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A Hypo-Status in Drug Dependent Brain Revealed by Multi-modal MRI

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Abstract

Drug addiction is a chronic brain disorder with no proven effective cure. Assessing both structural and functional brain alterations using multimodal, rather than purely unimodal imaging techniques, may provide a more comprehensive understanding of the brain mechanisms underlying addiction, which in turn may facilitate future treatment strategies. However, this type of research remains scarce in the literature. We acquired multi-modal MRI from 20 cocaine-addicted individuals and 19 age-matched controls. Compared to controls, cocaine addicts showed a multi-modal hypo-status with 1) decreased brain tissue volume in the medial and lateral orbitofrontal cortex (OFC), 2) hypo-perfusion in the prefrontal cortex (PFC), anterior cingulate cortex (ACC), insula, right temporal cortex, and dorsolateral prefrontal cortex (DLPFC), and 3) reduced irregularity of resting state activity in the OFC and limbic areas, as well as the cingulate, visual, and parietal cortices. In the cocaine-addicted brain, larger tissue volume in the medial OFC, ACC, and VS, and smaller insular tissue volume were associated with higher cocaine dependence levels. Decreased perfusion in the amygdala and insula were also correlated with higher cocaine dependence levels. Tissue volume, perfusion, as well as brain entropy in the insula and PFC, all showed a trend of negative correlation with drug craving scores. The three modalities showed voxel-wise correlation in various brain regions, and combining them improved patient vs control brain classification accuracy. These results, for the first time, demonstrate a comprehensive

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cocaine-dependence and craving-related hypo-status regarding the tissue volume, perfusion, and resting brain irregularity in the cocaine-addicted brain.

Keywords

Voxel Based Morphometry; arterial spin labeling; cerebral blood flow; brain entropy; resting state fMRI

Introduction

Drug addiction is a chronic relapsing brain disorder (Koob and Volkow, 2010). Identifying abnormal brain patterns that accompany addiction-related symptoms remains a high priority in addiction research. These patterns may help shed light on the neuro-mechanisms underlying addiction/relapse vulnerability or provide sensitive biomarkers for developing addiction interventions or monitoring disease. Using neuroimaging, various brain alterations have been found in the drug addicted brain (Lindsey et al., 2003; Volkow et al., 2003). In cocaine addiction, reduced grey matter volumes have been demonstrated by many researchers in brain regions that are critical for reward, memory, inhibition, and other functions known to be altered in drug addiction. Those regions include the frontal lobe (prefrontal cortex (PFC) (Alia-Klein et al., 2011; Franklin et al., 2002; Matochik et al., 2003; Sim et al., 2007), orbitofrontal cortex (OFC) (Alia-Klein et al., 2011; Franklin et al., 2002; Matochik et al., 2003)), anterior cingulate cortex (ACC) (Franklin et al., 2002), middle cingulate (Matochik et al., 2003), limbic area (amygdala (Makris et al., 2004), insula (Franklin et al., 2002), ventral striatum (Sim et al., 2007), thalamus (Sim et al., 2007), hippocampus (Alia-Klein et al., 2011), basal ganglia (Jacobsen et al., 2001)), temporal cortex (Alia-Klein et al., 2011; Franklin et al., 2002; Sim et al., 2007), premotor cortex, and cerebellum (Sim et al., 2007). Since brain tissue subserves brain function, the various structural changes in the drug-dependent brain implicate corresponding functional alterations in the same regions. Indeed, increased brain activation in mesocortico limbic and cortical regions associated with reward and motivation, memory, and learning including ventral striatum, amygdala, ACC, medial PFC, inferior PFC, basal ganglia, etc, have been shown in cocaine patients using both PET imaging (Childress et al., 1999; Volkow et al., 2003; Volkow et al., 2006) and fMRI (Kaufman et al., 2003). However, thus far, the structural and functional alterations have been assessed mainly in separate cohorts of patients or in the same cohorts but in separate reports. Their overlap has not been explicitly examined in the same cohort of subjects (Question No. 1). While functional alterations have been shown in the drug-addicted brain, previous studies only focused on either the baseline (or the tonic) or the dynamic (or the phasic) properties. A more comprehensive functional assessment should consider the two features together. In drug addiction, it is still not clear whether alterations to both features are involved (Question No 2).

Brain function can be measured with arterial spin labeling (ASL) perfusion MRI and the blood-oxygen-level-dependent (BOLD) fMRI. ASL MRI (Detre et al., 1992) provides a non-invasive way to quantify cerebral blood flow (CBF). Due to the coupling of regional CBF to regional brain metabolism, ASL CBF has been widely used as a marker for brain functions.

