Additive Effects of Type 2 Diabetes and Major Depression on Brain Biochemical Abnormalities
Shaolin Yang, Olusola Ajilore, Minjie Wu, Melissa Lamar, and Anand Kumar
1Department of Psychiatry, University of Illinois at Chicago, Chicago, IL, United States. 2Department of Radiology, University of Illinois at Chicago, Chicago, IL, United States

Introduction
Type 2 diabetes and major depression are mutual risk factors [1,2]. The accumulated evidences suggest that the combination of type 2 diabetes and major depression brings about more striking abnormalities in neuroanatomy, biochemistry, and cognitive functioning than type 2 diabetes alone [1-3]. However, it is unclear whether the reported abnormalities in diabetes and depression are more severe than in depression alone. The purpose of this study was to examine whether type 2 diabetes and major depression have additive or interactive effects on brain biochemical abnormalities using proton magnetic resonance spectroscopy (1H-MRS) at 3T. We hypothesized that (1) patients with both type 2 diabetes and major depression would exhibit combined effects of each disease on brain biochemical abnormalities, and (2) the biochemical abnormalities shared by two individual disorders, particularly higher tCho and Ins, would be more severe in patients with both diseases than patients with type 2 diabetes or major depression alone.

Materials and Methods
Four groups of subjects, healthy controls (HC, n=40), with type 2 diabetes alone, i.e., diabetic control, (DC, n=17), and with both type 2 diabetes and major depression (DD, n=24), age 30 and older, were recruited in the greater Chicago area through flyers, local advertisements, and outpatients clinics. Written informed consent was obtained from every subject. Each patient met current clinical standards for diagnosis of either major depression and/or type 2 diabetes as determined by formal clinical interview, psychiatric evaluation, medical record review, and laboratory testing.

1H-MRS scans were performed on a Philips Achieva 3T scanner with an 8-element phased-array head coil. A single-voxel PRESS sequence (TR/TE=3000/35ms) was applied. Each 1H-MRS scan included 128 averages with a 16-step phase cycling. Unsuppressed water signal was acquired at the beginning for eddy current correction and scaling in the spectral quantification. The spectra were acquired from three brain regions: rostral anterior cingulate cortex (ACC) (2×2×2 cm3), left dorsolateral frontal white matter (FWM) (2×1×2 cm3), and the subcortical regions encompassing the head of left caudate nucleus (Caud) (1×2×2 cm3) (Fig. 1). Spectral quantification was carried out in LCModel [4]. Only the metabolite concentrations with a Cramer-Rao Lower Bound (CRLB) less than 20% were included in the statistical analysis.

Two-way analysis of covariance (ANCOVA) was performed on the data for each metabolite of interest, with type 2 diabetes and major depression as two factors controlling for age, sex, and education. In addition, differences in the concentrations of metabolites between 4 subject groups were assessed using ANCOVA controlling for age, sex, and education too. Post hoc tests on the metabolites showing significant ANCOVA main effects were performed with Fisher’s least significant difference (LSD) test. All statistical analyses were carried out using SPSS ver. 18. Significant level was set at 0.05.

Results and Discussion
There was no significant difference in age, gender, and education between groups. Type 2 diabetes (with or without major depression), compared with free of type 2 diabetes status, was associated with higher concentration of Ins in ACC (5%, F1,105=3.15, p=0.08, approaching significance), FWM (15.6%, F1,84=15.03, df=, p<0.001), and Caud (27.1%, F1,77=20.67, p<0.001) and also higher Ins/total creatine (tCr) in ACC (5.6%, F1,105=5.98, p<0.02), FWM (14.9%, F1,84=15.20, p<0.001), and Caud (29.8%, F1,77=28.34, p<0.001), higher tCho/tCr in Caud (6.3%, F1,93=4.77, p=0.03) and ACC (3.6%, F1,105=3.57, p=0.06, approaching significance), and mildly higher Glx/tCr (4%, F1,105=3.53, p=0.06, approaching significance) in ACC. In contrast, major depression (with or without type 2 diabetes), compared with free of major depression status, was associated with higher concentration of tCho (5.4%, F1,84=6.64, p=0.01) and tCho/tCr (5.3%, F1,84=5.46, p=0.02) in FWM and mildly lower concentration of NAA (-3.5%, F1,105=3.84, p<0.05) and mildly lower NAA/tCr (-3%, F1,105=4.12, p=0.04) in ACC. Two-way ANCOVA showed no significant interaction between type 2 diabetes and major depression on any of the above metabolites.

Patients with type 2 diabetes and major depression showed combined effects of each disease on brain biochemical abnormalities, which followed an additive model. As a result, patients with both type 2 diabetes and major depression had most of the biochemical abnormalities that were seen in patients with each disease alone and exhibited the highest level of abnormalities in mainly tCho and Ins when synergistic effects existed (see Fig. 2). As Ins is the glial marker and tCho involves cell membrane synthesis, these findings suggest additional glial process/abnormalities due to the comorbid conditions.

References