Title

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Multimodal Analysis of the Hippocampus in Schizophrenia Using Proton Magnetic Resonance Spectroscopy and Functional Magnetic Resonance Imaging

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Abstract

Background—Studies have shown that individuals with schizophrenia suffer from memory impairments. In this study, we combined proton magnetic resonance spectroscopy (^{1}H-MRS) and functional magnetic resonance imaging (fMRI) to clarify the neurobiology of memory deficits in schizophrenia.

Methods—We used single-voxel MRS acquired in the left hippocampus and fMRI during performance of a memory task to obtain measures of neurochemistry and functional response in 28 stable, medicated participants with schizophrenia (SZ) and 28 matched healthy controls (HC).

Results—The SZ group had significantly decreased blood oxygen level-dependent (BOLD) signal in left inferior frontal gyrus (IFG) during encoding and in the anterior cingulate cortex (ACC) and superior temporal gyrus (STG) during retrieval. We did not find significant differences in *N*-acetylaspartate/creatine (NAA/Cr) or glutamate + glutamine (Glx/Cr) levels between the groups, but did find a significant positive correlation between NAA/Cr and Glx/Cr in the HC group that was absent in the SZ group. There were no significant correlations between BOLD and MRS measured in the hippocampus. Further analyses revealed a negative correlation between left IFG BOLD and task performance in the SZ group. Finally, in the HC group, the left IFG BOLD was positively correlated with Glx/Cr.

Conclusions—We replicated findings of reduced BOLD signal in left IFG and of an altered relationship between IFG BOLD response and task performance in the SZ. The absence of correlation between NAA/Cr and Glx/Cr levels in patients might suggest underlying pathologies of the glutamate-glutamine cycle and/or mitochondria.

Keywords

1 INTRODUCTION

One of the most replicated abnormalities in schizophrenia is impairment in episodic memory (Aleman et al., 1999). This impairment is not related to education level, gender, medication, duration of illness, or severity of illness (Saykin et al., 1994; Seidman et al., 1998) but instead seems to be a core feature of the illness that highlights disruption of neural memory circuitry, which includes the hippocampus. In addition, it is this memory impairment, along with dysfunctions in other cognitive domains, that puts the greatest limitation on the overall level of functioning in individuals with schizophrenia (Goldberg et al., 2007).

Episodic memory impairment in schizophrenia has been explored in some detail using several imaging modalities. Functional Magnetic Resonance Imaging (fMRI) has demonstrated reduced blood oxygen level dependent (BOLD) signal in the medial temporal lobe, including the hippocampus, and prefrontal regions during memory tasks in individuals with schizophrenia (Achim and Lepage, 2005; Ragland et al., 2004; Ragland et al., 2009). Proton magnetic resonance spectroscopy (^{1}H-MRS) studies of the hippocampus in schizophrenia have, in general, documented a reduction in *N*-acetylaspartate (NAA) levels (Brugger et al., 2011; Steen et al., 2005). Although NAA levels are thought to be an *in vivo* biomarker of neuronal integrity (Bates et al., 1996; Lentz et al., 2005; Stork and Renshaw, 2005), it is not known whether decreased NAA is related to memory impairment in schizophrenia. On the other hand, MRS studies measuring glutamate in the hippocampus in schizophrenia have been few and inconclusive (Karlsgodt et al., 2008; Olbrich et al., 2008; Tebartz van Elst et al., 2005)

The purpose of this study was to investigate the relationship between 1H-MRS metabolites and fMRI BOLD signal collected from the hippocampus of participants with schizophrenia (SZ) and matched healthy controls (HC). To our knowledge, despite known abnormalities, the relationships between NAA, glutamate, and the BOLD signal in the hippocampus have never been studied in schizophrenia. For the purpose of this study, we acquired single-voxel ^{1}H-MRS measurements exclusively in the left hippocampus, as prior studies have reported NAA reductions there (Bertolino et al., 1998; Maier M, 20002). For the functional study, we chose an episodic memory task known to activate the medial temporal and prefrontal cortices (Otten et al., 2001; Tebartz van Elst et al., 2005).

