

Altered Resting-State Connectivity of Hippocampus with Default Mode Network In Type 2 Diabetes

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Purpose:

Diabetes mellitus (DM) is highly prevalent worldwide, and is a major risk factor for cognitive impairment, vascular dementia and Alzheimer's disease (AD).^{[1][2][3]} Type 2 DM accelerates brain aging, leads to glucotoxicity, neurotoxicity and alters insulin resistance, and insulin transport to the brain through the blood-brain barrier. Therefore, inadequate insulin delivery may affect perfusion and cortical activity in cognitive associative networks with high energy demands^[1]. Intranasal insulin (INI) administration delivers insulin directly to the brain^[5] where it regulates neuronal signaling, perfusion and other processes.^[4] INI administration improved cognition and memory in healthy young and older people, but also in patients with cognitive impairment or mild AD^[2] and type 2 DM^[7] and increased baseline perfusion^[8]. The mechanism for INI-related improvement of memory (hippocampus function) remains unclear, and thus we hypothesized that INI may acutely modify signaling between the hippocampus and resting-state functional network. We therefore acquired resting state fMRI to identify functional connectivity between the hippocampus and default mode network (DMN) after the administration of intranasal insulin or placebo in older adults with and without type 2 DM.

Materials and Methods:

Design: Pilot, randomized, double-blind, placebo controlled study with cross-over design of intranasal insulin or saline intervention in type 2 DM and healthy older adults.

Subjects and Image Acquisition

Fourteen healthy (4M/10F, 60.1±9.9 years old) and 15 T2DM patients (8M/7F 62.1±7.9) were enrolled and signed an informed consent approved by the BIDMC Institutional Review Board. One DM subject was excluded from analyses due to motion artifacts within their MRI.

Each subject received 40IU of insulin (Novolin^R, Novonordisk) or sterile saline in a random order on two subsequent study days using a Via Nase device (Kurve Technologies, Inc). Resting state fMRI was performed 26.5±9.3 min after INI administration. Anatomical and functional studies were done on a 3T GE HDx MRI scanner, using the 3-D magnetization prepared rapid acquisition gradient echo sequence (MP-RAGE): PrepTime=1100ms (TR=6.6 ms, TE=2.8ms), FA=15, Bw=31.25 Hz, FOV=24, SL Thick =3mm, 52 SL, Matrix192x256, and resting state fMRI: TE=27ms, TR=3000ms, FA=60ms, FOV=25, SL Thick=5mm, Matrix=64x64, NEX=1.

Data Analysis

Statistical Parametric Mapping (SPM5) was used to preprocess data, and resting-state fMRI Data Analysis (REST 1.8) was used for the network correlation analysis. For each subject under each condition (insulin, placebo), the left and right hippocampus were selected as seeds and the correlations of time course between seeds and DMN regions were calculated. Connectivity maps were compared between the insulin and placebo condition for each subject in the DM and control group using a paired T-test. Two sample T-test was used to compare DM vs. control for between group comparisons. The threshold was corrected with Alphasim (Paired t test: p<0.05 and the minimum cluster size was set 270mm³; Two sample t test: p<0.01 and a minimum extent=270mm³).

Table 1: DM and Healthy contrast

| Region | Left Hippo as ROI | | | Right Hippo as ROI | | |
|--------|-------------------|------|--------------|--------------------|------|--------------|
| | cluster | size | Peak t score | cluster | size | Peak t score |
| MPFC | 135//10 | | 3.7//3.0 | 133//85 | | 3.5//2.9 |
| IPC | 25//0 | | 3.9//0 | 77//0 | | 4.2//0 |
| PCC | 22//17 | | 3.2//2.7 | -/- | | -/- |

PCC: Posterior cingulate cortex; MPFC: Medial prefrontal cortex; IPC: Inferior parietal cortex; -: no significant relationship

Results:

Insulin vs. placebo comparisons for diabetic and control subjects are displayed in the Fig.1. The DM subjects on insulin demonstrated increased connectivity between the hippocampus and several DMN regions as compared to the placebo (Table 1). Comparisons between the DM and control groups following INI vs. placebo administration are shown in Fig.2. On placebo, connectivity between the hippocampus and DMN was stronger in controls as compared to DM subjects. On insulin the connectivity increased more in DM group as compared to control subjects.

Conclusion:

Our preliminary results suggest that intranasal insulin administration may have acute effects on connectivity between hippocampus and DMN in older people with type 2 DM. Larger longitudinal studies are needed to validate these results.

References:

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Funding acknowledgements: V.N. has received grants from the NIH-NIDDK (5R21-DK-084463-02), NIH-NIA (1R01-AG-0287601-A2) include the Harvard Clinical and Translational Science Center(National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award #HL119001-04B) and financial contributions from Harvard University and its affiliated academic health care centers).

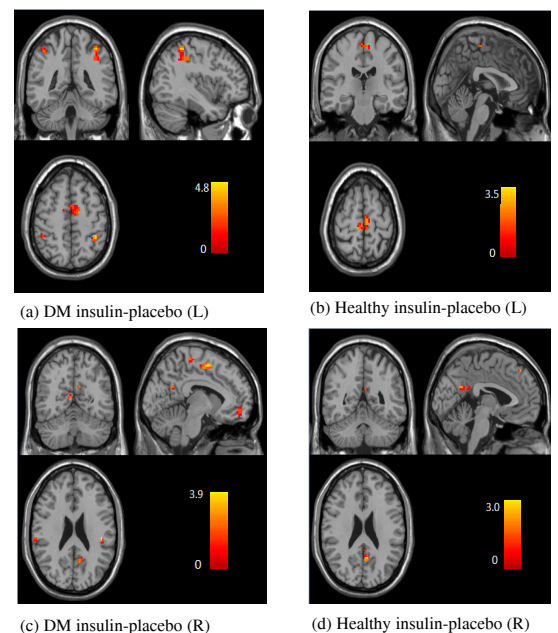


Figure 1. (a) and (b) are the results using left hippocampus as the seed. (c) and (d) are the results using right hippocampus as the seed, the threshold was set as p<0.05, a minimum cluster extent = 270mm³(corrected)

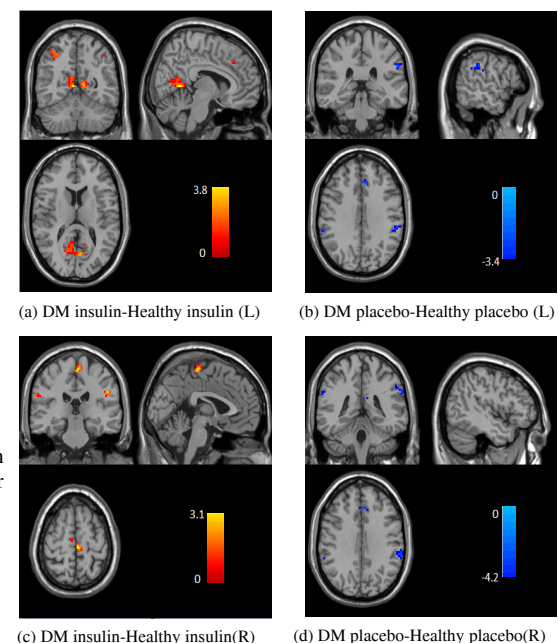


Figure 2. (a) and (b) are the results using left hippocampus as the seed. (c) and (d) are the results using right hippocampus as the seed, the threshold was set as p<0.01, a minimum cluster extent = 270mm³ (corrected)