

# Brain Biochemical Abnormalities and Cognitive Impairments in Patients with Type 2 Diabetes and Major Depression: A Combined <sup>1</sup>H-MRS and Neuropsychological Study

Shaolin Yang<sup>1,2</sup>, Olusola Ajilore<sup>1</sup>, Melissa Lamar<sup>1</sup>, Laura Korthauer<sup>1</sup>, and Anand Kumar<sup>1</sup>

<sup>1</sup>Department of Psychiatry, University of Illinois at Chicago, Chicago, IL, United States, <sup>2</sup>Department of Radiology, University of Illinois at Chicago, Chicago, IL, United States

## Introduction

Type 2 diabetes and major depression are mutual risk factors [1,2]. Biochemical abnormalities were reported in patients with either disease alone or in combination and the consistent findings are elevated concentrations of *myo*-inositol (Ins) and/or choline-containing compounds (tCho) in cortical and subcortical regions. These diseases may be also linked to cognitive impairment. In the current study, we measured metabolites in focal brain regions that are implicated in the circuits of depression using <sup>1</sup>H MR spectroscopy (MRS) and conducted a battery of neuropsychological tests on subjects to assess cognitive function. We examined whether brain biochemical abnormalities would be correlated with cognitive performance.

## Materials and Methods

Four groups of subjects, healthy control (HC, n=40), patients with major depression alone (MDD, n=39), with type 2 diabetes alone (DC, n=17), and with both diseases (DD, n=20), were recruited from relevant clinics and the local area community. Subject groups met current clinical standards for a diagnosis of either depression and/or diabetes as determined by clinical interview, psychiatric evaluation, medical record review, and laboratory testing.

A battery of neuropsychological tests was conducted on each subject and five neuropsychological domains were the focus of the current study: verbal memory (California Verbal Learning Test-2<sup>nd</sup> Edition immediate total recall and long delay free recall, Wechsler Memory Scale-3<sup>rd</sup> Edition (WMS-III) Logical Memory I and II); visual memory (WMS-III Visual Reproduction I and II); attention & information processing (Stroop Color and Word trials, Trail Making Test A and Wechsler Adult Intelligence Scale 3<sup>rd</sup> Edition (WAIS-III) Digit-Symbol Coding); executive function (Delis-Kaplan Executive Function System Category Switching, Trail Making Test B, Stroop Interference Score, WAIS-III Backwards Digit Span, and Self-Ordered Pointing Task Total Errors); and language (Animal Fluency total correct, percent in cluster, and association index). Raw scores from the neuropsychological battery were standardized using healthy control sample means and standard deviations. Relevant scores were reversed so that high scores consistently reflected better performance. Composite Z scores were calculated for each domain listed above.

The <sup>1</sup>H-MRS scans were performed on a Philips Achieva 3T scanner using a single-voxel PRESS sequence (TR/TE=3000/35 ms, NEX=128). Spectral data were acquired from rostral anterior cingulate cortex (ACC) ( $2 \times 2 \times 2 \text{ cm}^3$ ), frontal white matter (FWM) ( $2 \times 1 \times 2 \text{ cm}^3$ ), and head of caudate nucleus (Caud) ( $1 \times 2 \times 2 \text{ cm}^3$ ) (see Fig.1). Spectral quantification was performed in LCModel [3] using unsuppressed water signal for scaling. Only the metabolite concentrations with Cramer-Rao Lower Bound less than 20% were included in data analysis.

Between-groups differences in metabolite concentration and cognitive performance were assessed using an analysis of covariance (ANCOVA) controlling for age, sex, and education. Correlations between metabolites and composite Z scores were analyzed using partial Pearson's product-moment correlations controlling for age, sex, and education. Significant level was set at 0.05. Statistical analyses were performed using SPSS v18.

