Glutamate, glutamine, NAA, and GABA levels in hippocampus in schizophrenia as measured by 1H-MRS at 3T

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INTRODUCTION

Schizophrenia is a debilitating disease whose phenomenology has long been recognized, but the pathophysiology has only been partially understood. Although multiple brain regions appear to be affected in the disease, there is convergent evidence for hippocampus involvement. Alterations in this area have been documented by both neuroimaging and postmortem studies [1,2]. Based upon pharmacological challenge and postmortem chemistry, glutamate transmission decrease appears to be one of the prevailing mechanistic explanations of the disease [3]. Numerous 1H-MRS studies have focused on assessment of glutamate and glutamine concentration in the hippocampus in schizophrenia [4,5]. Here, we present 1H-MRS measurements of glutamate (Glu), glutamine (Gln), N-acetylaspartate (NAA), and GABA in the hippocampus in patients with schizophrenia at 3T.

METHODS

We measured Glu, Gln, NAA and GABA levels in patients with schizophrenia in comparison with matched normal controls at 3T. We enrolled 13 volunteers with schizophrenia with an average age of 41.1 yrs and 14 normal volunteers with an average age of 33.5 yrs. Amongst the schizophrenia subjects, 3 subjects were not medicated at the time of the brain scan, whereas 10 subjects were on a drug regimen. No medication changes were made. Schizophrenia volunteers were recruited via a local Schizophrenia Research Clinic; at their initial visit, the subjects underwent a diagnostic workup, including a psychiatric history, a urine toxicology screen, and a battery of standardized assessments of positive, negative, and cognitive symptoms. Psychiatric symptom assessments comprised the Positive and Negative Syndrome Scale and the Clinical Global Impression Scale. On the day of the scan, the subjects were tested for illicit drug use where necessary.

MRS experiments were carried out on a whole-body Philips 3T scanner (Philips Medical Systems). A standard birdcage head RF coil was used for transmission and signal reception. Data were collected from a single voxel of 50×15×15 mm that was placed over the left hippocampus, as shown in Fig. 1. Glu, Gln, and NAA were measured using a triple-refocusing method [6], with an echo time of 115 ms. GABA was measured using difference editing (MEGA) [7] at TE = 70 ms. MP-RAGE (*m*agnetization *p*repared *ra*pid *g*radient *e*cho) images were used for voxel positioning. MRS data were acquired in 32 blocks, each with 16 averages, with repetition time of 2 s (scan time 17 min). The data were corrected for field drift using the NAA singlet prior to the summation of the data. The data were apodized with a 1-Hz exponential function. LCModel software [8] was used to analyze the spectra. The metabolite concentrations were normalized with respect to Cr.

RESULTS AND DISCUSSION

Figure 1 presents *in vivo* spectra from the hippocampus of a normal volunteer (NV) and schizophrenia volunteers on-medication (SV-ON) and off-medication (SV-OFF), obtained with the triple refocusing and GABA editing methods. In triple refocusing, the Glu and Gln C4-proton resonances are induced at 2.29 and 2.39 ppm, respectively, with negligible overlap. In difference editing, a GABA peak is generated at 3.0 ppm via subtraction between subspectra while the overlapping Cr peak at 3.03 ppm is canceled.

Figure 2 shows the concentration ratios of Glu, Gln, NAA, and GABA with respect to Cr, for 14 NV, 10 SV-ON, and 3 SV-OFF subjects. The Glu-to-Cr concentration ratio, [Glu]/[Cr], was observed to be similar between NV and SV-ON. However, [Glu]/[Cr] in SV-OFF was estimated to be significantly lower than (~30%) in both NV and SV-ON ($p = 0.02$ and 0.04, respectively). For Gln, the concentrations were about the same between the three groups ($p \geq 0.2$). [NAA]/[Cr] was observed to be reduced (by 10%) in SV-ON, but not in SV-OFF, compared to NV. So, the reduced NAA levels in SV-ON may be due to a treatment effect. The GABA data showed some difference between SV-OFF and SV-ON ($p = 0.05$). However, the result may not be conclusive because of the large variations in GABA estimates in NV and SV-ON. Further study on SV-OFF patients is currently underway.

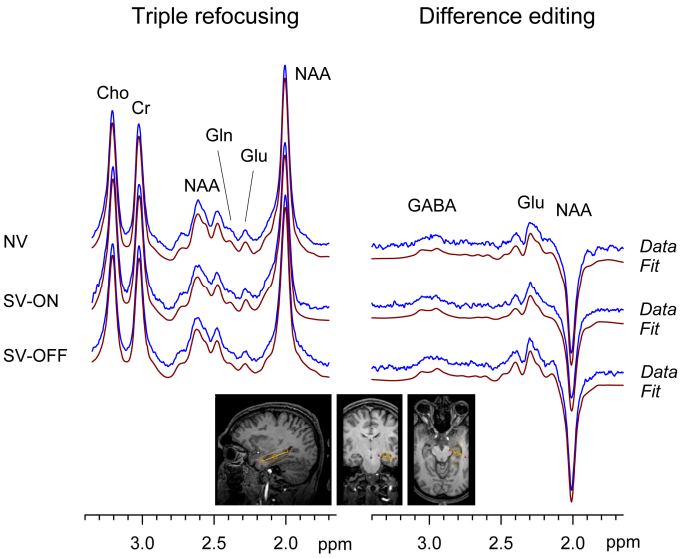

FIG. 1. In vivo spectra from the hippocampus of a normal volunteer (NV), a schizophrenia volunteer on medication (SV-ON) and a schizophrenia volunteer off medication (SV-OFF), obtained with triple refocusing (left) and GABA difference editing (right), are shown together with LCModel fits. The voxel size was 50x15x15 mm^3. TR = 2 s. NEX = 512. Data were apodized with a 1-Hz exponential function.

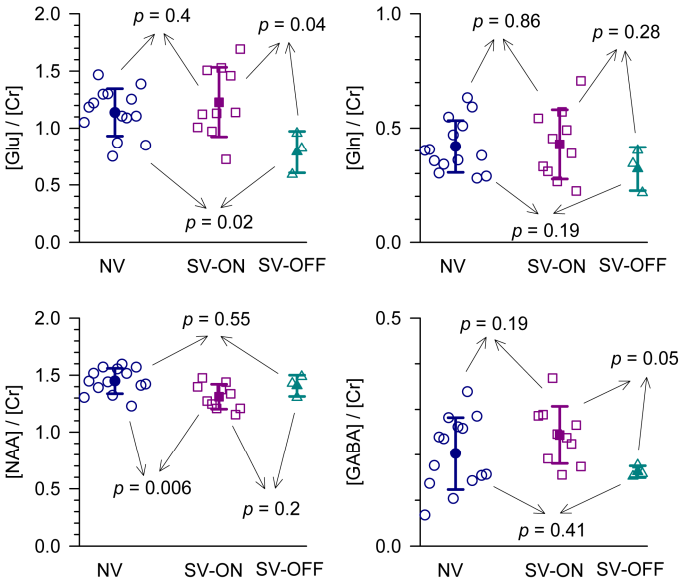

FIG. 2. Scatter diagrams of [Glu]/[Cr], [Gln]/[Cr], [NAA]/[Cr], and [GABA]/[Cr] for 14 normal volunteers (NV), 10 schizophrenia volunteers on medication (SV-ON) and 3 schizophrenia volunteers off medication (SV-OFF). Mean values and standard deviations are indicated with filled symbols and error bars, respectively.

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