Figures 1 and 2).

The inter-rater reliability and the intra-rater reliability for the volumetric hippocampal measurement was high (intraclass correlation coefficients, ICC, were 0.93 and 0.99).

Proton magnetic resonance spectroscopy:

As described previously (Scherk et al. 2008), single-volume 1H MRS was performed on a 1.5-Tesla Siemens Magnetom Sonata (Siemens, Erlangen) using a spin-echo sequence with water-suppression and 128 scan averages (TE = 30 ms, TR = 1.500 s). Region of interest was defined in the left hippocampus (voxel size = $10 \times 35 \times 10$ mm^3) and this region was identified according to an exactly predefined and standardized algorithm with multiple rechecking procedures in a T2 gradient echo image (TrueFISP) with 24 slices each in three orthogonal orientations.

The positions of the voxels were visually inspected and adjusted based on identifiable anatomical landmarks in reference to standard brain atlases (Talairach and Tournoux 1998).

Postprocessing of all spectra was arranged using the Siemens Medical Solutions spectroscopy software package on a Leonardo workstation. Following acquisition, low frequency filtering for removal of the residual water signal and correction for frequency shifts were performed.

Data were zero-filled from 1024 to 2048 points and a discrete probability mass function was used for apodization of the time domain signal with 700 ms width. Then the data were Fourier transformed to the frequency domain and the spectra were baseline corrected with a sixth-order polynomial and first-order phase-corrected. Lorentzian (CH_2-peak of creatine/phosphocreatine, dd2 peak of inositol/myoinositol) or Gaussian (all other peaks) line shapes at known frequencies were used to apply curve fitting to the metabolic peaks. The same line form was used for every single peak in all study subjects (schizophrenia patients and controls).

Relative metabolite concentrations for *N*-acetyl aspartate (NAA), choline containing compounds (Cho), creatine and phosphocreatine (Cre), inositol

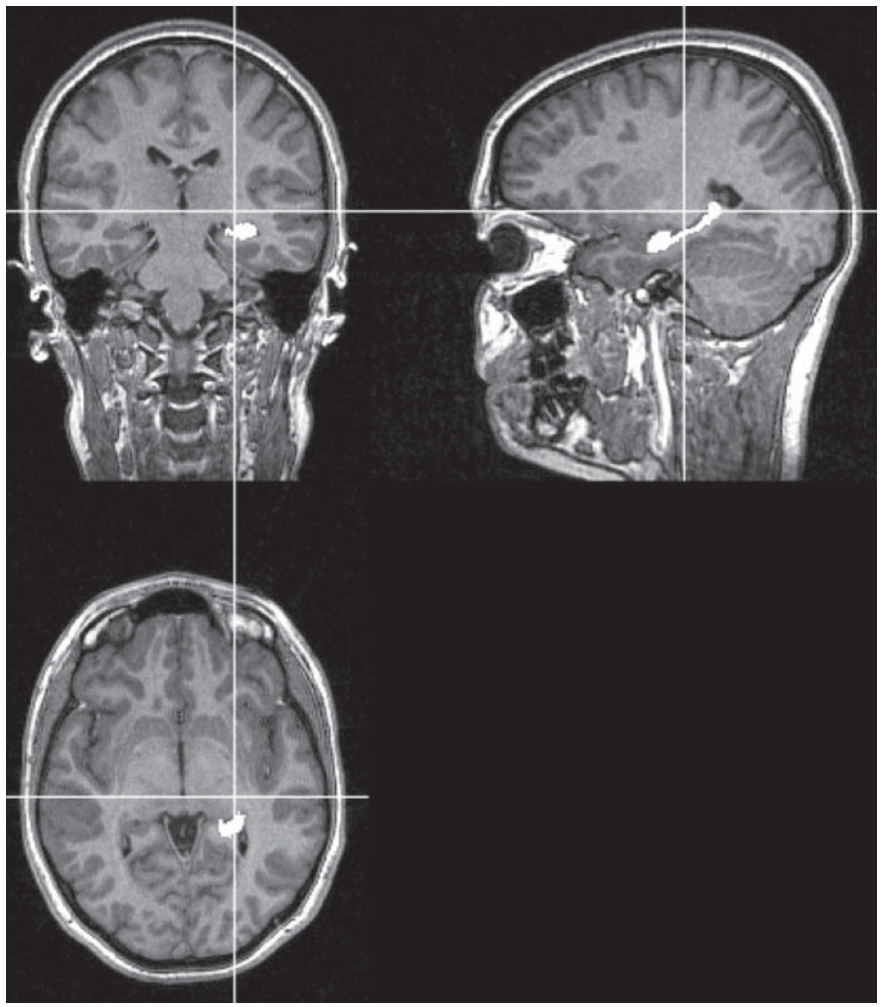

Figure 2. Tracing of hippocampal contours from lateral (A) to medial (F), for details see Methods section.

plus myoinositol (Ins), and glutamate plus glutamine (Glu+Gln) were determined, and the metabolic ratios NAA/Cre, NAA/Cho, Cho/Cre, Ins/Cre and (Glu+Gln)/Cre were calculated.

Cognitive testing

A widely used test of verbal intelligence ("Wortschatztest", WST), which is comparable to the Boston Naming Test, was used to estimate the premorbid intelligence (Schmidt and Metzler 1992).

To access verbal declarative memory, related to hippocampal function, the German version of the Rey Auditory Verbal Learning Test (Verbaler Lern- und Merkfähigkeitstest, VLMT) was used (Helmstaedter et al. 2009; Muller et al. 1997). Composite measures of short term memory (STM) and long-term memory (LTM) were based on previous factor analyses of this test. The VLMT is an easily practicable neuropsychological test of verbal learning and memory with only minor requirement of language and motor skills. Briefly, this test investigates the encoding capacity, the direct and delayed recall performance and episodic recognition abilities (Muller et al. 1997; Helmstaedter et al. 2009). According to recent work from our department (Jamrozinski et al. 2009), we analyzed verbal learning performance (STM) (VLMT, sum of trials 1–5), performance decrease after delay (LTM) (VLMT trial 5 minus trial 7, difference between maximum performance of immediate and delayed recall, higher raw values indicating greater decrease) and delayed recognition (VLMT corrected recognition score, recognized words (W) minus failures (F)).