## Results and Discussion

Ins and tCho were significantly different between subject groups in respective brain regions (all  $F$ 's  $>3.37$ ,  $p$ 's  $<0.02$ ), but no significant group difference was found in cognitive function. However, there were significant correlations between concentrations of tCho and composite Z scores of cognitive functions in patients with both type 2 diabetes and major depression: tCho in FWM was negatively correlated with executive function ( $r(14)=-0.53$ ,  $p=0.04$ ) and language ( $r(14)=-0.60$ ,  $p=0.01$ ); tCho in ACC was negatively correlated with executive function ( $r(15)=-0.51$ ,  $p=0.03$ ); tCho in Caud was negatively correlated with verbal memory ( $r(9)=-0.80$ ,  $p=0.003$ ) and visual memory ( $r(9)=-0.73$ ,  $p=0.009$ ), respectively. The concentration of Ins in FWM of patients with type 2 diabetes alone was negatively correlated with attention & information processing ( $r(9)=-0.63$ ,  $p=0.03$ ), as was Ins in Caud of patients with both diseases ( $r(6)=-0.73$ ,  $p=0.03$ ). Ins was negatively correlated with visual memory in FWM ( $r(11)=-0.567$ ,  $p=0.043$ ) and ACC ( $r(11)=-0.55$ ,  $p=0.05$ ) of patients with diabetes alone and in ACC of healthy controls ( $r(30)=-0.43$ ,  $p=0.01$ ).

All the significant (negative) correlations between tCho and cognitive function were observed in patients with both type 2 diabetes and major depression. In contrast, the significant correlations between Ins and visual memory were seen in controls and patients with type 2 diabetes alone, but not in patients with both diseases. This finding is similar to a recent report that the correlation between Ins and visuospatial impairments seen in healthy controls is not present in patients with both diseases [2]. Further study is needed to determine the reasons for the different patterns of correlations among subject groups.

**References:** [1] Ajilore O et al., Neuropsychopharmacology 2007; 32:1224-1231. [2] Haroon E et al., Psychiatry Res. 2009; 171:10-19. [3] Provencher SW, MRM 1993; 30:672-679.

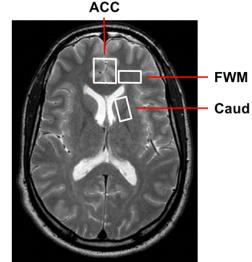


Fig. 1. Voxel placement in 3 brain regions (rostral anterior cingulate cortex, ACC; left dorsolateral frontal white matter, FWM; left head of caudate nucleus, Caud)

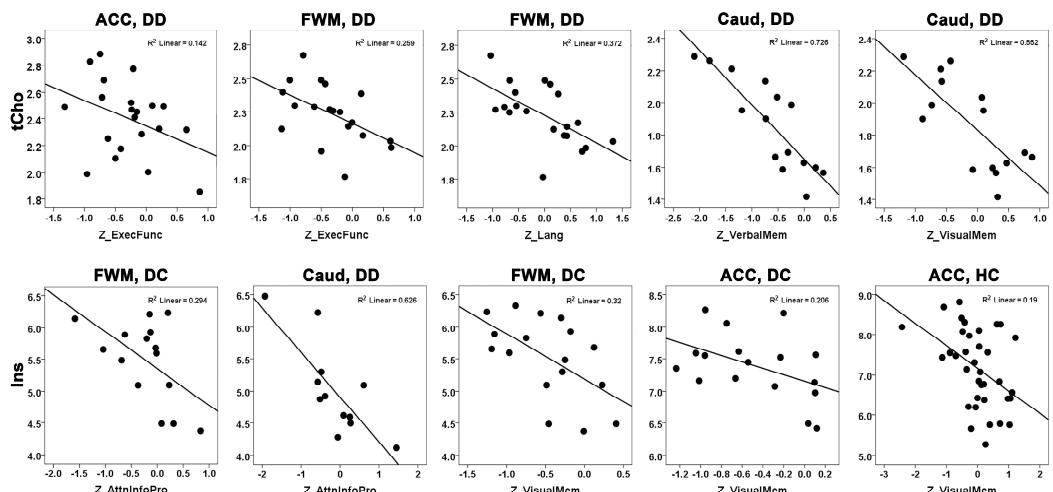


Fig. 2. Scatterplots of Ins or tCho with Z scores of cognitive function