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The brain default mode network in patients with type 1 diabetes and hypoglycemia unawareness under different blood glucose levels

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Introduction

Cognitive dysfunction in patients with diabetes mellitus is well documented in the literature. Many investigators have chosen to focus on the impact of type 1 diabetes (T1DM) on brain function with the hope of excluding the confounding effects of hypertension, vascular disease, and other co-morbidities seen in patients with type 2 diabetes. Patients with type 1 diabetes have been found to have white matter microstructural defects [1] and reduced gray matter density [2], but whether these structural changes are preceded by changes in the default mode network is unknown. In the present study we aimed at characterizing the default mode network of individuals with T1DM and healthy controls during resting-state fMRI (RS-fMRI) studies, while their blood glucose level was controlled by hyperinsulinemic clamps.

Methods

Six subjects with T1DM and hypoglycemia unawareness and seven control subjects with similar age, gender and body mass index were recruited for the study. Exclusion criteria for both groups of subjects include history of stroke, seizures, neurosurgical procedures, or arrhythmias, and use of drugs that can alter glucose metabolism (other than insulin for the patients with diabetes). RS-fMRI studies were performed on a 3 T scanner with GRE-EPI (300 volumes of 30 slices, 192×192 mm^2 field of view, 3 mm thickness, 0.8 mm gap, TR = 2000 ms, TE=30 ms, flip angle = 77°, matrix 64x64, for a $3 \times 3 \times 3$ mm^3 voxel resolution, scan time = 10 min). High resolution 3D T1-weighted acquisitions were also performed for anatomical references. Subjects underwent a two step hyperinsulinemic (2.0 mU/kg/min) clamp study while in the scanner. At first, blood glucose was maintained at 100 mg/dL and then it was allowed to drop to 50 mg/dL. RS-fMRI measurements were performed as soon as the desired levels of glucose concentration were stable for at least 10min. Extraction of the default mode network was performed with independent component analysis (ICA) using Brain Voyager QX (Brain Innovation, Maastricht, The Netherlands). Finally, we used self-organizing group analysis as described in [3] and [4], in order to identify across-subject sets of components which are spatially similar to each other, for each combination of patient/control and glycemic condition.
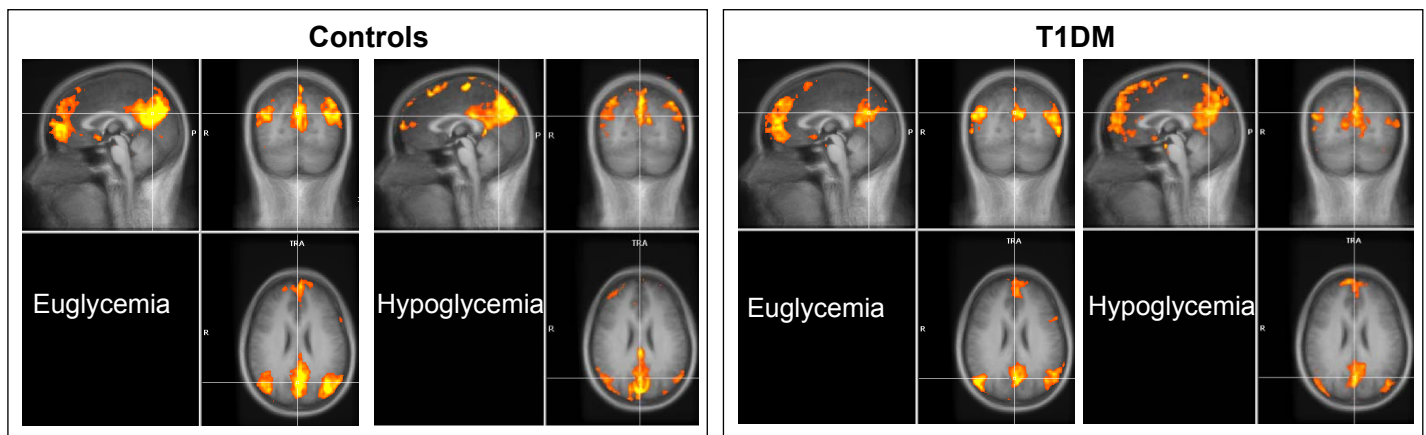
Results and Discussion

Figure 1. *Average default mode network as identified by ICA in the group of controls and subjects wth T1DM, in conditions of normal glycemia and hypoglycemia.Colors from orange to yellow indicate inter-subjects average z-score from 1 to 3.*

The classical default mode network was readily identified by the independent component analysis algorithm under normal glycemic conditions in both patients and controls (Figure 1). From the maps of the default mode network averaged across subjects for each condition, decreased connectivity in the precuneus, posterior cingulate and parietal cortex were observed in patients as compared to controls at baseline. Since a relatively small number of patients were enrolled, we were not able to determine if such imaging findings correlated with the severity of cognitive dysfunction in patients with T1DM. Nevertheless, the results showed MRI changes in T1DM which are consistent with known outcomes of the disease [1-2]. Interestingly, during the hypoglycemic condition, the prefrontal cortex lacked functional connectivity to the other regions of the default mode network in healthy controls, which might suggest an involvement of this region to the stress response induced by hypoglycemia. On the other hand, this response was largely reduced in T1DM unaware patients.

In conclusion, both glycemic levels, as well as a metabolic disease as diabetes, were shown to affect the default mode network as measured by RS-fMRI in the human brain.

References: [1] Kodl et al. Diabetes 2008;57:3083 [2] Musen et al. Diabetes 2006;55:326 [3] Esposito et al. NeuroImage 2005;25:193 [4] Esposito et al. MRI 2008;26:905.