Assessment of Prefrontal and Fronto-Striatal Glutamate Concentration in Healthy Children at 7T

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INTRODUCTION

The period of myelination and maturation of the prefrontal and frontal-striatal systems is a critical time for development of executive function and self-regulatory skills [1]. Disturbances of neural circuits including the frontal cortex and its striatal-thalamic-cerebellar connections contribute to development of a variety of childhood psychiatric disorders, especially those including atypical behavioral, emotional, and cognitive regulation [2]. Studies in younger children – including both patients and controls - are particularly valuable as they may help to assess the neuropathology early in the course of a disease. The main aims of our ^{1}H MRS study were to measure the concentration of the neurotransmitter glutamate (Glu), implicated in the neuropathology of several psychiatric disorders, in prefrontal and fronto-striatal regions, assess the reliability of Glu measurement, and evaluate the compliance with the MRI/MRS protocol at 7T in healthy children. The relationship between frontal Glu levels and neurobehavioral data was also examined in exploratory analyses.

METHODS

16 healthy typically developing children 5-10 years old (mean age 7.5 ± 1.6 years, 7 boys) participated in the IRB-approved study. The participants were initially screened by a telephone interview (Diagnostic Interview for Children and Adolescence-IV). A neuropsychological evaluation (tests of IQ, language, reading, neuromotor function, attention, spatial working memory, auditory working memory, and perception) performed in the morning was followed-up by a lunch break, a 10-20 min session in a mock scanner and a 7T-MRI/MRS examination. A questionnaire on the expected versus actual experience in the 7T scanner was presented to the child before and after the scan. The questionnaire examined the overall experience and specific issues of concern: dizziness, upset stomach, feeling uncomfortable, or loud noise. Responses were rated on a 1 (worst) to 10 (best experience) Likert scale. **MRI/MRS** was performed at 7T using a 32-channel Nova Medical volume head coil. The protocol included 3D-MPRAGE and single voxel ^{1}H MRS (TR/TE/TM=3000/14/26 ms, SW=3000 Hz, 2048 data points, NS=96 and 4 w/o water suppression). The VAPOR technique was used for water suppression. Spectra were acquired in the left hemisphere in the anterior cingulate (ACC), dorsolateral prefrontal cortex (DLPFC), striatum (STR) and the premotor cortex (PMC). The voxel volumes were 5-9 ml. Spectra were processed using the LCModel with an in-house created basis set, including 21 metabolites and macromolecules. Concentrations of glutamate (Glu), glutamine (Gln), myo-inositol (Ins), total choline (Cho), total creatine (Cr), N-acetylaspartate (NAA), and N-acetylaspartylglutamate were assessed. Linear mixed-effects models (LME) analyses with the Fisher's LSD as a post-hoc test were used to examine regional, sex- and age-related differences in metabolite concentrations. Data are presented as means ± standard deviations. Correlation analysis was applied to examine the relationship between neurobehavioral parameters and frontal Glu concentrations (ACC and DLPFC).

RESULTS

At 7T, the signal of the C-4 protons of Glu was well-resolved (Figure 1) and the overall reliability in assessment of Glu concentration was excellent (Figure 2; mean Cramér-Rao lower bounds (CRLB) for Glu: 5.7±2.0%). Glu concentrations in the DLPFC and PMC were higher ($p<0.0001$) than in the ACC and STR, which had the lowest Glu concentration. Figure 2 also shows that Gln and NAAG was measured with a relatively good reliability. The Gln and NAAG concentrations did not differ among the studied cortical regions. DLPFC tended to have the highest concentration of Ins, NAA ($p<0.05$ compared with ACC and STR) and Cr ($p<0.05$ compared with ACC, $p=0.06$ compared with STR). No regional differences in Cho were detected. The LME analyses did not reveal any age- or sex-related differences in any of the evaluated metabolite.

Both the pre- and post-scan mean ratings were positive, although the actual experience was rated worse than anticipated (8.5 ± 2.0 vs. 5.9 ± 2.4,T-test: $p<0.05$). The mean ratings on dizziness, upset stomach, feeling uncomfortable, or loud noise were all positive, with a range between 6.4 (dizziness) and 9.1 (upset stomach), suggesting that the children did not experience discomfort.

Exploratory analyses revealed several significant negative correlations ($p<0.05$) between test scores and frontal Glu concentrations, in particular for measures evaluated in the tests of intelligence (SB-V test) and language performance (CELF-4).

CONCLUSION

In agreement with previous 7T data in adults [3], Glu can be measured with high reliability with 7T single voxel ^{1}H MRS in children. Improved reliability was also observed for other metabolites, including NAAG and Gln. The MRI/MRS protocol of 45 min duration was well tolerated. The data from our study are encouraging for future 7T studies in children with neuropsychological disorders.

Figure 1

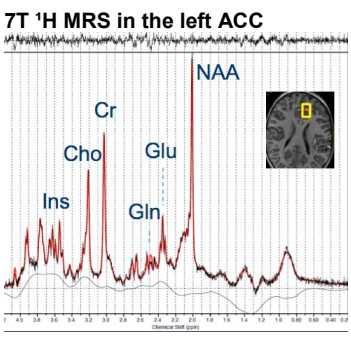


Figure 2

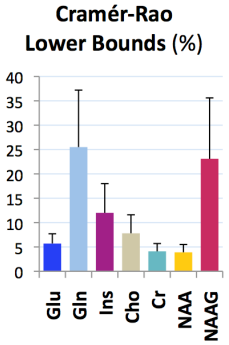
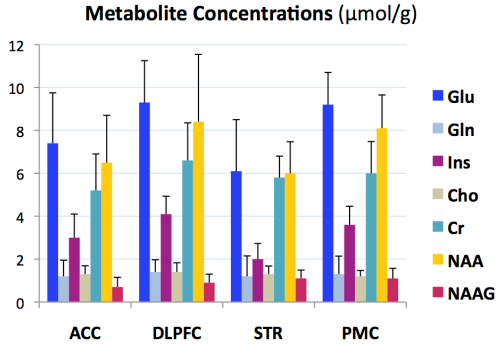


Figure 3



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