One aim of our study was to investigate if there is a specific association between verbal memory (according to VLMT) and hippocampal size or neurochemistry in healthy as well as first-episode subjects and to investigate if reduced cognitive performance correlates with reduced hippocampal integrity. For that reason, neuropsychological tests, claimed not to be specific for the hippocampus were implemented in

the study. To examine further aspects of working memory and cognitive flexibility (executive function) the Self Ordered Pointing Task (SOPT) was applied (Petrides and Milner 1982). Finally, the Wisconsin Card Sorting Test (WCST) was used to detect disturbances in cognitive flexibility (sum of administered trials and percentage of perservative responses) and executive functions which are linked to the frontal lobe (Heaton et al. 1993; Laws 1999).

Statistics

For statistical analyses, SPSS for Windows 17.0 was used. Level of significance was set at $\alpha = 0.05$. All tests were two-tailed.

Intervening variables. As initial analyses, Pearson correlations between age, education and dependent variables (hippocampal volumes, hippocampal 1H MRS quotients, neuropsychological test results) were calculated and ANOVA was performed to analyze if the factor gender influenced the dependent variables. If a significant influence of these confounding variables was found, it was adjusted for these variables in the main analyses.

Pearson correlations between medication, documented as cumulated and daily chlorpromazine (CPZ) dose equivalents, and duration of treatment with neuroleptics, and dependent variables were calculated to exclude an influence of antipsychotic medication.

MRI data. ANCOVA (factors: diagnosis, gender; covariates: education, age) were used to detect volume differences in total grey matter volume and absolute left and right hippocampal volumes between schizophrenia patients and healthy controls. ANOVA (factor diagnosis) was performed to compare relative left and right hippocampal volumes between the two diagnostic groups.

Partial correlations (part. corr.) adjusted for intervening variables according to the initial analyses were used to investigate a correlation between absolute hippocampal volume and performance in each neuropsychological test.

1H MRS data. ANCOVA was used to analyze if 1H MRS data differed between controls and schizophrenia patients. Age and education were used as covariates, if they had a significant influence in the initial analyses. 1H MRS results were correlated with neuropsychological test performance.

Neuropsychological data. ANCOVA was used to compare the neuropsychological data between the groups. Analyses were adjusted for factor gender and covariates age and education if a significant influence of these variables was found in the initial analyses. As described previously from our group, we selected from each test a small number of variables for further inspection to reduce the large number of variables available. This selection was based on the literature, theoretical considerations and previous exploratory discriminant function analysis (Wobrock et al. 2009).

As age was of particular importance for our main outcome measures, we assembled a smaller age matched control group (supplementary Table 1 available online). The eldest control subjects were excluded, until the mean age between the two diagnostic groups were statistically non significant. Using this aged matched control group, we repeated the statistical analyses for our main findings.

Results

For statistical reasons and due to the situation that some subjects did not complete all tests and measurements, we formed different groups within our sample (see Table I). First-episode patients were significantly younger ($P < 0.0005$) and less educated ($P < 0.02$) compared to control subjects. The proportion of male subjects was higher in the schizophrenia group compared to the control group (MRI sample $P = 0.006$, 1H MRS sample $P = 0.003$, neuropsychology sample $P = 0.020$), but, except for grey matter volume and VLMT performance (see below), we did not detect a gender effect in our sample ($P > 0.05$). Groups did not differ in handedness ($P > 0.05$).

For all dependent variables, there were neither significant Pearson correlations with cumulated or daily CPZ dose equivalents nor with duration of antipsychotic treatment ($P > 0.05$).

MRI and correlation with neuropsychology

In our sample, there were significantly negative correlations of age with total grey matter volume ($r = -0.56$, $P < 0.0005$). Education correlated significantly positive with total grey matter volume ($r = 0.50$, $P < 0.0005$). In the control sample, there was no significant influence of factor gender on total grey matter volume ($F = 1.5$, df = 1, 51, $P = 0.23$). Including the factor diagnosis in a two-way ANOVA (gender x diagnosis), we found a significant influence of factor gender on grey matter volume ($F = 8.3$, df = 1, 90, $P = 0.005$). There were no significant influences of gender, age or education on relative hippocampal volumes.

From ANOVA we found a significant effect of factor diagnosis for relative left hippocampus

Table II. Structural MRI and 1H MRS data.

	Healthy control subjects		First-episode patients		ANOVA/ANCOVA[1]		
	Mean	SD	Mean	SD	*F*	df	*P*
Total gray matter (cm^3)	718.53	78.69	757.39	73.35	0.29	1, 86	0.59
Absolute volume							
Left Hippocampus (mm^3)	2653	504	2534	744	4.49	1, 86	0.037*
Right Hippocampus (mm^3)	2623	453	2611	588	0.91	1, 86	0.34
Relative volume							
Left Hippocampus (%)	0.371	0.071	0.334	0.090	4.93	1, 92	0.029*
Right Hippocampus (%)	0.367	0.061	0.346	0.074	2.31	1, 92	0.13
MRS ratios							
NAA/Cho	3.973	0.793	4.012	0.620	0.1	1, 90	0.75
NAA/Cr	1.283	0.257	1.294	0.184	0.0	1, 90	0.83
Cho/Cr	0.326	0.046	0.326	0.044	0.5	1, 92	0.48
Ins/Cr	1.088	0.403	1.081	0.331	0.0	1, 93	0.93
(Gln + Glu)/Cr	2.494	0.946	2.404	0.640	0.5	1, 90	0.48

Data are presented as mean ± standard deviation unless otherwise indicated.