Baseline CBF indicates the tonic brain energy spend, and can be used to assess the tonic property of brain function. In drug addiction, we have used ASL MRI to probe the cue-induced activation and abstinence-induced activation in smoking (Franklin et al., 2011; Franklin et al., 2007; Wang et al., 2007b; Wang et al., 2008b), but ASL MRI still remains underexplored in cocaine addiction studies (Question No. 3) with only two publications (Adinoff et al., 2015; Adinoff et al., 2016) which found hypoperfusion only in the parahippocampus.

BOLD fMRI has higher temporal signal-to-noise-ratio than ASL and can be used to characterize the dynamic features of brain activity. Entropy indicates the irregularity of a dynamic system (Sandler, 2006), and is an important trait for life as well as the human brain. Characterizing brain entropy (BEN) in the human brain may provide an informative approach to assess brain states and functions, including changes that may occur as a result of disease. Recently, we have demonstrated that regional BEN can be reliably mapped in the normal brain using resting state fMRI (rsfMRI) where entropy was approximately measured with the Sample Entropy (SampEn) (Wang et al., 2014).

Different from the other widely used rsfMRI analysis methods such as the seed-based functional connectivity analysis, network analysis, and the low-frequency fluctuation amplitude analysis, BEN is not constrained to a specific frequency band, but rather accounts for the irregularity (or randomness) of the assessed signal. Higher irregularity means more unpredictability, which might be a requirement for the brain to adapt to the dynamic natural environment, characterized by the high occurrence of unpredictable events. Assessing such functional adaptability may gain a new perspective for understanding brain mechanism underlying brain disorders. Resting BEN alterations have been demonstrated in Schizophrenia (Sokunbi et al., 2014b), attention deficit hyperactivity disorder (ADHD) (Sokunbi et al., 2014a), and multiple sclerosis (Zhou et al., 2016). Drug addiction has been repeatedly shown to induce changes in brain function. Such alterations may manifest as a functional capacity (or equivalently the activity irregularity) change and can be assessed with BEN mapping. Because BEN is still relatively new to the literature, it remains fresh new to drug addiction with only one paper published thus far regarding cigarette smoking (Li et al., 2016) (Question 4).

The purpose of this study was to examine both the structural and functional brain alterations in cocaine addiction regarding the above mentioned questions using multi-modal MRI including brain tissue volume, baseline CBF, and BEN. Based on previous unimodal imaging studies, we first hypothesized that cocaine-addicted brains would show both structural and functional alterations compared to controls, which are correlated with addiction-related behaviors. Because each modality carries different information about the brain from the others, our second hypothesis was that the multimodal brain alteration patterns in cocaine patients would show spatial overlap as well as discrepancies. The third hypothesis was that combining multiple modalities (brain tissue, CBF, and the dynamic resting state property) will provide better brain discrimination sensitivity, as compared to single modality -based approaches. By testing these hypotheses, we aimed to show reproducibility information of previously identified uni-modal brain patterns in addiction; to demonstrate the spatial overlap and discrepancy of the structural and functional brain

alterations; to identify CBF changes and BEN changes in cocaine addiction; to demonstrate the benefit of combining multiple modalities for cocaine addiction study.

Materials and methods

Subjects

The same cocaine dependent cohort and control subjects as in (Wang et al., 2015) were included in the current study. The study was approved by a local ethic review board and signed written consent was collected before any experiment was performed. Twenty treatment-seeking cocaine patients (DRUG) (age 42.15 ± 4.3 (mean $\pm$ standard deviation (std)), years of education 10.07 ± 1.7 , all African-American men) with a DSM-IV diagnosis of cocaine dependence and 19 age/ethnicity/race-matched controls (CTL) were recruited from the local community of West Philadelphia (age, 39.9 ± 4.5 ; education, 14.9 ± 2.9 yrs; all African-American men). The two groups were matched in age ($p=0.13$ for the age difference). CTL had more years of education than DRUG ($p=0.0006$). Detailed demographic data is listed in Table 1. Defined by the M.I.N.I. (Sheehan et al., 1998), 6 patients had a diagnosis of alcohol dependence; 2 with alcohol abuse; 1 had marijuana dependence; and 2 had marijuana abuse.