We hypothesized that we would replicate findings of reduced NAA levels within the left hippocampus, as well as reduced temporofrontal functional engagement during the memory encoding and retrieval tasks in SZ. Since glutamatergic transmission plays a key role in hippocampal memory processes (Bliss and Collingridge, 1993), we hypothesized that glutamate + glutamine (Glx) levels would correlate positively with the BOLD signal measured in the hippocampus during task performance in HC but not in SZ.

2 METHODS AND MATERIALS

2.1 SUBJECTS

Thirty-nine stable, medicated SZ were recruited from the psychiatry clinics at the University of Alabama at Birmingham (UAB). Forty-one HC, matched on age, gender, and parental occupation, were recruited by advertisements in fliers and the University's newspaper. Exclusion criteria were major medical conditions, substance abuse within 6 months of imaging (Supplement), previous serious head injury, neurological disorders, loss of consciousness, and pregnancy. The study was approved by the UAB IRB, and all participants gave written informed consent.

Diagnoses were established using participants' medical records and the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994). The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998) and the Brief Psychiatric Rating Scale (BPRS) (Overall JE, 1962) were used to characterize general cognitive function and symptom severity, respectively.

Several subjects were excluded from the analyses (Supplement), leaving a combined group of 28 HC and 28 SZ (Table 1).

2.2 IMAGE ACQUISITION: fMRI and MRS

All imaging was performed on a 3T head-only scanner (Siemens Allegra, Erlangen, Germany), equipped with a circularly polarized transmit/receive head coil. fMRI data were acquired using the gradient recalled echo-planar imaging (EPI) sequence (repetition time/ echo time [TR/TE] = 2100/30 msec, 70° flip angle, 24×24 cm^2 field of view, 64×64 matrix, 4-mm slice thickness, 1-mm gap, 26 axial slices). A high-resolution structural scan was acquired using the T1-weighted magnetization prepared rapid acquisition gradient-echo (MPRAGE) sequence (TR/TE/inversion time [TI] =2300/3.93/1100 msec, 12° flip angle, 256×256 matrix, 1-mm isotropic voxels). An IFIS-SA system (In Vivo Corp., Orlando, Florida) running E-Prime software (version 1.2; Psychology Software Tools, Inc., Pittsburgh, Pennsylvania) controlled stimulus delivery and recorded responses and reaction times.

T1-weighted anatomic scans (gradient-recalled echo sequence, TR/TE = 250/3.48 ms, 70° flip angle, 5-mm slice thickness, 1.5-mm gap, 512×512 matrix) were acquired for spectroscopic voxel placement. Slices were aligned to the anatomical midline to control for head tilt. To facilitate voxel placement, the axial images were obtained along the long axis of the hippocampi, as viewed from the sagittal images. The voxel was placed in the left hippocampus such that the amount of gray matter was maximized (Figure 1). Following manual shimming and water suppression, spectra were acquired using the point-resolved spectroscopy sequence (PRESS; TR/TE = 2000/80 msec, 640 averages, $2.7 \times 1.5 \times 1$ cm voxel size, 21 min 20 sec scanning time) to optimize the glutamate signal (Bottomley, 1987).

2.3 MRS Analyses

MRS data were analyzed in jMRUI (version 3.0) (Naressi et al., 2001) as previously described (Reid et al., 2010). After removing the residual water peak, spectra were quantified in the time domain using the AMARES algorithm (Vanhamme et al., 1997). Prior knowledge derived from *in vitro* and *in vivo* metabolite spectra was included in the model (Reid et al., 2010), which consisted of peaks for NAA, choline (Cho), creatine (Cr), and three peaks for Glx. Amplitude, line width, and chemical shift were optimized for each peak. Cramer–Rao lower bounds (CRLB) (Ratiney et al., 2004) were calculated for each peak. Exclusion criteria were 1) line width of water greater than 25 Hz at full width at half maximum (FWHM) during shimming, 2) CRLB greater than 30%, and 3) failure of the fitting algorithm. No data were excluded on the basis of these criteria. One HC was scanned on 5 consecutive days (Figure 1) to assess reproducibility (Supplement). NAA and Glx were quantified with respect to Cr.