M, mean; SD, standard deviation; *F*, *F* statistic; df, degrees of freedom; *P*, error probability of falsely rejecting the null hypothesis, that there are no mean differences between first-episode patients and healthy controls.

[1]Total gray matter volume, absolute hippocampus volumes: ANCOVA (factors diagnosis, gender, covariates age, education), relative hippocampus volumes: ANOVA (factor diagnosis); 1H MRS ratios: ANCOVA (factor diagnosis, covariates age, education).

*$P < 0.05$.

volume ($F = 4.93$; df = 1, 92, $P = 0.029$). Total brain volume and volume of the right hippocampus did not differ between groups (see Table II). Schizophrenia patients showed a significantly positive partial correlation adjusted for age, education and gender between relative volume of the left hippocampus and VLMT performance (STM, immediate recall, sum of trials 1 to 5, raw value: part. corr. = 0.39, df = 32, $P = 0.024$). In contrast to these results, our analysis did not reveal a correlation between hippocampal volumes and other neurocognitive tests (WCST, SOPT).

1H MRS and correlation with neuropsychology

In our sample there was no significant influence of factor gender on MRS ratios. Age correlated significantly negative with Cho/Cr ($r = -0.030$, $P = 0.035$) and education correlated negatively with NAA/Cho ($r = -0.032$, $P = 0.027$), NAA/Cr ($r = -0.035$, $P = 0.016$) and (Gln + Glu)/Cr ($r = -0.33$, $P = 0.022$).

After correction for the covariates age and education, ANCOVAs did not reveal significant differences in any of the spectroscopy ratios between groups.

Regarding the verbal memory, schizophrenia patients showed a significantly negative partial correlation between NAA/Cho and VLMT recognition (raw value: part. corr. = –0.51, df = 35, $P = 0.001$, *T* value: part. corr. = –0.51, df = 35, $P = 0.001$) and a significant positive correlation between Cho/Cr and VLMT recognition (raw value: part. corr. = 0.37, df = 35, $P = 0.023$, *T* value: part. corr. = 0.39, df = 35, $P = 0.018$). Our analysis did not reveal a correlation between any MRS ratio and other neurocognitive tests (WCST, SOPT).

1H MRS and MRI correlations

Analysis did not reveal a correlation between left 1H MRS parameters and left hippocampal volume. However, relative hippocampal volume (right) correlated significantly with the NAA/Cho of the left hippocampus in healthy controls (part. corr. = 0.374, df = 40, $P = 0.015$), but not in schizophrenia patients (part. corr. = 0.198, df = 34 , $P = 0.25$). These results were adjusted for age, gender and education.

Group comparison neuropsychology

In the control sample age correlated significantly negative with VLMT 1 to 5 ($r = -0.51$, $P < 0.001$) and VLMT recognition ($r = -0.40$, $P = 0.004$). We observed significant effects of factor gender for VLMT performance (VLMT 1–5: male: 52.6, female: 59.0, $F = 8.2$, df = 1,50; $P = 0.006$). An ANCOVA with factor diagnosis and intervening variables gender and age, that were included if they showed a significant influence in the initial analyses, revealed that schizophrenia patients showed impairments in the performance of all neurocognitive tests compared to healthy controls. An overview of neurocognitive measurements and performance is presented in Table III.

Table III. Neuropsychological test scores for schizophrenia patients and healthy controls.

	Healthy control subjects			First-episode patients			ANOVA/ANCOVA [1]		
	n	Mean	SD	*n*	Mean	SD	*F*	df	*P*
WST (*T* value)	52	56.27	6.18	48	49.12	8.13	24.05	1, 98	$<0.0005^*$
VLMT 1–5 (raw-value)	52	56.13	8.57	50	47.92	10.63	26.39	1, 95	$<0.0005^*$
VLMT 5–7 (raw-value)	52	1.77	1.83	50	2.30	2.71	1.35	1, 100	0.25
VLMT rec (raw-value)	52	13.25	2.51	50	12.00	3.06	16.83	1, 97	$<0.0005^*$
VLMT 1–5 (*T* value)	52	54.98	8.38	49	44.73	9.74	32.20	1, 99	$<0.0005^*$
VLMT 5–7 (*T* value)	52	49.33	10.71	50	50.34	11.00	0.22	1, 100	0.64
VLMT rec (*T* value)	52	50.08	6.80	50	46.34	7.71	6.75	1, 100	0.011^*
SOPT	30	3.60	2.39	35	5.74	3.25	8.92	1, 63	0.004^*
WCST TA	51	88.86	17.61	52	106.48	20.67	21.64	1, 101	$<0.0005^*$
WCST PT (*T* value)	51	66.71	13.17	52	64.48	17.30	0.54	1, 101	0.47

M, mean; SD, standard deviation; *F*, *F* statistic; df, degrees of freedom; *P*, error probability of falsely rejecting the null hypothesis, that there are no mean differences between first-episode patients and healthy controls. WST, Wortschatztest; VLMT 1–5, immediate recall, sum of trials 1–5; VLMT 5–7, difference between maximum immediate and felayed recall, trial 5 minus 7; VLMT rec, corrected recognition score W-F; SOPT, Subject Ordered Pointing Task, number of errors; WCST TA, number of trails administered; WCST PT, perserverative responses, Score; VLMT, Verbaler Lern- und Merkfähigkeitstest; WCST, Wisconsin Card Sorting Test. Data are presented as mean ± standard deviation unless otherwise indicated.

[1]VLMT 1–5, raw value; ANCOVA (factors diagnosis, gender, covariate age), VLMT rec (raw value); ANCOVA (factor diagnosis, covariate age), other neuropsychologic tests; ANOVA (factors diagnosis).

$^*P<0.05$.