All subjects underwent full physical and psychological examinations. Severity of drug dependence (days of the past 30) was assessed using the Addiction Severity Index (ASI) (McLellan et al., 1980). Inclusion criteria required cocaine usage of at least 8 days within the last 30. Patients were not using medications that may cause sedation or are known to modify brain dopamine systems during the previous 60 days. Subjects were not receiving any psychotropic medications or medications which impact the CNS as a whole had no cardiovascular, hematologic, hepatic, renal, neurological, or endocrinological abnormalities; no history of head trauma or injury; no gambling problems; no history of psychosis or neurocognitive disorders unrelated to drug abuse; and no other severe psychiatric disorders, with the exception of dependence on other substance as described above. Patients had 4–8 days of residential stabilization prior to study entry, during which they were drug-free, verified by urine drug screens (cocaine, amphetamines, cannabinoids, opiates, and phencyclidine, and alcohol). CTL were not dependent on any substances including alcohol and nicotine. Drug craving scores were recorded before the MRI scan using the Brief Substance Craving Scale (Somoza et al., 1995). Both patients and controls were informed not to consume caffeine 2 hours before MRI scans.

MRI data acquisition

MR imaging was conducted in a 3-T whole-body scanner (Siemens Medical Systems, Erlangen, Germany). High-resolution structural images were acquired for spatial brain normalization using a 3D MPRAGE sequence (TR/TE/TI = 1620/3/950ms). ASL perfusion MRI was acquired using a pseudo-continuous ASL sequence (Dai et al., 2008). 45 control/label image pairs were acquired with parameters of: labeling time = 1.5 sec, post-labeling delay = 1.5 sec, FOV=22cm, matrix=64×64, bandwidth=3kHz/pixel, TR/TE=4000/17 ms, 12 slices with a thickness of 7 mm plus 1.25 mm gap. Gradient-echo echo-planar imaging sequence was used for resting BOLD fMRI data acquisition with parameters of: TR = 2s, TE

= 30 ms, FOV = 220×220 mm², matrix = 64×64×32, slice thickness= 4.5 mm. Participants were asked to lie still in the scanner at rest and keep eyes open. 180 images were acquired.

Brain registration and voxel based morphometry

Structural images were spatially registered to a local template generated from the all the subjects and subsequently to the MNI standard space. Structural images were first segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using the unified segmentation implemented in SPM8. An exponentiated Lie algebra algorithm (DARTEL) (Ashburner, 2007) was then used to derive the local template from the segmented structural images from both patients and controls' structural images, along with transformations from the template to each individual brain. Affine transformation was used to map the local template to the MNI space using SPM8. The combination of the affine transform and the DARTEL transform was used to map the individual structural images into the MNI space. Using the flow fields that parameterize the deformation information during the above DARTEL process and DARTEL transformations, Jacobian modulation was applied to preserve and restore the original GM and WM volumes. The Jacobian scaled warped tissue images were then smoothed with a Gaussian kernel with an FWHM of 10 and compared between patients and controls using voxelwise two-sample t-test. Total brain volume, age, and education years were included as nuisance variables.

Functional image processing and BEN calculation

All data preprocessing was performed using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>) based batch scripts available in ASLtbx (Wang et al., 2008a) with the following steps: motion correction, temporal filtering, spatial smoothing with an isotropic Gaussian kernel (full width half maximum = 6mm), coregistration, and normalization. The amended algorithm (Wang, 2012) was used for ASL image motion corrections. High pass filtering (cutoff=0.5) was used for temporal ASL image de-noising. Residual motions and global signal was regressed out from the control/label ASL images (Wang, 2012) before CBF calculations. Outlier CBF images were removed using the adaptive outlier cleaning algorithm (Wang et al., 2013). Resting BOLD fMRI images were detrended to remove the linear signal drift. Head motion time courses, the mean CSF signal and mean WM signal were treated as nuisance variables and were regressed out from each voxel's time series (Fair et al., 2008) using a multiple regression model. Resting BOLD fMRI images were also band-pass filtered to be within 0.01Hz–0.08Hz. They were further zero-meaned and normalized to have a unit norm at each voxel before the calculation of BEN.

BEN was calculated at each voxel using the approximate entropy form, SampEn as implemented in the Brain Entropy mapping toolbox (<https://cfn.upenn.edu/~zewang/BENtbx.php>) (Wang et al., 2014). The window length and the cutoff threshold were set to be 3 timepoints and $r=0.6$ according to (Wang et al., 2014).

The registration transform generated during DARTEL processing was used to register the resting CBF maps and BEN maps into the MNI space.

Group level analyses of tissue volume, CBF, and BEN

Voxel-wise patient vs CTL comparisons on tissue volume, CBF, and BEN were performed using two sample t-test implemented in SPM8. Age and education years were included as nuisance variables. Correlations between the imaging measures (tissue volume, CBF, and BEN) and cocaine dependence were examined at each voxel using simple regression. Age was included in the regression model as nuisance.