We conducted a MANCOVA to assess between-group differences in NAA/Cr and Glx/Cr levels. For all analyses, NAA/Cr and Glx/Cr levels were corrected for age. Because positive correlations between NAA and Glx have been identified in healthy controls (Waddell et al., 2011; Walter et al., 2009), we also assessed the correlations between NAA and Glx in each group. These analyses were tested with an alpha level of .05.

2.4 fMRI TASK

The episodic memory task consisted of an intentional encoding phase, followed by a recognition memory phase after a 15 minute delay. To maximize retrieval performance, a deep encoding paradigm utilizing an animacy decision was used. During the encoding task, participants saw a series of 60 words, presented one at a time for 300 msec followed by a fixation screen. A 2-second prestimulus cue ("Alive?") indicated that the participant had to answer by button press whether the upcoming word was alive or not alive. Following a 15 minute interval, participants performed the retrieval task, where they saw 60 words, including 30 words previously seen (old words) and 30 new words, presented one at a time for 300 msec. A 2-second warning stimulus ("Ready?") indicated that the participant had to answer by button press whether the upcoming word was "old" or "new." For each task, the inter-stimulus interval (fixation screen) was jittered, ranging from 3 to 5 seconds. Behavioral measures were compared across groups using a one-way ANOVA. The alpha level was set at .05.

2.5 fMRI Analysis and Design

Data analyses were implemented in SPM8 running in MATLAB (version R2010b). Preprocessing of the fMRI data included slice timing correction, realignment and reslicing to the mean functional volume, artifact/motion correction (movement > 1mm) using ArtRepair (Mazaika PK, 2005), coregistraton to the structural scan, and normalization to MNI space using DARTEL (Ashburner, 2007) with 4-mm FWHM Gaussian kernel smoothing. Participants were excluded from further analyses if 33% or more of their data were repaired during artifact and motion correction.

The subject-level statistical analysis consisted of an event-related GLM. We included the following regressors: encode correctly and incorrectly retrieved for the encoding condition, and Hits, Misses, Correct Rejects and False Alarms for the retrieval condition (Ragland et al., 2001; Ragland et al., 2004). All events were modeled using a canonical hemodynamic response function, and data were high-pass filtered (cutoff = 256 seconds). Statistical parametric maps were generated for the following contrasts: encode correctly retrieved > encode incorrectly retrieved, and retrieve high (Hits) > retrieve low (Correct Rejects). At the group level, the two contrasts for each individual were entered as conditions in a diagnosis-

by-condition factorial design (Achim and Lepage, 2005). Whole-brain results were corrected for multiple comparisons using a cluster-level FDR correction. The cluster size threshold was defined within SPM8, based on Gaussian random field theory, as the number of contiguous voxels with p < .05 (uncorrected) in order to accept the false discovery rate of 0.05 (Chumbley and Friston, 2009).

2.6 MRS, fMRI Correlations

The BOLD signal was extracted as percent signal change using MarsBaR (Brett M, 2002) from a region of interest, defined as the left hippocampus, in WFU pick-atlas's IBASPM 116 definitions (Maldjian et al., 2003). The relationships between metabolite levels and percent signal change were analyzed by Pearson correlation, which were compared using Fisher's r to Z transform. The family-wise alpha was held at .05 by using a Holm multiple comparison correction (Holm, 1979).

Since Ragland et al. (2001) found an association between target discriminability and activation in the left IFG similar to the one observed in this study, we conducted exploratory correlations between BOLD response in that region, defined as the LIFG in the pick-atlas, and the index of discriminability, Pr. We also conducted correlations between hippocampal metabolites, LIFG BOLD response, and Pr.

3 RESULTS

3.1 Behavioral

Behavioral results are summarized in Table 2. The SZ group performed significantly worse compared to HC on all behavioral measures except for the measure of response bias (Br). The percentage of correct responses during encoding and retrieval demonstrated that both groups were attentive and engaged during the task.

3.2 MRS

NAA/Cr and Glx/Cr did not significantly differ between the groups (Table 3) (Scatter plots in Supplement). NAA/Cr and Glx/Cr were significantly correlated in the HC group (r = 0.450, p = .019) but not the SZ group (r = 0.010, p = .959). The correlation in the HC group did not survive a multiple comparisons correction (Figure 2).