Replication of analyses with an age-matched control group

After the elder control subjects were excluded, the age-adjusted sample included 25 (MRI), 24 (1H MRS) and 25 (neuropsychology) control subjects. This group did not differ in age compared to FE-SZ ($p>0.70$). Analyses on the adjusted sample were controlled for gender and education where necessary. FE-SZ displayed reduced volumes for the left hippocampus (absolute volume: $F=4.19$, $df=1$, 60, $P=0.045$; relative volume: $F=3.97$, $df=1$, 64, $P=0.051$ (trend level)). However, this analysis still did not reveal a significant difference between groups for 1H MRS ratios. FE-SZ showed a reduced performance in the WCST ($P<0.0005$), the WST ($P<0.0005$), the VLMT raw values (sum of trials 1 to 5: $P<0.0005$; delayed recall: $P=0.003$) and the VLMT T-values (sum of trials 1 to 5: $P<0.0005$; delayed recall: $P=0.003$), whereas SOPT group differences did not remain significant (supplementary table 2 and 3).

Discussion

In the present study we investigated the relationship between hippocampal integrity and memory functions in a well characterized group of 57 first-episode schizophrenia patients. Our main findings were a significant positive correlation between reduced left hippocampal volume and poor verbal learning performance (immediate recall) and correlations between neurochemical ratios (NAA/Cho and Cho/Cr) and long-term verbal memory (delayed recognition) in first-episode patients. To the best of our knowledge, our study reveals for the first time significant correlations between structural as well as spectroscopic hippocampal alterations and verbal memory performance in a first-episode schizophrenia sample.

Consistent with published literature, schizophrenia patients presented smaller volumes of the left hippocampus and exhibited poorer performance in nearly all neurocognitive tests compared to healthy controls (Aleman et al. 1999; Galderisi et al. 2009; Mesholam-Gately et al. 2009). We did not find significant differences in hippocampal neurochemistry between groups. Neurocognitive tests, being considered as tests of the frontal lobe, did not correlate with the hippocampal MRI and 1H MRS measurements.

General remarks

Impairments in immediate verbal memory are a well–known finding in first–episode schizophrenia (Mesholam-Gately et al. 2009). However, a significant correlation with hippocampus volume appears to be a controversial finding (DeLisi et al. 1991; Gur et al. 2000; Seidman et al. 2002). This is particularly important, because the specificity of cognitive impairments in schizophrenia is unclear and some aspects of memory may be affected to a greater extent than others (Aleman et al. 1999). Our results suggest that hippocampal volume reductions are associated with

poorer performance in verbal memory tasks, but not with tasks of cognitive flexibility, working memory and executive functioning. In all these domains of frontal brain functions (WCST, SOPT) schizophrenia patients performed poorer compared to our control group, which is a well established finding (Galderisi et al. 2009; Mesholam-Gately et al. 2009). However, we did not find a correlation between either hippocampal volume (MRI) or hippocampal integrity (1H MRS) and these neurocognitive tests of frontal brain functions. This indicates that the verbal memory impairment in schizophrenia may be related to disturbed hippocampal integrity, but not to abnormalities of frontal lobe and that the poor performance in verbal memory tasks cannot be simply explained by an overall poor cognitive performance. Interestingly, the correlation between hippocampal volume reduction and cognitive impairment was only obvious in diseased brains, namely in schizophrenia subjects, but not in healthy controls. This may imply that brain volume is not necessarily associated with cognitive performance under normal conditions.

The variables "VLMT 1–5" and "VLMT recognition score" test different aspects of verbal memory (Helmstaedter et al. 2009; Muller et al. 1997), the first short-term and the latter long-term memory. Both are part of the verbal memory complex, but each domain requires different patterns of hippocampal activation and encoding. Using the concept of immediate verbal memory and delayed recognition, one recent meta-analysis showed that disturbances in immediate verbal memory are a more consistent finding with a higher effect size in first-episode schizophrenia compared to delayed verbal memory (Mesholam-Gately et al. 2009). Our findings may therefore be specific for first–episode schizophrenia. The combination of an inverse correlation between the neurochemical markers and delayed verbal memory and between immediate verbal memory and hippocampal size may reflect different stages of cognitive abnormalities in the brains of schizophrenia patients.

Proposed mechanisms of action

Our 1H MRS findings might appear contradictory to the positive correlation of hippocampal volume and immediate memory performance. In schizophrenia patients the negative correlation between NAA/Cho and delayed recognition (low NAA/Cho ratios correlated with high values of VLMT recognition score) is inconsistent with the widely accepted view on NAA as a marker for neuronal integrity, synaptic abundance and neuronal loss (Maier et al. 1995; Yildiz-Yesiloglu and Ankerst 2006). However, one recent study discussed a negative correlation between NAA and hippocampal volume (Klar et al. 2010). The authors conclude that hippocampal volume losses as well as NAA concentration are characteristics of the pathophysiology of schizophrenia, but that these two processes do not run in parallel. The authors discussed the link between NAA and a dysfunctional glutamatergic neurotransmission, which may cause neurotoxicity (Klar et al. 2010). A dysfunctional glutamatergic neurotransmission (NMDA receptor hypofunction or hyperfunction) and a glutamate-dependent neurotoxicity in schizophrenia have been discussed controversially (Konradi and Heckers 2003; Paz et al. 2008). The enhanced NAA/Cho ratio could reflect such a hyperglutamatergic state and this may be linked to poor memory performance (delayed recognition). However, this hypothesis is not supported by the results of the (Glu + Gln)/Cre-ratios (no group differences, no correlations) in our study.

