Verbal Memory Function, Glutamate, and Cerebral Blood Flow in Older Adults with Schizophrenia

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Target audience: Researchers interested in schizophrenia, MRS, and ASL.

Introduction: Memory impairments, a subset of the cognitive impairments associated with schizophrenia (SZ), are associated with poorer functional outcomes and lower quality of life measures[1]. Older adults with SZ have significant memory impairments when compared to healthy age-matched controls, and the pathophysiology of these memory impairments is poorly understood. With the number of older individuals with SZ expected to increase, there is a critical need for treatments and interventions tailored to older adults with SZ to improve functional outcomes and quality of life. As a first step in understanding the neurobiology of memory impairments, MRS and ASL were used to assess glutamate (Glu), which has been implicated in memory formation and SZ, and cerebral blood flow (CBF), which is coupled to tissue metabolism. Thus, assessments of declarative verbal memory, Glu, and CBF from brain regions associated with verbal memory function (hippocampus and anterior cingulate) in older adults with SZ were conducted.

Methods: Stable, chronic adults with SZ (5 younger (YSZ), 5 older (OSZ)) and age-matched healthy controls (4 younger (YHC), 4 older (OHC)) were recruited for this study. Each participant was scanned using a Siemens TIM Trio 3T MRI system with a 32-channel phased array head coil. Voxels were placed in the anterior cingulate (AC), left hippocampus (LHP), and right hippocampus (RHP). PRESS spectroscopic sequence parameters were: TR/TE=2000/30ms, AC VOI = 6cm^3, AC NEX= 128, LHP & RHP VOI = 4.5cm^3, LHP & RHP NEX = 256, 2.5kHz spectral width, 2048 complex points). A water reference (NEX=16) was acquired for phase and eddy current correction as well as quantification. Simulated metabolite basis sets were generated in GAVA and imported into LCModel for quantification[2,3]. Psuedo-Continuous Arterial Spin Labeling (pCASL) was applied with the following parameters[4]: TR/TE = 4000/16ms, FOV = 220x220mm, Number of slices = 23, Slice thickness = 5 mm, Voxel size = 3.4x3.4x5.0 mm^3, Bandwidth=1594 Hz/pixel, 136 measurements, labeling offset = 90 mm, labeling duration of 1.85 s, post labeling delay of 0.93s. ASL data were processed with pCASL MATLAB scripts and with SPM8 using ASL tbx[5]. Regional CBF (rCBF) from the AC, LHP, and RHP were quantified from the regions corresponding to the spectroscopic voxel. Declarative verbal memory was assessed with the Hopkins Verbal Learning Task – Revised. Two-way ANOVAs were computed with age and group as main effects. Pearson product moment correlations were computed to assess the association between HVLT-R, Glu, and rCBF.

Results: Boxplots showing LHP rCBF and Glu levels as well as HVLT-R scores from the 4 groups are shown in Figure 1. The quality of the spectra were excellent across groups as evidenced by average signal-to-noise ratio and full width half maximum reported by LCModel ranging from (mean ± stdev): 40.8 ± 6.8 and 0.031 ± 0.01 ppm for the AC; 14.7 ± 2.1 and 0.054 ± 0.02 ppm for the LHP; and 14.3 ± 3.8 and 0.054 ± 0.03 ppm for RHP. On average, Glu CRLBs across groups were 3.3% for the AC, 6.9% for the LHP, and 7.3% for the RHP. Two-way ANOVAs for Glu levels showed a significant interaction in the RHP (p<0.05) and a trend (p=0.117) in the LHP. Glu levels in OSZ were observed to be lower than OHCs in all 3 regions. Although not statistically different on two-way ANOVAs, rCBF in the OSZ was lower than the other groups in all regions with large to medium effect sizes (Cohen's d) between older and younger SZ for AC (d= 1.2), RHP (d=0.9), and LHP (d=0.82). Two-way ANOVA on HVLT-R scores showed a trend for age x group interaction (p=0.137), and post-hoc tests revealed that OSZ has lower verbal memory performance than OHC (p<0.02). In older adults, LHP Glu and CBF were moderately correlated at r=-0.3 while in younger adults, Glu and CBF were correlated in ACC (r=0.411) and LHP (r=-0.306). In older adults, there was a strong correlation between HVLT-R score and Glu levels from the LHP (r=0.710).

Discussion: To our knowledge, this is the first study to measure HVLT-R, Glu levels, and CBF in older adults with SZ and compare them to YSZ and healthy age-matched controls. Results showed OSZ had lower Glu, lower rCBF, and poorer memory function than OHC groups. The correlation analyses suggest that compromised anterior cingulate and hippocampal glutamatergic and metabolic function likely contributes to memory impairments in OSZ. Future studies will investigate the impact of an intervention such as exercise or TMS to improve memory function on rCBF and glutamate levels in OSZ.

References: [1]Al-Uzri MM et al. Br J Psychiatry 2006;189:132. [2]Soher Bj et al. J Magn Reson 2007;185:291.[3]Provencher SW. Magn Reson Med 1993;30:672. [4]Wu WC et al. Magn Reson Med 2007;58:1020.[5]Wang Z et al.Magn Reson Imaging 2008;26:261.

Figure 1. Representative plots of LHP CBF (a), LHP Glu (b), and HVLT-R scores (c) highlight lower Glu and CBF levels observed in OSZ as well as their poorer declarative verbal memory performance. A representative LHP spectrum is shown in (d) showing the excellent quality data from this deep brain structure.