3.3 fMRI

In the between-group comparison of the encode contrast, the SZ group showed significantly reduced BOLD signal in the left IFG compared to HC (Table 4). During the retrieve contrast, the SZ group showed significantly reduced BOLD signal in the anterior cingulate cortex (ACC) and the left superior temporal gyrus (STG) compared to HC (Table 4) (Figure 3). Within-group results can be found in Supplement. Although the encode and retrieve contrasts were based on correct responses, we also analyzed a subset of subjects matched on Pr (HC = 14; SZ = 15). During encode there was a significant group difference in the IFG, but there were no significant group difference during retrieve (Supplement). To evaluate the functional connectivity (FC) between the left IFG and left hippocampus during encode, we conducted a psycho-physiological interaction (PPI) analysis (Friston et al., 1997) within SPM8 (Supplement). In each group, there was a significant FC between these regions and no significant group difference (Supplement).

3.4 fMRI/MRS Correlations

MRS and hippocampal BOLD measures were not significantly correlated. However, the retrieve BOLD signal in left IFG and Pr were negatively correlated in SZ (r = -0.386, p = .

042) but not in HC (r = 0.163, p = .408), a difference that was statistically significant (z = -2.02, p = .043) (Figure 4). The IFG BOLD was significantly correlated with Glx/Cr in HC (r = 0.489, p = .008) but not in SZ (r = 0.139, p = 0.480) (z = 1.4, p = .162) (Figure 5). There were no significant correlations between metabolites and Pr. Glx/Cr was significantly correlated with the IFG/hippocampus FC beta weights in the HC group (r = 0.428, p = 0.026) but not in the SZ group (r = .078, p = .699) (Supplement).

4 DISCUSSION

To our knowledge, this is the first study utilizing MRS and fMRI to study hippocampal pathology in a group of stable, medicated SZ patients and matched HC. We observed that patients showed reduced BOLD signal in left IFG during memory encoding and in the ACC and STG during memory retrieval. There were no significant group difference in functional connectivity between IFG and hippocampus. Although NAA/Cr and Glx/Cr did not significantly differ between the groups, we found a positive correlation between NAA/Cr and Glx/Cr in controls that was not present in the patients. We did not find any correlations between hippocampal BOLD and MRS measures. Exploratory analyses revealed a negative correlation between the IFG BOLD response and task performance in patients, but not in controls, a difference that was statistically significant. Finally, in controls, the BOLD signal in IFG was positively correlated with hippocampal Glx/Cr.

Our fMRI results are consistent with two meta-analyses (Achim and Lepage, 2005; Ragland et al., 2009) that found evidence of reduced left IFG activation during encoding and reduced ACC and temporal lobe activation during retrieval in schizophrenia. These reductions are thought to reflect a dysfunction of cognitive processes engaged during a memory task (Ragland et al., 2009). We did not find significantly reduced hippocampal activation in the schizophrenia group, a finding consistent with Ragland's (2009) but not with Achim and Lepage's (2005) meta-analysis.

We did not find a significant decrease in NAA/Cr between the groups; however, the direction was that of a reduction of about 3% in our patients. A meta-analysis of 64 MRS studies in schizophrenia found consistent evidence of reductions of NAA in hippocampus of approximately 5% (Steen et al., 2005); thus, our sample sizes may have prevented us from detecting the small drop in NAA/Cr.

We reliably quantified Glx/Cr in a group of medicated patients and found no significant differences compared to controls. Only a few studies in schizophrenia have reported glutamate measurements in hippocampus. One study (van Elst et al, 2005) reported higher glutamate levels in a group of acutely exacerbated medicated patients, while another (Lutkenhoff et al, 2010) failed to identify such differences in stable medicated participants. In addition, Olbrich (Olbrich et al, 2008) did not find a glutamate difference in a small group of medicated, first-episode patients. Clearly, these results need to be replicated with larger, well-characterized groups of participants.