In contrast, Cho/Cr correlated positively with the verbal recognition in schizophrenia patients. This finding is surprising, as the ratio includes the total levels of mobile choline (acetylcholine, glycerophosphorylcholine and phosphocholine) and might be in relation to the membrane turnover in the hippocampus (Valenzuela and Sachdev 2001; Watanabe et al. 2010). Furthermore, choline is high in inflammatory processes and demyelinating diseases and we expected to find a negative correlation between Cho/Cr and memory performance. However, different studies in Alzheimer patients revealed inconsistent findings concerning Cho/Cr. Some studies have described elevated Cho, some reduced choline and other studies did not detect any change (Jessen et al. 2000, 2001; Watanabe et al. 2010). Our results could possibly be caused by the temporal variability even in healthy subject and so the role of this ratio to evaluate brain function in schizophrenia may be limited (Rose et al. 1999; Jessen et al. 2000). Another important point is that it is unlikely that this ratio reflects acetylcholine neurotransmission, since acetylcholine contributes little to the spectroscopic peak of choline (Bluml et al. 1999).

Influence of antipsychotic medication

All patients were treated with antipsychotic drugs during the study, but no patient was treated with benzodiazepines, beta-blocking agents or anticholinergic drugs at the time of the neuropsychological assessment. We did not find an influence of antipsychotic medication on cognitive dysfunction and on hippocampal volume or neurochemistry. This is in line with one longitudinal study and supports the opinion that volume alterations and neurochemical disturbances may be independent from the actions of antipsychotic drugs (Panenka et al. 2007; Klar

et al. 2010; Tamminga et al. 2010). Furthermore, the influence of antipsychotics on neurocognitive performance is of only limited value in schizophrenia (Remillard et al. 2005).

Limitations

The major limitation is that our two study groups were not matched demographically. As our intervening variables (age, gender, and education) might have an influence on our dependent variables, we performed MANCOVAs intending to adjust the group comparisons for the effects of the intervening variables. However, we are aware that this procedure is inferior to a perfect group matching, but an adequate matching for all confounding variables would have reduced the sample size (maximum $N = 20$ in each group) and therefore the statistical power. Importantly, our results which have been adjusted for intervening variables are in line with previously published literature. Furthermore, we do not expect that our effect of a reduced hippocampus volume in FE-SZ patients, who are younger than the controls, is driven by the age difference. During the aging process and the disease course of schizophrenia, a reduction of hippocampal volume is a common finding (Raz et al. 2004). Therefore, our age difference would rather reduce the volume difference between groups than enhance it. Finally, the age range of our study sample is not the typical range to expect a large impact of age on hippocampal shrinkage (Raz et al. 2004; Steen et al. 2006; Tamminga et al. 2010). However, as age may influence MRI, MRS and neuropsychological measures, we performed additional analysis which replicated most of our main findings with a smaller, but age adjusted group. It should be noted that the differences in age could explain the lack of a significant difference between groups in MRS ratios (Maudsley et al. 2009).

From a statistical point of view the multitude of different techniques and tests applied in this study may lead to false positive findings caused by multiple testing. But the fact that we could confirm our main hypothesis and that we found specific correlations between a hippocampal-specific task and the hippocampal volume/neurochemistry, but no correlations of the non hippocampal-specific measures and the hippocampal volume measure stands in contrast to this assumption. One further methodological limitation might be the use of ratios rather than absolute values of the 1H MRS metabolites, although ratios may also present some technical advantage as discussed recently (Stern et al. 2008). Since in MRS ratios one metabolite refers to another measured by the same technique this might compensate possible measurement errors. Furthermore, we did not obtain a differentiation between grey or white matter in the investigated volumes of interest. Therefore, an influence of different grey and white matter proportions between different subjects on the metabolite concentrations cannot be excluded. To reduce this probability, the positioning of the volume of interests were visually inspected and adjusted based on identifiable anatomic landmarks according to a standard brain atlas.

Conclusions

These results point to disturbed hippocampal integrity in first-episode schizophrenia, and towards a relationship between verbal memory performance and hippocampal integrity in schizophrenia. Therefore, using a multidimensional approach, we were able to reveal different clusters of memory impairment in FE-SZ.

Acknowledgements

Alkomiet Hasan is supported by the Deutsche Forschungsgemeinschaft (DFG grant HA 6091/1-1).

Statement of Interest

The authors deny any potential conflict of interest as it relates to the subject of this report.

References

Aleman A, Hijman R, de Haan EH, Kahn RS. 1999. Memory impairment in schizophrenia: a meta-analysis. Am J Psychiatry 156:1358–66.

Antonova E, Sharma T, Morris R, Kumari V. 2004. The relationship between brain structure and neurocognition in schizophrenia: a selective review. Schizophr Res 70:117–45.

Bassett AS, Collins EJ, Nuttall SE, Honer WG. 1993. Positive and negative symptoms in families with schizophrenia. Schizophr Res 11:9–19.

Bluml S, Seymour KJ, Ross BD. 1999. Developmental changes in choline- and ethanolamine-containing compounds measured with proton-decoupled (31)P MRS in in vivo human brain. Magn Reson Med 42:643–54.

DeLisi LE, Stritzke PH, Holan V, Anand A, Boccio A, Kuschner M, et al. 1991. Brain morphological changes in 1st episode cases of schizophrenia: are they progressive? Schizophr Res 5:206–8.

Endicott J, Spitzer RL, Fleiss JL, Cohen J. 1976. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry 33:766–71.

Gaffan D. 2005. Neuroscience. Widespread cortical networks underlie memory and attention. Science 309:2172–3.

Galderisi S, Davidson M, Kahn RS, Mucci A, Boter H, Gheorghe MD, et al. 2009. Correlates of cognitive impairment in first episode schizophrenia: the EUFEST study. Schizophr Res 115:104–14.

Green MF. 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 153:321–30.

Gruber O, Falkai P, Schneider-Axmann T, Schwab SG, Wagner M, Maier W. 2008. Neuregulin-1 haplotype HAP(ICE) is associated with lower hippocampal volumes in schizophrenic patients and in non-affected family members. J Psychiatr Res 43:1–6.