Inter-modality relation analysis and multi-modalities based classification

Originating from the same cohort of subjects, the 3 imaging modalities may present a strong correlation, and it still remains unclear whether or not combining them will provide a more sensitive way to study the cocaine-addicted brain. To explicitly address this question, we calculated the voxel-wise inter-modality correlation and ran a multi-modal imaging-based patient vs control brain classification. The suprathreshold clusters identified from each of the two-sample t-tests for each modality as previously mentioned were used as regions-of-interest (ROIs) to extract data from the corresponding modality images. These ROI data were then used as multivariate features in a support-vector machine (SVM) learning-based patients vs control brain classification (Wang et al., 2007a; Zhang et al., 2014). Each modality feature was input into a separate SVM model, and the 3 models were subsequently combined using the multi-kernel combination approach (Zhang et al., 2011). Linear SVM was used because it is widely considered sufficient for neuroimaging data (Wang et al., 2007a). 39 leave-one-out cross-validations were used to verify the classification accuracy. For each validation, one subject was selected as the testing sample while the others were used as the training samples. The classifier was trained using the imaging data and the known categories of the subjects (cocaine patients marked by 0s, and controls marked by 1s). The imaging data of the testing subject was then input into the model to predict whether the subject was a patient or control. The prediction accuracy was then calculated as the ratio of correct predictions to the total number of subjects. This process was repeated for each modality separately and in combination.

Results

A $p < 0.005$ (uncorrected) was used to collect the suprathreshold clusters, which was further thresholded with a cluster threshold of 76 voxels (corrected for multiple comparison using Monto-Carlo simulation through the AlphaSim provided in AFNI (<http://afni.nimh.nih.gov/afni/>), $\alpha < 0.05$).

Tissue volume/CBF/BEN alterations in cocaine patients

Fig. 1 shows the cross-sectional GM volume (hot color), CBF (violet), and BEN (green) analysis results. Compared to the age-matched controls, cocaine patients showed significant grey matter atrophy (hot color) in ventro-medial prefrontal cortex (VMPFC) and right orbital frontal cortex (OFC), and hypoperfusion (violet color) in prefrontal cortex (PFC), right insula, anterior cingulate cortex (ACC), right inferior frontal cortex (IFC), dorso-lateral prefrontal cortex (DLPFC), and right middle and superior temporal cortex. Patients showed lower BEN (green clusters) in VMPFC, OFC, DLPFC, VS, basal ganglia, visual cortex, and parietal cortex.

Imaging versus (vs) clinical measure correlations

Fig. 2 shows the imaging vs drug dependence level (measured by the ASI severity score) correlation analysis results. GM tissue volume was positively related to cocaine dependence in the VS and anterior cingulate cortex (ACC)/VMPFC, while negative correlation between GM tissue volume and cocaine dependence was found in the right insula (Fig. 2a). A trend (the suprathreshold cluster didn't survive the cluster wise multiple comparison correction using AlphaSim) of negative correlation between CBF vs drug dependence (the cluster didn't survive multiple comparison correction) was observed in right amygdala and inferior insula.

Only BEN showed significant negative correlation with drug craving in two big clusters (Fig. 3): one in left insula, putamen, and VS, the other in prefrontal cortex. Tissue volume showed a trend (the suprathreshold cluster didn't survive the cluster wise multiple comparison correction using AlphaSim) of negative correlation with self-reported level of craving in ACC and visual cortex. CBF showed a trend (the suprathreshold cluster didn't survive the cluster wise multiple comparison correction using AlphaSim) of negative correlation to craving level in ACC.

Inter-modality correlations and multi-modal classification results

Fig. 4 shows the inter-modality voxel-wise correlation coefficient maps. Significance level was defined here at $p < 0.05$ and a cluster size > 100 voxels. Tissue volume showed both positive and negative correlations with CBF (Fig. 4A) and BEN (Fig. 4B). Positive tissue vs CBF correlations were found in prefrontal cortex, ventral striatum, and thalamus, while negative tissue-CBF relation was found in OFC, insula, hippocampus and parahippocampus, and precuneus. Extensive positive correlation between tissue volume and BEN was found in OFC and PFC including ACC, insula, putamen, and temporal cortex, while negative tissue vs BEN correlation was shown in parahippocampus and parietal cortex. Interestingly, BEN and CBF only showed positive correlations to each other (Fig. 4C). The BEN vs CBF correlations were shown in OFC, ACC, hippocampus, putamen, thalamus, temporal cortex, and lateral PFC.