We identified a positive correlation between NAA/Cr and Glx/Cr in controls but not in patients. Such correlations have been previously identified in healthy controls (Waddell et al., 2011; Walter et al., 2009). NAA and Glx are inherently linked through a series of biochemical reactions, including the tricarboxylic acid cycle (TCA) in the mitochondria and the glutamate-glutamine cycle between neurons and glia (Moffett et al., 2007). The altered correlation could be driven by a variety of underlying pathologies. Postmortem studies in schizophrenia have revealed abnormalities in mitochondrial morphology, function, and gene expression (Clay et al., 2011; Rosenfeld et al., 2011), including in the hippocampus (Altar et al, 2005); abnormal expression of the enzymes regulating the glutamate-glutamine cycle

(Bauer et al., 2008; Bruneau et al., 2005; Steffek et al., 2008), and alterations of the glutamatergic signaling pathway (Harrison, 2004; Tamminga et al., 2010). These findings support the notion that the regulation between NAA and Glx could be altered in schizophrenia.

This study points towards significant functional deficit in left IFG during memory processing in schizophrenia. First, the IFG BOLD response was decreased in patients, even when the groups were matched on a behavioral index of discriminability. Second, replicating prior results (Ragland et al., 2001), we found the relationship between IFG BOLD response and task performance to be altered in patients. While HC showed a small positive correlation between IFG BOLD and Pr, these were negatively correlated in patients. Interestingly, a large number of patients had a *decreased* BOLD response in IFG during task, and those were the ones with high Pr (Figure 4). Speculatively, these SZ might have relied on compensatory neural network to perform the task. Although functional connectivity between the prefrontal cortex and hippocampus has been found impaired in schizophrenia (Benetti et al., 2009; Meyer-Lindenberg et al., 2005), we did not find significant differences in functional connectivity between the groups. This discrepancy could be related to differences in seed region or task type.

In addition, we observed a robust correlation between hippocampal Glx and left IFG activation in controls and found this correlation contained more variation in patients. A previous study using MRS and electroencephalography found correlations between hippocampal glutamate levels and frontally-recorded theta activity during task performance, which suggests a coupling between these regions (Gallinat et al., 2006). Interestingly, in our study, Glx levels were correlated with the beta weight of the IFG/hippocampus functional connectivity. Hippocampal Glx levels might provide an index of the coupling between these two regions during a memory task.

A major limitation of this study was that all patients were treated with antipsychotic drugs, which complicates the interpretation of the fMRI and MRS data (Bustillo et al., 2008; Choe et al., 1996; Fannon et al., 2003).