Gur RE, Turetsky BI, Cowell PE, Finkelman C, Maany V, Grossman RI, et al. 2000. Temporolimbic volume reductions in schizophrenia. Arch Gen Psychiatry 57:769–75.

[AQ3] Guy W BR. 1976. CGI: Clinical Global Impressions. National Institute of Mental Health.

Harrison PJ. 2004. The hippocampus in schizophrenia: a review of the neuropathological evidence and its pathophysiological implications. Psychopharmacology (Berlin) 174:151–62.

[AQ4] Heaton RK CG, Talley JL, Kay GG, Curtiss G. 1993. Wisconsin Card Sorting Test Manual – Revised and expanded. Florida: PAR.

Helmstaedter C, Wietzke J, Lutz MT. 2009. Unique and shared validity of the "Wechsler logical memory test", the "California verbal learning test", and the "verbal learning and memory test" in patients with epilepsy. Epilepsy Res 87:203–12.

Henseler I, Falkai P, Gruber O. 2009. A systematic fMRI investigation of the brain systems subserving different working memory components in schizophrenia. Eur J Neurosci 30:693–702.

Henseler I, Falkai P, Gruber O. 2010. Disturbed functional connectivity within brain networks subserving domain-specific subcomponents of working memory in schizophrenia: relation to performance and clinical symptoms. J Psychiatr Res 44: 364–72.

Hopfinger JB, Buonocore MH, Mangun GR. 2000. The neural mechanisms of top-down attentional control. Nat Neurosci 3:284–91.

Jamrozinski K, Gruber O, Kemmer C, Falkai P, Scherk H. 2009. Neurocognitive functions in euthymic bipolar patients. Acta Psychiatr Scand 119:365–74.

Jessen F, Block W, Traber F, Keller E, Flacke S, Papassotiropoulos A, et al. 2000. Proton MR spectroscopy detects a relative decrease of N-acetylaspartate in the medial temporal lobe of patients with AD. Neurology 55:684–8.

Jessen F, Block W, Traber F, Keller E, Flacke S, Lamerichs R, et al. 2001. Decrease of N-acetylaspartate in the MTL correlates with cognitive decline of AD patients. Neurology 57:930–2.

Kay SR, Fiszbein A, Opler LA. 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13:261–76.

Klar AA, Ballmaier M, Leopold K, Hake I, Schaefer M, Bruhl R, et al. 2010. Interaction of hippocampal volume and N-acetylaspartate concentration deficits in schizophrenia: a combined MRI and 1H-MRS study. Neuroimage 53:51–7.

Konradi C, Heckers S. 2003. Molecular aspects of glutamate dysregulation: implications for schizophrenia and its treatment. Pharmacol Ther 97:153–79.

Kubicki M, McCarley RW, Nestor PG, Huh T, Kikinis R, Shenton ME, et al. 2003. An fMRI study of semantic processing in men with schizophrenia. Neuroimage 20:1923–33.

Laws KR. 1999. A meta-analytic review of Wisconsin Card Sort studies in schizophrenia: general intellectual deficit in disguise? Cogn Neuropsychiatry 4:1–30; discussion 31–5.

Maier M, Ron MA, Barker GJ, Tofts PS. 1995. Proton magnetic resonance spectroscopy: an in vivo method of estimating hippocampal neuronal depletion in schizophrenia. Psychol Med 25:1201–9.

Maudsley AA, Domenig C, Govind V, Darkazanli A, Studholme C, Arheart K, et al. 2009. Mapping of brain metabolite distributions by volumetric proton MR spectroscopic imaging (MRSI). Magn Reson Med 61:548–59.

Mesholam-Gately RI, Giuliano AJ, Goff KP, Faraone SV, Seidman LJ. 2009. Neurocognition in first-episode schizophrenia: a meta-analytic review. Neuropsychology 23:315–36.

Muller H, Hasse-Sander I, Horn R, Helmstaedter C, Elger CE. 1997. Rey Auditory-Verbal Learning Test: structure of a modified German version. J Clin Psychol 53:663–71.

Panenka WJ, Khorram B, Barr AM, Smith GN, Lang DJ, Kopala LC, et al. 2007. A longitudinal study on the effects of typical versus atypical antipsychotic drugs on hippocampal volume in schizophrenia. Schizophr Res 94:288–92.

Paz RD, Tardito S, Atzori M, Tseng KY. 2008. Glutamatergic dysfunction in schizophrenia: from basic neuroscience to clinical psychopharmacology. Eur Neuropsychopharmacol 18: 773–86.

Petrides M, Milner B. 1982. Deficits on subject-ordered tasks after frontal- and temporal-lobe lesions in man. Neuropsychologia 20:249–62.

Ragland JD, Gur RC, Valdez J, Turetsky BI, Elliott M, Kohler C, et al. 2004. Event-related fMRI of frontotemporal activity during word encoding and recognition in schizophrenia. Am J Psychiatry 161:1004–15.

Raz N, Rodrigue KM, Head D, Kennedy KM, Acker JD. 2004. Differential aging of the medial temporal lobe: a study of a five-year change. Neurology 62:433–8.

Remillard S, Pourcher E, Cohen H. 2005. The effect of neuroleptic treatments on executive function and symptomatology in schizophrenia: a 1-year follow up study. Schizophr Res 80: 99–106.

Rose SE, de Zubicaray GI, Wang D, Galloway GJ, Chalk JB, Eagle SC, et al. 1999. A 1H MRS study of probable Alzheimer's disease and normal aging: implications for longitudinal monitoring of dementia progression. Magn Reson Imaging 17:291–9.

Scherk H, Backens M, Zill P, Schneider-Axmann T, Wobrock T, Usher J, et al. 2008. SNAP-25 genotype influences NAA/Cho in left hippocampus. J Neural Transm 115:1513–8.

