Alterations of brain structure and functional connectivity in chronic cocaine users

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Introduction

Cocaine dependent individuals show deficits in brain structure, function and metabolism (1-3). Voxel-based morphometry (VBM) studies have reported gray matter (GM) density/volume decreases in the frontal and temporal cortices in cocaine users (CU) (2, 4). However, whether these GM deficits affect brain functional networks is unknown. Resting-state functional connectivity (rsFC) techniques (5) now make it possible to address this question. In this study, we test the hypothesis that structural changes in brain GM affect functional connectivity of brain networks related to these structures. Specifically, brain regions with a GM volume decrease in CU were identified using VBM, and these regions were then used as seeds in a functional connectivity analysis to examine the integrity of brain networks associated with these structural deficits.

Fig 1. Compared to healthy controls, cocaine users showed significant gray matter volume decrease in right rostral ACC and bilateral superior and middle temporal gyrus, overlaid on DARTEL created custom template (p_c<0.05).

Methods

Participants: Thirty-nine active CU and 39 healthy controls (HC) matched on gender (10 vs 16 females), age (mean±SD: 40±5.1 vs 38±6.2 years), race (34 African American, 3 Caucasian and 2 mixed-race CU vs 28 African American, 9 Caucasian, 1 Hispanic and 1 Asian HC), WAIS vocabulary score (mean±SD: 58±7.2 vs 58±8.2), and education (mean±SD: 12.9±1.3 vs 13.2±1.7 years) were recruited under an Institutional Review Board approved protocol.

Data acquisition: Thirty-nine 4-mm thick AC-PC parallel slices without interslice gap were prescribed to cover the whole brain. Resting state fMRI data were acquired using a single-shot gradient-echo EPI sequence with repetition time (TR) of 2 s, echo time (TE) of 27 ms, flip angle (FA) of 77°, field of view (FOV) of 220×220 mm^2, and an in-plane resolution of 3.44×3.44 mm^2. For VBM study and for registration purpose, high resolution anatomical images were acquired using a 3-D MPRAGE T1-weighted sequence with TR of 2.5 s, TE of 4.38 ms, FA of 7°, and a voxel size of 1 ×1×1 mm^3.

Data processing and analysis: Anatomical images were affine transformed to Talairach space using AFNI and then segmented using unified segmentation model provided in SPM5. The parameter files produced by the segmentation was used to generate rigidly aligned GM and white matter (WM) images and these images were imported into DARTEL (6) to estimate the nonlinear deformations for further inter-subject alignment. A custom template was created based on the registration results and each individual's GM and WM images were transformed to the DARTEL template space, modulated by the determinant of the Jacobian of the transformation, and smoothed by a Gaussian kernel of 8 mm FWHM. A two-sample t-test was performed between CU and HC group of GM. Five regions with significant GM volume changes were identified at corrected p<0.05 based on a nonparametric permutation test. These areas were transformed to Talairach space to be used as seed regions in the connectivity analysis. Preprocessing steps for rsFC included slice-timing correction, volume registration, linear detrending, spatial normalization, nonlinear across-subject alignment (7), spatial smoothing (FWHM=6 mm) and low-pass filtering (cutoff frequency=0.1 Hz). Reference time courses (TC) were generated by averaging TCs of voxels within the seed regions identified by VBM analysis. Correlation coefficients (CCs) of each voxel in the brain were calculated between the voxel TC and the reference TC, which were then converted to z values using Fisher z transform. Global fluctuations, originating presumably from systemic effects such as respiration and cardiac-induced pulsations, were accounted for by extracting the first three principal components each from voxels in WM and cerebrospinal fluid (8). Student t-tests were performed on the z-value maps to obtain group rsFC maps and to assess significant connectivity strength changes between CU and HC groups for each seed region.

Fig 2. Significant decrease of functional connectivity strength in cocaine addicts observed as compared to matched controls with seed regions identified by significant gray matter volume reduction (p_c<0.05).

Results

Compared to HC group, significant GM volume decreases (p_c<0.05) were found in right rostral anterior cingulate (rACC), bilateral superior temporal gyrus (STG), and bilateral middle temporal gyrus (MTG) in the CU group (Fig.1). The total GM volume of the CU group was significantly smaller than that of HC (p<0.001). These 5 regions served as seeds in an rsFC analysis. Connectivity strength in the CU group was generally lower than those in HC (Fig.2). Specifically, the right rACC seed revealed significantly less synchronized fluctuation with the bilateral insula/STG and left amygdala in the CU group. The left MTG showed lower connectivity with bilateral medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC). Similarly, the rsFC between the right MTG and bilateral mPFC and left inferior temporal gyrus (IFG) were also decreased in CU group. No other significant alterations were found.

Discussion

Consistent with findings from previous VBM studies, GM volume decreases were found in the ACC and temporal cortices in CUs, which closely parallel the brain regions activated in cue-induced craving (ACC) (9,10) and regions involved in discriminating the stimulus associated with different rewards (STG) (11). Using regions showing reduced GM volume as seeds in rsFC analysis, decreased connectivity strength was found among mPFC/ACC, insula/STG, amygdala and PCC. The mPFC and amygdala are known to mediate reversal learning that has been shown compromised in drug addiction, while insula is involved in responding to drug cues (10) and in the experience of conscious urges (12). Together, these findings suggest that GM structural deficiencies may underlie the functional disruption of corresponding brain networks.

References

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5. Biswal et al., Magn Reson Med 1994.   6. Ashburner, Neuroimage 2007.   7. Geng et al., Neuroimage 2009.   8. Behzadi et al., Neuroimage 2007.   9. Grant et al., PNAS 1996.   10. Garavan et al., Am J Psychiatry 2000.   11. Liu et al., Cerebral Co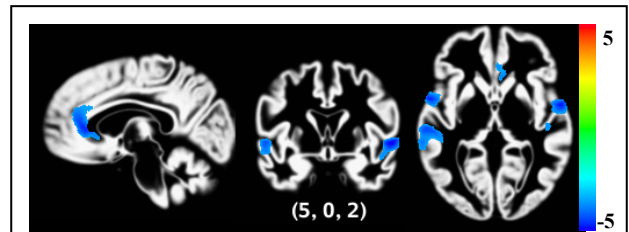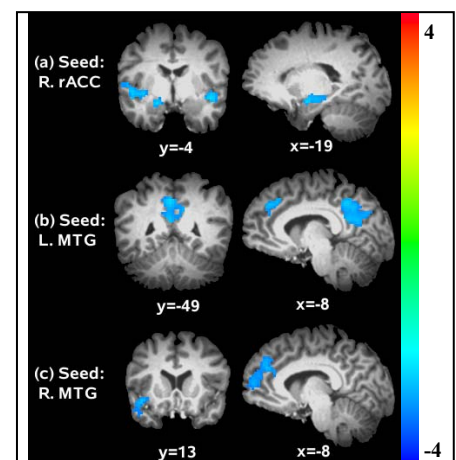rtex 2008.   12. Brody et al., Arch. Gen. Psychiatry 2002.