In conclusion, we replicated findings of reduced BOLD signal in left IFG during memory encoding and in ACC and STG during memory retrieval, as well as altered relationship between left IFG BOLD response and task performance in patients. We found that the positive correlation between NAA and Glx levels in healthy controls was absent in patients, perhaps suggesting underlying pathologies of the glutamate-glutamine cycle and/or mitochondria. Finally, we observed an altered relationship between hippocampal Glx and IFG BOLD response, suggesting an uncoupling between hippocampal biochemistry and IFG function in schizophrenia. These data further our knowledge of hippocampal pathology in schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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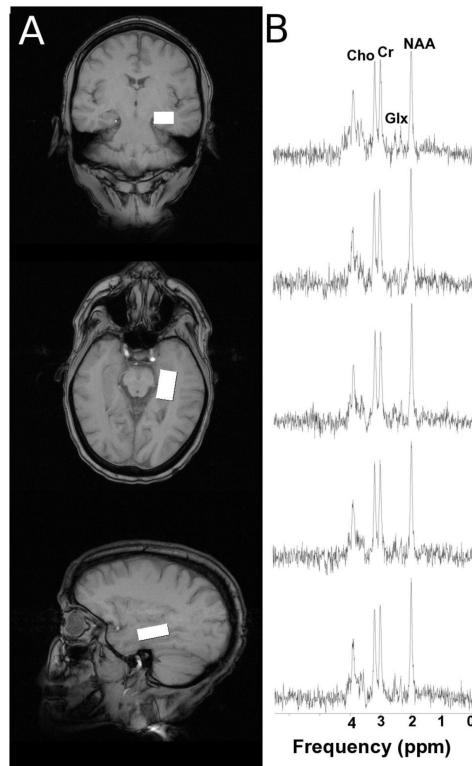
Figure 1.
(A) Example of magnetic resonance spectroscopy (MRS) voxel placement in the left hippocampus. Image is displayed in radiological convention (right side of image is subject's left side). (B) Spectra obtained from one healthy control scanned on 5 consecutive days to assess reproducibility of MRS data. Cho, choline; Cr, creatine; Glx, glutamate + glutamine; NAA, *N*-acetylaspartate; ppm, parts per million.
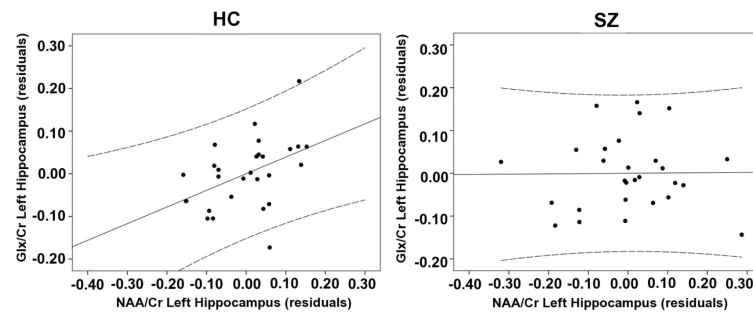
Figure 2.
Association between the metabolites NAA/Cr and Glx/Cr both measured in the left hippocampus of healthy controls (HC, n = 28) and participants with schizophrenia (SZ, n = 28). The HC group showed a positive correlation (r = 0.450, p = .019) that was not seen in the SZ group (r = 0.010, p = .959) (Z = 1.68, p = .093). The healthy control group's positive correlation did not survive multiple comparison testing. Solid lines are linear regressions and dashed lines are 95% confidence intervals.
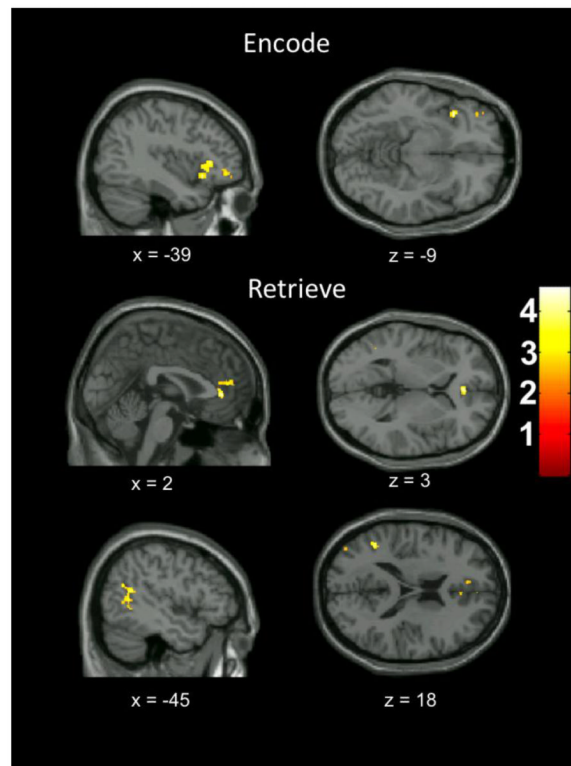
Figure 3.
Whole-brain between-group difference (healthy control participants > participants with schizophrenia) during the encode task and retrieve task. For encode, the single cluster shown is located at the inferior frontal gyrus (MNI coordinate: x = -39, y = 19, z = -9). For retrieve, the top slices show a cluster located at the anterior cingulate (MNI coordinates: x = 2, y= 39, and z = 3). The bottom slices show a cluster in the left superior temporal gyrus (MNI coordinates: x = -45, y= -53, and z = 18). Multiple comparisons corrected by using a cluster level false discovery rate (FDR) of .05. Activation overlaid on the SPM8 single-subject T1 template. Left, sagittal slices; right axial slices. Numbers below slices indicate x and z coordinates in MNI convention. Color bar indicates *t* values.
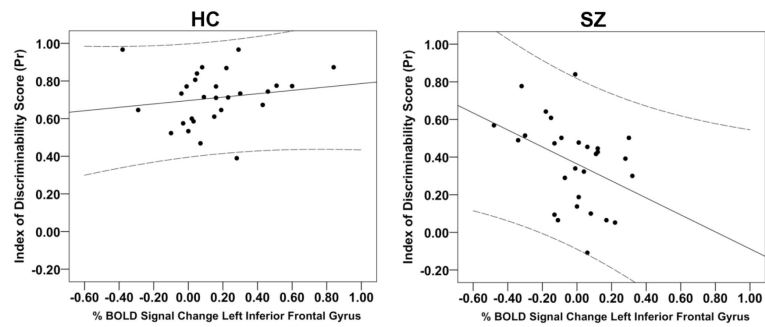
Figure 4.
Association between blood oxygen level-dependent (BOLD) acquired in the left inferior frontal gyrus and a behavioral index of discriminability, Pr (see methods). BOLD mean percent signal change was acquired during the encode task. A significant negative correlation was found for the SZ group (r = -0.386, p = .042) but not the HC (r = 0.163, p = .408). These two correlations were significantly different (Z = -2.02; p = .043). Solid lines are linear regressions and dashed lines are 95% confidence intervals.
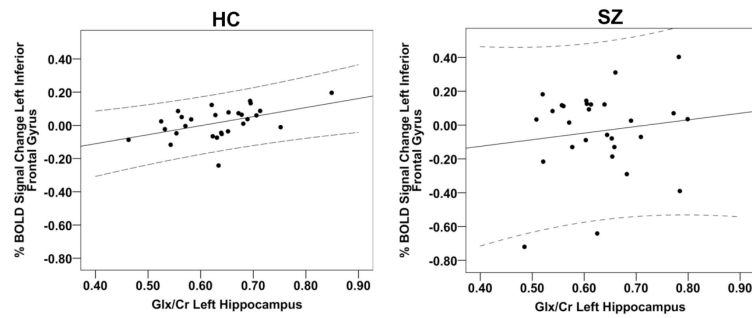
Figure 5.
Association between blood oxygen level-dependent (BOLD) mean percent signal change during the retrieve task and the MRS metabolite Glx/Cr. The BOLD measurement was collected in the left inferior frontal gyrus and the MRS measurement was measured in the left hippocampus. HC showed a significant positive correlation (r = 0.489, p = .008) that was not present in SZ group (r = 0.139, p = .480). These two correlations are not significantly different (Z = 1.4, p = .162). Solid lines are linear regressions and dashed lines are 95% confidence intervals.