Schmidt KH, Metzler P. 1992. Wortschatztest WST. Weinheim: Beltz.

Seidman LJ, Faraone SV, Goldstein JM, Kremen WS, Horton NJ, Makris N, et al. 2002. Left hippocampal volume as a vulnerability indicator for schizophrenia: a magnetic resonance imaging morphometric study of nonpsychotic first-degree relatives. Arch Gen Psychiatry 59:839–49.

Steen RG, Hamer RM, Lieberman JA. 2005. Measurement of brain metabolites by 1H magnetic resonance spectroscopy in patients with schizophrenia: a systematic review and meta-analysis. Neuropsychopharmacology 30:1949–62.

Steen RG, Mull C, McClure R, Hamer RM, Lieberman JA. 2006. Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. Br J Psychiatry 188:510–8.

Stern AJ, Savostyanova AA, Goldman A, Barnett AS, van der Veen JW, Callicott JH, et al. 2008. Impact of the brain-derived neurotrophic factor Val66Met polymorphism on levels of hippocampal N-acetyl-aspartate assessed by magnetic resonance spectroscopic imaging at 3 Tesla. Biol Psychiatry 64:856–62.

Szeszko PR, Goldberg E, Gunduz-Bruce H, Ashtari M, Robinson D, Malhotra AK, et al. 2003. Smaller anterior hippocampal formation volume in antipsychotic-naive patients with first-episode schizophrenia. Am J Psychiatry 160:2190–7.

Talairach J, Tournoux P. 1998. Coplanar sterotaxic atlas of the human brain. New York: Thieme Medical Publishers.

[AQ5]
Tamminga CA, Stan AD, Wagner AD. 2010. The hippocampal formation in schizophrenia. Am J Psychiatry.

Thoma RJ, Monnig M, Hanlon FM, Miller GA, Petropoulos H, Mayer AR, et al. 2009. Hippocampus volume and episodic memory in schizophrenia. J Int Neuropsychol Soc 15:182–95.

Torres IJ, Flashman LA, O'Leary DS, Swayze V 2nd, Andreasen NC. 1997. Lack of an association between delayed memory and hippocampal and temporal lobe size in patients with schizophrenia and healthy controls. Biol Psychiatry 42: 1087–96.

Valenzuela MJ, Sachdev P. 2001. Magnetic resonance spectroscopy in AD. Neurology 56:592–8.

Velakoulis D, Wood SJ, Wong MT, McGorry PD, Yung A, Phillips L, et al. 2006. Hippocampal and amygdala volumes according to psychosis stage and diagnosis: a magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra-high-risk individuals. Arch Gen Psychiatry 63:139–49.

Watanabe T, Shiino A, Akiguchi I. 2010. Absolute quantification in proton magnetic resonance spectroscopy is useful to differentiate amnesic mild cognitive impairment from Alzheimer's disease and healthy aging. Dement Geriatr Cogn Disord 30:71–7.

Weiss AP, Zalesak M, DeWitt I, Goff D, Kunkel L, Heckers S. 2004. Impaired hippocampal function during the detection of novel words in schizophrenia. Biol Psychiatry 55: 668–75.

Wittchen HU, Wunderlich U, Gruschwitz S, Zaudig M. 1997. Strukturiertes Klinisches Interview für DSM-IV. Achse I: Psychische Störungen. A German, advanced adaptation of the original SCID version by Spitzer RL, Williams JB, Gibbon M, First MB. Göttingen: Hogrefe-Verlag.

Wobrock T, Ecker UK, Scherk H, Schneider-Axmann T, Falkai P, Gruber O. 2009. Cognitive impairment of executive function as a core symptom of schizophrenia. World J Biol Psychiatry 10:442–51.

Yildiz-Yesiloglu A, Ankerst DP. 2006. Neurochemical alterations of the brain in bipolar disorder and their implications for pathophysiology: a systematic review of the in vivo proton magnetic resonance spectroscopy findings. Prog Neuropsychopharmacol Biol Psychiatry 30:969–95.

Zierhut K, Bogerts B, Schott B, Fenker D, Walter M, Albrecht D, et al. 2010. The role of hippocampus dysfunction in deficient memory encoding and positive symptoms in schizophrenia. Psychiatry Res 183:187–94.

Zilles D, Burke S, Schneider-Axmann T, Falkai P, Gruber O. 2009. Diagnosis-specific effect of familial loading on verbal working memory in schizophrenia. Eur Arch Psychiatry Clin Neurosci 259:309–15.

Supplementary material available online

Supplementary Tables 1–3.

Supplementary material for Hasan A, Wobrock T, Falkai P, Schneider-Axmann T, Guse B, Backens M, Ecker K.H.U, Heimes J, Michael Galea J, Gruber O & Scherk H. Hippocampal integrity and neurocognition in first-episode schizophrenia: A multidimensional study. The World Journal of Biological Psychiatry 2011 doi: 10.3109/15622975.2011.620002

Supplementary Table 1. Demographic and clinical data of the age adjusted study sample control subject, split into the different parts of the study.

