Increased striatal iron accumulation in methamphetamine users

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Introduction: Recent studies in animal and *in vitro* models have provided preliminary evidence of the role of iron as a biomarker and potential source of methamphetamine (MA) induced toxicity.[1, 2, 3] However, the effects of MA administration on iron accumulation have not yet been demonstrated in human MA users. Magnetic resonance imaging (MRI) provides noninvasive methods to indirectly measure iron accumulation *in vivo* in human subjects. Iron is paramagnetic, and its presence shortens the transverse relaxation (T_2) time constant of nearby water protons causing decreased signal intensity on T_2 weighted images. The purpose of this study was to investigate regional cerebral T_2-weighted MRI signal intensity (SI) differences between healthy controls and subjects with a history of MA abuse. It was predicted that MA users will have increased iron concentrations as measured by decreased T_2-weighted SI values within basal ganglia structures compared to aged match healthy controls.

Methods: Subject data sets were acquired retrospectively from a previous study investigating the effects of MA on measures of white matter integrity, using diffusion tensor imaging. This study included 37 individuals with a history of MA abuse and 33 healthy control subjects. All MA subjects met DSM-IV criteria for MA dependence based on interview and chart review of available records. Control subjects' drug use history was assessed by interview. Control subjects had never used substances aside from alcohol, tobacco and marijuana and were excluded if they had ever met criteria for abuse or dependence on alcohol or marijuana. All MRI data were acquired on a Siemens 3T TIM Trio and included a high-resolution, T_1-weighted, whole-brain 3D MPRAGE sequence (FOV = 20x20x16 cm, matrix 256x256x144, TE=4ms, TI=900ms, TR=2300ms, flip angle=8º) and an axial 2D double spin echo EPI T_2 weighted image (FOV=256x256 mm, matrix 128x128, 72 2mm thick slices, 2mm gap width, TR9100ms, TE = 90ms). Bilateral, subcortical regions of interest (ROI), including caudate, putamen, and pallidum, were identified on the MPRAGE images using FMRIB's Integrated Registration and Segmentation Tool.[4] These identified ROI's were transformed to the individual's T_2-weighted image space and mean SI values within each ROI were obtained (Fig. 1). Mixed effect linear models were constructed to assess the effects MA use on T_2-weighted SI in each ROI. Iron content estimates were calculated for control subjects using published regression equations from postmortem data based on age and subcortical region.[5] Voxel wise analysis of the T_2-weighted images was carried out using tools from FSL[6] and AFNI[7] as an unbiased confirmation of the ROI approach (Fig 2).

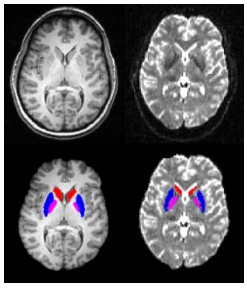

Figure 1: Subcortical region of interest (ROI) identification.

Results and Discussion: Individuals with a history of MA dependence had reduced T_2 SI values in the caudate ($F(1,67)=6.04$, $p=0.0166$) and putamen ($F(1,67)=8.42$, $p=0.005$), but not in the pallidum ($F(1,67)=1.01$, $p=0.31$)(Fig. 3). These findings were further confirmed with a voxel wise analysis approach which identified reduced T_2-weighted SI measurements in the right striatum of MA users (Fig 2). The iron content estimates obtained by applying the regression formulas based on postmortem data of iron content by region and age[5] significantly correlated with the measured T_2-weighted SI values in control subjects ($R^2=0.88$, $p<0.0001$). T_2-weighted SI measurements also demonstrated a strong effect of age in the caudate ($F(1,67)=22.08$, $p<0.0001$) and putamen ($F(1,67)=17.22$, $p<0.0001$), consistent with the established age-related increase in iron seen in these subcortical areas (Fig 3).[5, 8, 9] Taken together, these results provide some of the first evidence that suggests increased iron accumulation within the striatum in human MA users.

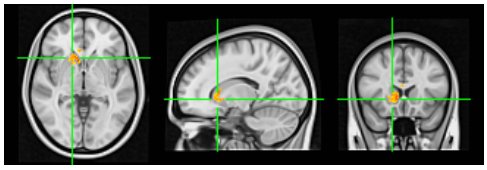

Figure 2: Voxel wise analysis demonstrating striatal areas of lower T_2-weighted signal intensity in methamphetamine users.

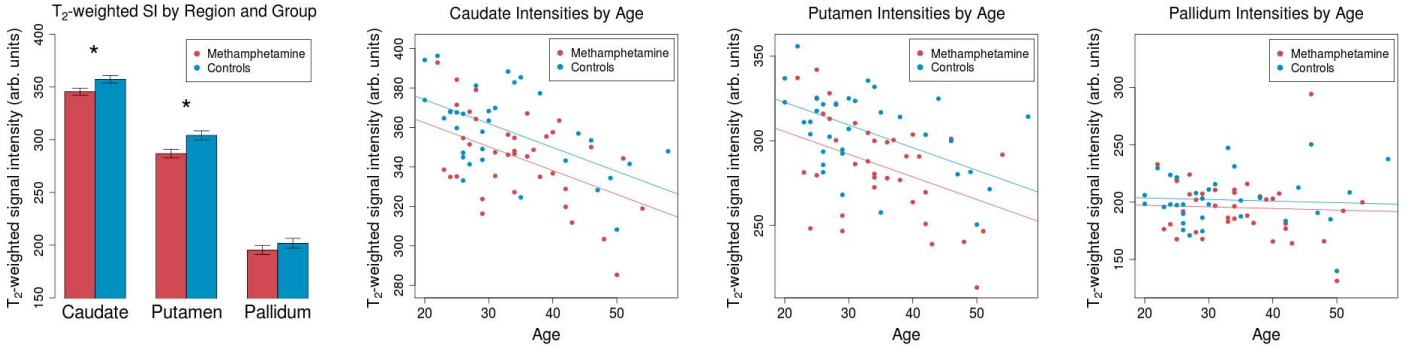

Figure 3: Region of interest analysis demonstrating the main effects of methamphetamine use and age on T_2-weighted signal intensity measurements in the caudate and putamen. * = p<0.05 after Bonferroni corrections.

References: 1: Melega, Laćan, Harvey, & Way. Neuroreport. 2007; 18:1741-1745. 2: Yamamoto, & Zhu. J Pharmacol Exp Ther. 1998; 287:107-114. 3: Lotharius, Falsig, van Beek, Payne, Dringen, Brundin, & Leist. J Neurosci. 2005; 25:6329-6342. 4: Patenaude. D. Phil. Thesis. University of Oxford. 2007. 5: Hallgren, & Sourander. J Neurochem. 1958; 3:41-51. 6: Andersson, Jenkinson, & Smith. www.fmrib.ox.ac.uk/analysis/techrep/, 2007. 7: Ward. http://afni.nimh.nih.gov/pub/dist/doc/manual/3dRegAnam.pdf, 2006. 8: Bartzokis, Tishler, Lu, Villablanca, Altshuler, Carter, Huang, Edwards, & Mintz. Neurobiol Aging. 2007; 28:414-423. 9: Pfefferbaum, Adalsteinsson, Rohlfing, & Sullivan. Neuroimage. 2009; 47:493-500.

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