Table 1

Group demographics (mean ± stdev)

Characteristic	HC (n = 28)	SZ (n = 28)
Age, years	35.6 ± 11.1	36.7 ± 12.2
Duration of illness, (years)		15.9 ± 11.9
Gender, M/F	17/11	20/8
Parental Occupation[a]	5.7± 4.3	6.0 ± 4.3
RBANS[b]		
Total index	101.7 ± 12.3	70.4 ± 13.8 ***
Immediate memory	102.8 ± 10.2	72.9 ± 15.1 ***
Visuospatial	96.4 ± 15.9	79.6 ± 18.2 **
Language	100.4 ± 11.7	81.8 ± 15.6 ***
Attention	108.8 ± 15.6	77.0 ± 20.4 ***
Delayed memory	99.1 ± 7.5	70.3 ± 19.8 ***
BPRS[c]		
Total		40.5 ± 12.7
Positive		8.4 ± 4.2
Negative		5.5 ± 2.2

HC, healthy control; F, female; M, male; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SZ, patient with schizophrenia.

[a] Ranks determined from Diagnostic Interview for Genetic Studies (1–18 scale); higher rank (lower numerical value) corresponds to higher socioeconomic status; information not available for three SZ and two HC participants.

[b] Repeatable Battery for the Assessment of Neuropsychological Status

[c] Brief Psychiatric Rating Scale, scored on a 1–7 scale; positive subscale (conceptual disorganization, hallucinatory behavior, and unusual thought content); negative subscale (emotional withdrawal, motor retardation, and blunted affect); data not available for one HC and four SZ participants.

*
P< .05 significant difference between HC and SZ in independent samples t-test.

