Brain morphometry in methamphetamine users in relation to cumulative drug exposure

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INTRODUCTION: Methamphetamine (METH) is a major drug of abuse in the United States and in many countries throughout the world. Preclinical and clinical studies demonstrated significant neurotoxic effects and brain changes associated with the drug. However, few studies have evaluated morphometric changes associated with METH abuse [1-3]. We performed voxel based morphometry to determine whether active and recently abstinent METH users have brain structural abnormalities, and how such changes might relate to the estimated cumulative amount of METH abused.

METHODS: Forty-nine subjects [22 current or recently (< 6 months) abstinent METH users (4 women, 18 men aged 36±9, 20-52 years) and 27 controls (5 women, 22 men aged 36±11, 22-57 years)] were recruited and underwent a detailed clinical evaluation, including drug usage information. All subjects were scanned with an MPRAGE sequence (TE/TR 4.91/2200ms, 256mm FOV, either 144x1.4mm or 160x1mm slices) on a Siemens Trio 3 Tesla scanner. A template and prior images were created for a subsequent Voxel-Based Morphometry (VBM) study based on 31 randomly selected subjects from this group. All images were segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) images with 1x1x1 mm^3 voxel size using an optimized VBM procedure [4] and the customized T1-weighted template. Intensity modulated segmented images were calculated to determine changes in GM, WM and CSF volumes. After segmentation and smoothing (12 mm Gaussian kernel), differences in GM, WM and CSF volumes between METH and control groups, as well as their correlation with the Log of the estimated cumulative METH used (in grams), were calculated in SPM2 (http://www.fil.ion.ucl.ac.uk/spm). Significance was defined at the cluster level ($p<0.05$, $K>1000$), corrected for multiple comparisons.

RESULTS: The METH subjects had used an estimated cumulative lifetime use of 2605±3224 (range 93-12936) grams of METH. Compared to control subjects, METH users showed increased gray matter volume in right parietal and right frontal brain regions, and even more pronounced increased white matter volumes throughout the frontal lobes (Figure 1, left). Conversely, the CSF volumes were reduced in the temporo-parietal regions bilaterally in the METH subjects (Figure 1, right). Opposite contrasts were all non-significant. The regression analyses showed an inverse relationship between Log of cumulative lifetime METH exposure and gray matter volume in the frontal lobe bilaterally and the midline occipital lobe ($p<0.0001$, cluster sizes all > 9,000 voxels) (Figure 2). Higher METH usage was also associated with increased CSF volume in an area adjacent to the posterior cingulate ($p<0.0001$; cluster size 3809 voxels; not shown).

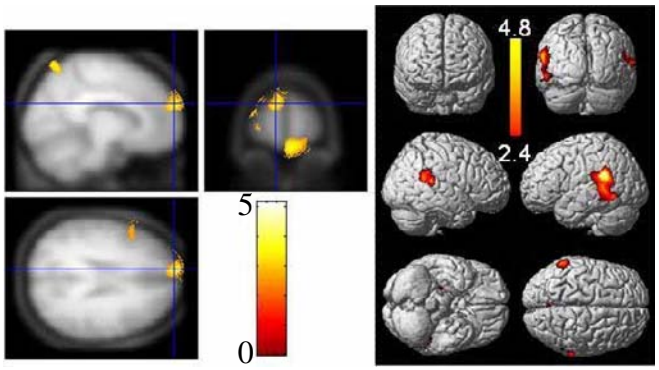

Figure 1. Volume differences between METH and control subjects for WM (left, METH>control, $p<0.001$, $k>2000$ voxels) and CSF (right, control>METH, left parietal $p<10e-20$, $k=15144$ voxels).

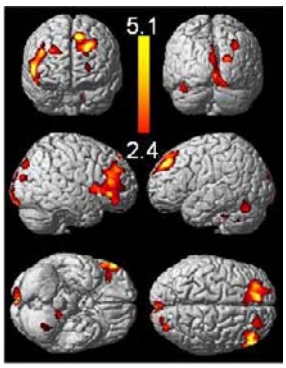

Figure 2. Inverse correlations between GM volume and lifetime METH exposure.

DISCUSSION: The findings of increased frontal and parietal gray matter and frontal white matter volumes in abstinent METH users are in agreement with two recent reports [1-3]. The increased brain volumes might be due to increased inflammation in these brain regions, since prior MRS studies have reported elevated myo-inositol in frontal brain regions [5]. These changes may also represent a compensatory response. METH users with the greatest cumulative drug exposure also demonstrated reduced gray matter and increased CSF volumes in the prefrontal and posterior cingulate brain regions, which suggest brain alterations associated with METH abuse. These structural brain abnormalities might account for the drug users' inability to remain abstinent. However, without further longitudinal follow-up evaluations, we cannot rule out the possibility that these changes were present prior to their drug use.

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