	Healthy control subjects			First-episode patients			Statistics[1]		
Subjects with neuropsychology	n	mean	SD	n	mean	SD	F/Chi²	df	P
Age (years)	25	28.27	6.058	53	28.36	7.82	0.00	1, 76	0.96
Education (years)	25	15.73	2.59	53	12.54	2.77	22.80	1, 76	< 0.0005*
Gender (male/female)	25	9/16		53	34/19	–	5.44#	1	0.020*
Hand Preference (r/n.r.)	25	23/2		53	44/9		1.13#	1	0.29
PANSS total score	–	–	–	53	93.54	17.10	–	–	–
PANSS positive subscore	–	–	–	53	22.28	6.57	–	–	–
PANSS negative subscore	–	–	–	53	22.70	6.62	–	–	–
CPZ daily dose				53	368.11	314.14			
Subjects with MRI data									
Age (years)	25	28.97	12.37	41	28.35	7.05	0.13	1, 64	0.72
Education (years)	25	15.78	2.76	41	12.79	2.77	18.85	1, 64	< 0.0005*
Gender (male/female)	25	9/16		41	28/13		6.58#	1	0.010*
Hand Preference (r/n.r.)	25	23/2		41	34/7		1.09#	1	0.30
PANSS total score	–	–	–	41	91.34	17.86	–	–	–
PANSS positive subscore	–	–	–	41	21.56	6.45	–	–	–
PANSS negative subscore	–	–	–	41	22.77	6.83	–	–	–
CPZ daily dose	–	–	–	41	320.49	303.49	–	–	–
Neuroleptics (no/typical/atypical)	–	–	–	41	1/2/38				
Subjects with MRS data									
Age (years)	24	29.57	6.55	46	29.22	7.49	0.04	1, 68	0.85
Education (years)	24	15.65	2.68	46	12.86	2.69	16.71	1, 68	<0.0005*
Gender (male/female)	24	8/16		46	32/14		8.45#	1	0.004*
Hand Preference (r/n.r.)	24	22/2		46	38/8		1.06#	1	0.30
PANSS total score	–	–	–	46	91.91	17.99	–	–	–
PANSS positive subscore	–	–	–	46	21.70	6.01	–	–	–
PANSS negative subscore	–	–	–	46	22.43	7.04	–	–	–
CPZ daily dose				46	290.00	203.30			

Data are presented as mean ± standard deviation unless otherwise indicated.

[1]Values are expressed as Chi² statistics (indicated by #) for categorical variables and F statistics for continuous variables. F = F statistic, df = degrees of freedom, p = error probability of first kind, r: right; n.r.: not right, *$p < 0.05$

Supplementary Table 2. Structural MRI and 1H MRS data of the age adjusted study sample.

	Healthy control subjects		First-episode Patients		ANOVA/ANCOVA[1]		
	Mean	sd	mean	sd	F	df	P
Total gray matter (cm^3)	762.58	73.73	757.39	73.35	1.57	1, 60	0.22
Absolute Volume							
Left Hippocampus (mm^3)	2845	466	2534	744	4.19	1, 60	0.045*
Right Hippocampus (mm^3)	2792	422	2611	588	1.70	1, 60	0.20
Relative Volume							
Left Hippocampus (%)	0.376	0.068	0.334	0.090	3.97	1, 64	0.051**
Right Hippocampus (%)	0.369	0.063	0.346	0.074	1.70	1, 64	0.13
MRS ratios							
NAA/Cho	3.905	0.766	4.012	0.620	0.0	1, 67	0.90
NAA/Cr	1.312	0.295	1.294	0.184	0.8	1, 67	0.36
Cho/Cr	0.337	0.042	0.326	0.044	1.4	1, 67	0.25
Ins/Cr	1.054	0.254	1.081	0.331	0.7	1, 67	0.41
(Gln+Glu)/Cr	2.574	0.691	2.404	0.640	0.9	1, 67	0.35

Data are presented as mean ± standard deviation unless otherwise indicated. Legend: m = mean, sd = standard deviation, F = F statistic, df = degrees of freedom, p = error probability of first kind.
[1]Total gray matter volume, absolute hippocampus volumes: ANCOVA (factors diagnosis, gender, covariate education), relative hippocampus volumes: ANOVA (factor diagnosis); 1H MRS ratios: ANCOVA (factor diagnosis, covariate education), *$p < 0.05$; **$0.05 < p < 0.06$

Supplementary Table 3. Neuropsychological test scores for schizophrenia patients and healthy controls of the age adjusted study sample.

	Healthy control subjects			First-episode Patients			ANOVA/ANCOVA[1]		
	n	Mean	sd	n	Mean	Sd	F	Df	P
WST (T-Value)	25	57.60	6.01	48	49.12	8.13	20.4	1, 71	<0.0005*
VLMT 1 to 5 (raw-value)	25	59.28	6.99	50	47.92	10.63	18.0	1, 71	<0.0005*
VLMT 5 – 7 (raw-value)	25	1.44	1.56	50	2.30	2.71	2.1	1, 73	0.15
VLMT rec (raw-value)	25	14.00	1.50	50	12.00	3.06	9.5	1, 73	0.003
VLMT 1 to 5 (T-value)	25	56.32	8.46	49	44.73	9.74	25.5	1, 72	<0.0005*
VLMT 5 – 7 (T-value)	25	54.24	9.00	50	50.34	11.00	2.4	1, 73	0.13
VLMT rec (T-value)	25	51.48	4.12	50	46.34	7.71	9.7	1, 73	0.003
SOPT	6	4.17	2.40	35	5.74	3.25	1.3	1, 39	0.26
WCST TA	24	86.08	16.72	52	106.48	20.67	17.9	1, 74	<0.0005*
WCST PT (T-value)	24	63.71	14.15	52	64.48	17.30	0.04	1, 74	0.85

Legend: m = mean, sd = standard deviation, F = F statistic, df = degrees of freedom, p = error probability of first kind. WST: Wortschatztest. VLMT 1-5: immediate recall, sum of trials 1 to 5; VLMT 5-7: difference between maximum immediate and felayed recall, trial 5 minus 7; VLMT rec: corrected recognition score W-F; SOPT: Subject Ordered Pointing Task, number of errors; WCST TA: Number of trails administered; WCST PT: Perserverative responses, Score; VLMT: Verbaler Lern- und Merkfähigkeitstest; WCST: Wisconsin Card Sorting Test. Data are presented as mean ± standard deviation unless otherwise indicated.
[1]VLMT 1 to 5, raw value: ANOVA (factors diagnosis, gender), other neuropsychologic tests: ANOVA (factors diagnosis), *$p < 0.05$