**
P< .01 significant difference between HC and SZ in independent samples t-test.

***
P < .001 significant difference between HC and SZ in independent samples t-test.

†
P< .05 significant difference between HC and SZ in the chi-square test.

Table 2

Task Performance (mean ± stdev)

Measure	HC (n= 28)	SZ (n= 28)
Encode		
Percent Correct[b]	0.92 ± 0.06	0.79 ± 0.17 ***
"Alive" Correct Reaction Time (ms)	1057.9 ± 244.0	1315.6 ± 404.0 **
"Not alive" Correct Reaction Time (ms)	1093.8 ± 281.0	1367.8 ± 384.0 **
Retrieve		
Hit Rate, HR[c]	0.83 ± 0.13	0.64 ±0.19 ***
Percent Correct[d]	0.86 ± 0.07	0.68 ± 0.12 ***
False Alarm Rate, FAR[e]	0.11± 0.10	0.27 ± 0.19 ***
Discrimination Index, Pr[f]	0.71±0.14	0.37 ± 0.23 ***
Response Bias, Br[g]	0.39 ±0.27	0.43 ± 0.23
"Old" (Previously Seen) Correct RT (ms)	1078.21± 235.12	1234.01 ± 278.90 *

HC, healthy control; RT, Reaction Time; SZ, schizophrenia.

[a] Mean ± SD unless indicated otherwise.

[b] Encode Percent Correct = correct animacy decision/60

[c] Retrieve Hit Rate, HR = [number of correctly identified old words(Hits)]/30

[d] Retrieve Percentage Correct = (hits + correct rejections)/60

[e] False alarm rate, FAR = number false alarms/30

[f] Index of discriminability, Pr = (HR – FAR)

[g] Response bias, Br = [FAR/(1-Pr)].

[*] P< .05 significant difference between HC and SZ in independent samples t-test.

[**] P< .01 significant difference between HC and SZ in independent samples t-test.

[***] P < .001 significant difference between HC and SZ in independent samples t-test.

Table 3

Results of multiple analysis of covariance, controlling for age, comparing the metabolite ratios in the left hippocampus.

Metabolite	HC (n=28) Mean ± SD CRLB ± SD (CRLB range)	SZ (n=28) Mean ± SD CRLB ± SD (CRLB range)
NAA/Cr[a, b]	1.27 ± 0.10 3.7% ± 0.5% (2.7%-4.5%)	1.23 ± 0.15 3.7% ± 0.9% (2.4%-6.8%)
Glx/Cr[b]	0.63 ± 0.08 9.9% ± 1.7% (7.5%-13.9%)	0.63 ± 0.09 10.8% ± 3.4% (7.2%-19.9%)

Cr, creatine; CRLB, Cramer-Rao Lower Bounds; Glx, glutamate and glutamine; HC, healthy control participants; HIP, hippocampus, NAA, N-acetylaspartate; SZ, participants with schizophrenia.

[a] There was no significant difference in the raw amplitudes of Cr between groups (t = −.673, p = .78).

[b] There were no differences between the groups for water line width, metabolite peak line width, CRLBs or gray or white matter contents of the left hippocampus (all p > 0.05) (see Supplement for details).

[*] P< .05 significant difference between HC and SZ in independent samples t-test.

Table 4

Whole-brain between-group differences in activation[a] during the encode[b] and retrieve[c] conditions

Contrast	Hem	Lobe	Region	BA	Peak t value	Volume (voxels)	x, y, z[d]
Encode							
HC > SZ							
	L	Frontal	Inferior frontal gyrus, Triangular part	47	4.60	675	−39, 19, −9
Retrieve							
HC > SZ							
	R	Limbic	Anterior cingulate gyrus	32	4.46	323	2, 39, 3
	L	Temporal	Superior temporal gyrus	49	3.88	360	−45, −53, 18

BA, Brodmann Area, HC, healthy control; Hem, hemisphere; SZ, schizophrenia.

[a] Cluster level False Discovery Rate (FDR) of 0.05 was used to control for multiple comparisons

[b] Encode condition: encode correctly retrieved > encode incorrectly retrieved

[c] Retrieve condition: retrieve Hits > retrieve Correct Rejects

[d] x,y, and z refer to Montreal Neurological Institute coordinates