

Cerebral Atrophy in Streptozotocin-induced Type 1 Diabetic Rats Revealed by Voxel-based Morphometry

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Introduction Clinical neuroimaging studies have shown that chronic diabetes causes cerebral atrophy and white matter lesions [1]. Diffuse cerebral atrophy was also observed in a mouse model of streptozotocin (STZ)-induced type 1 diabetes at 8 months after induction of diabetes [2]. In both human and animal models, cerebral atrophy may have contributed to cognitive decline in the diabetic subjects [2,3,4]. Voxel-based-morphometry (VBM) is the most widely used method to analyze volumetric neuroimaging data in human studies [5]. In this study, we measured cerebral volumetric changes in a rat model of STZ-induced type 1 diabetes with VBM toolkit embedded in SPM and tissue probability maps (TPMs) for rat brain generated in-house.

Materials and methods Eight-week old male Sprague-Dawley rats, weighting 300.3±18.8 g, were used. Type 1 diabetes (n=17) was induced by a single-dose intraperitoneal (i.p.) injection of STZ (62 mg/kg). Control animals (n=15) received i.p. injection of the same amount of solvent (0.01 mol/L citric acid). STZ-treated rats with fasting blood glucose < 18.8 mmol/L on day 3 were excluded from the study. All rats were scanned at 4 weeks (4w) after diabetes induction on a 7 T/20 cm Bruker Biospec scanner under isoflurane anesthesia (1.8-2.5%, in pure O₂). A volume coil was used for RF transmission, and a 4-channel phase-array coil for signal detection. High resolution anatomical images were acquired with a RARE sequence with FOV 3.5 cm×3.5 cm, matrix size 512×384, slice thickness 0.58 mm, 54 slices, TR 5800 ms, TE_{eff} 40 ms, RARE factor 4 and 8 averages. VBM analysis of changes in grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) volumes was performed with 'SEGMENT' in SPM8 and the TPMs generated in-house. Unmodulated normalized tissue images were first generated for each animal using the in-house TPM templates. The resulting tissue images were then averaged respectively to produce three mixed group TPMs. Modulated normalized images containing volumetric information were then generated using the mixed group TPMs as the templates. These images were smoothed with a 0.2-mm FWHM Gaussian kernel, and compared voxel-wise with two-sample t-tests. Statistical significance was set to a threshold of p≤0.005 (uncorrected).

Results Compared to the control rats, the STZ-treated rats had significantly increased fasting blood glucose level (Fig. 1A) and decreased body weight after the onset of diabetes (Fig. 1B). The VBM results showed that the STZ-treated rats had diffuse gray matter atrophy in cortex (Cg1, Cg2, M2, M1, GI, S1, S1J, S1JO, S1BF, S1DZ, S2, RSA, AuD, AuV, Au1, V1M, V2L, V2MM, V2ML), amygdala (Amy), caudate putamen (Cpu), hippocampus (Hip), thalamus and periaqueductal gray matter (PAG) (Fig. 2A and a), and significant white matter atrophy in cingulum (cg), corpus callosum (cc), external capsule (ec), internal capsule (ic), cerebral peduncle (cp), optic tract (opt) and fimbria (fi) (Fig. 2B and b).

Discussion Many clinical neuroimaging studies have demonstrated that chronic diabetes is associated with progressive brain atrophy [1,6]. The most reported brain regions affected are cortex, hippocampus and cerebellum [4,7,8]. In a mouse model of STZ-induced type 1 diabetes, cerebral atrophy was observed in the primary motor/sensory cortex, primary visual cortex, caudate putamen, corpus callosum, internal capsule, hippocampus and cerebral peduncle at 8 months [2]. In this previous study, the volumes of brain regions were measured manually with a region-of-interest approach. In this study, we employed the VBM method to analyze the volumetric changes in the brain of STZ-induced type 1 diabetic rats. Significant cerebral atrophy was already evident at 4 weeks after induction of diabetes, which may be due to the fact that blood glucose was not controlled in our study and the conditions of the STZ-treated animals deteriorated quickly. In addition to the atrophic brain regions observed in the previous study [2], significant volume reduction was also observed in other brain regions such as cingulate cortex, granular insular cortex, retrosplenial agranular cortex, auditory cortex, Amy, thalamus, PAG and white matter structures. This can be partially, at least, attributed due to the voxel-based nature of VBM and its higher sensitivity in detecting small volumetric changes [5].

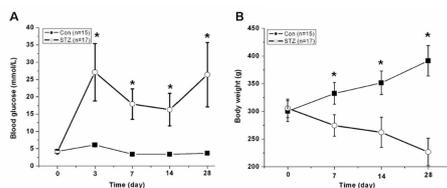


Figure 1. Compared to the control animals (Con), the STZ-treated (STZ) rats had significantly increased fasting blood glucose level (A) and decreased body weight (B). *p < 0.005 compared to Con.

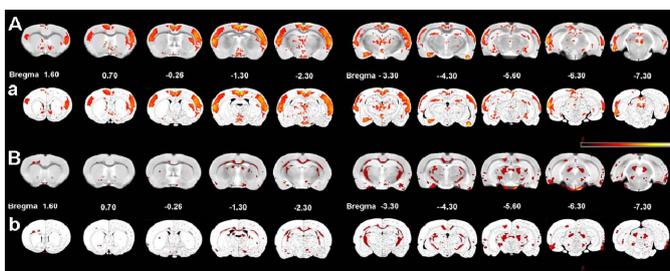


Figure 2. Coronal slices showing significant volume differences between the control rats and STZ treated rats at 4w after diabetes induction (p<0.005, uncorrected). Significantly reduced gray matter volume is seen in Cg1, Cg2, M2, M1, GI, S1, S1J, S1JO, S1BF, S1DZ, S2, RSA, AuD, AuV, Au1, V1M, V2L, V2MM, V2ML, Amy, Cpu, Hip, thalamus, PAG (A, a). Significantly reduced white matter volume is seen in cg, cc, ec, ic, cp, opt, fi (B, b).

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