# Multimodal assessment of medial temporal lobe function in schizophrenia

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## Introduction

The goal of this study was to examine the relationship between medial temporal lobe (MTL) biochemistry measured with proton magnetic resonance spectroscopy (^{1}H-MRS), MTL activation measured with functional magnetic resonance imaging (fMRI), and integrity of the major white matter tract from the hippocampus measured with diffusion tensor imaging (DTI) tractography in healthy and schizophrenia subjects. It was hypothesized that these measures would differentiate groups and be related to relational learning performance in both groups.

## Methods

Seventeen stable outpatients with schizophrenia treated with antipsychotic medication and 17 healthy volunteers participated in this study. MR scanning was conducted on at 3T (Philips Achieva) using an 8-channel head coil. DTI data was acquired with a spin echo single shot, echo-planar imaging sequence with sensitivity encoding (SENSE=2.5) encoding (2.2mm isotropic voxels, 212 X 212mm FOV, 96x96 acquired matrix), TR/TE = 6338/69ms, 60 slices for whole brain coverage, with diffusion gradients applied along 32 noncollinear directions at a b-factor of 700 s/mm$^2$. A minimally weighted image with b=0 s/mm$^2$ was also acquired. For tractography, regions of interests (ROIs) were drawn on the axial and coronal slices where the fornix was most prominent. 3D tract reconstruction was automatically computed in DTIStudio using the Fiber Assignment by Continuous Tracking algorithm (FACT). Fibers that did not anatomically fall within the fornix were eliminated through visual inspection using a white matter atlas as a guide (1). Inter-rater reliability was good (intraclass correlation ICC = 0.9). Spectra were acquired with a point resolved pulse sequence ('PRESS', TR =2000 ms, TE=35 ms, 1024 points, 2000 Hz spectral width, 256 averages water-suppressed and 16 averages without water suppression) from 1.5X 1.5 X 2.0 cm voxel placed in the left hippocampal region. Water suppression was achieved using three chemical-shift selected (CHESS) pre-saturation pulses. Spectra were analyzed using fully automated curve fitting software, 'LCModel' (2). Spectra were normalized to the unsuppressed water signal. Metabolites were corrected for the proportion of CSF in the spectroscopic voxel. Figure 1 illustrates spectroscopic voxel placement, fornix tractography, and a representative spectrum. fMRI was acquired with single-shot gradient echo, echo-planar imaging. Volumes were obtained with ascending oblique slices parallel to the hippocampal axis (TR = 2.3s, TE =30, flip angle =70, slice thickness=2.5, gap=0.5, slices=44, and FOV=240X240) while subjects performed the hippocampal-dependent relational learning task, transverse patterning. fMRI analyses were conducted with SPM2.



Figure 1. Illustration of voxel placement, fornix tractography, and representative spectrum.

MRS Voxel Placement   DTI tractography: Fornix

Hippocampal Spectrum

## Results

A logistic regression was used to test if hippocampal fMRI BOLD signal change, fornix tractography FA, and hippocampal glutamate predicted group membership. This proved to be a good model (Chi-square = 14.9, p = 0.002; Cox and Snell $R^2$= 0.45). The model resulted in 80% prediction. The best predictor was fornix FA (p < 0.05), followed by hippocampal glutamate (p = 0.1) and hippocampal BOLD signal change (p = 0.25). Removing glutamate or hippocampal BOLD or both variables from the model resulted in a poorer model fit. Linear regression models were tested to determine if fMRI hippocampal BOLD signal, fornix FA, and hippocampal glutamate predicted relational learning in healthy and schizophrenia subjects. Linear regression models were tested for each group. Results revealed that multimodal MTL measures formed a good model for predicting relational learning in healthy ($R^2$ = 0.81, F(10) = 9.8, p < 0.005) but not schizophrenia ($R^2$=0.13, F(11=0.48, p = 0.7) subjects.

## Discussion

Results support the hypothesis that MTL activation, neurochemistry, and the fornix integrity together predict healthy and schizophrenia subject membership. Subjects with schizophrenia have altered MTL activation, elevated hippocampal glutamate, and compromised fornix integrity. These results support the hypothesis that relational learning relies on the MTL in healthy but not schizophrenia subjects.

References: 1) Mori et al. (2005) MRI atlas of human white matter. Elsevier B.V., Amsterdam, The Nederlands.
2) Provencher SW (2001). NMR Biomed 14(4):260-4