Table 2 lists the multi-modality based patient vs control classification accuracy. For signal modality, BEN provided the highest classification accuracy, while tissue volume provided the lowest. Combining tissue volume with any of the other two modalities brought down the classification accuracy slightly, while combining BEN and CBF resulted in much higher accuracy. Combining all three modalities yielded the highest classification accuracy than any other combination (84.6%), but tissue volume and CBF did not substantially add to the accuracy of BEN alone (79.5%).

Discussion

Using multimodal MRI data, we demonstrated the hypothetical multimodal brain variations in cocaine-dependent individuals. The distributed multi-modal brain alterations showed large spatial discrepancy though they still overlapped to a certain extent. The multi-modal changes were partly consistent with previous reports and were mainly observed in the mesocortical

limbic areas, including the VMPFC, OFC, PFC, DLPFC, ACC, insula, VS, basal ganglia, and temporal cortex. Structural alterations were found to be mainly located in VMPFC and OFC, consistent with the results of previous studies (Alia-Klein et al., 2011; Ersche et al., 2012; Franklin et al., 2002; Matochik et al., 2003; Sim et al., 2007). VMPFC and OFC are involved in inhibition and decision-making, which are known to be deficient in drug addiction (Goldstein and Volkow, 2002; Lindsey et al., 2003). Hypo-perfusion in cocaine patients was discovered in the dorsal ACC, IFC, insula, and DLPFC, indicating an effect on several important brain functions governed by these cortical regions such as executive function, risk-taking and moral decision-making, motivation (Fuster, 2008), as demonstrated in previous addiction neuroimaging studies (Goldstein and Volkow, 2002; Lindsey et al., 2003; Volkow et al., 2003).

The insula is a complex functional area and has been implicated in drug addiction in many ways, including the motivational drug-seeking behavior, risk-taking, and goal-directed drug-seeking (Naqvi et al., 2014). Low insular perfusion indicates a hypo-status induced by the over-stimulation of drug to those involved brain functionalities. We didn't find hypoperfusion in parahippocampus, which is the only suprathreshold region shown in (Adinoff et al., 2015). This discrepancy may reflect a difference in inter-subject variances between our study and theirs.

Entropy indicates system irregularity. Lower resting BEN was found in a large portion of the brain in cocaine-addicted patients, consistent with the whole-brain hyper-connectivity reported in (Wang et al., 2015). Lower entropy means higher regularity, and technically results in greater inter-regional correlations, meaning increased inter-regional functional connectivity. Lower BEN in VMPFC, OFC, DLPFC, VS, basal ganglia, superior temporal lobe, visual cortex, precuneus, and parietal cortex represents a more regularized resting brain activity in cocaine patients. A decrease in the entropy or irregularity of resting brain activity is indicative of a diminished capacity for processing complexity in the resting brain, which has been postulated to be indicative of aging or pathological conditions (Goldberger et al., 2002). In drug addiction, this complexity capacity loss may indicate a loss of ability of the brain to interact with, or respond to, internal or external inputs other than drug-related information. These inputs can be internal inhibition or decision-making signal. Cocaine patients showed both hypoperfusion and lower BEN in DLPFC, which may reflect the inability of the drug users to inhibit drug-seeking and using behaviors, a hallmark of drug addiction (Jovanovski et al., 2005). Reduced BEN in the temporal cortex, fusiform gyrus, visual cortex, parietal cortex may reflect alterations to baseline (tonic) memory/learning, visual, and spatial perception/imagination functions as shown in previous addiction studies (Koob and Volkow, 2010; Naqvi et al., 2007; Volkow et al., 2003).

The cross-sectional imaging difference was paralleled by our imaging-behavior relation analysis, where the imaging-behavior correlations were mainly located in the limbic and frontal areas, two critical regions implicated in drug addiction. In the insula, we found that decreased tissue volume in the right posterior superior insula, and a trend of lower CBF in the inferior insula are predictive of severer drug dependence as measured by the drug dependence level. These findings implicate functional insula impairments in the drug-dependent cohort. Additionally, lower BEN in the left inferior insula was related to higher

drug craving scores. Dorsal and rostral ACC showed a negatively correlated trend between drug craving scores and tissue volume and CBF. Decreased CBF in the amygdala was also shown to be associated with higher drug dependence level, which is consistent with our early PET study (Childress et al., 1999).

Interestingly, we found larger VS tissue volume to be related to higher drug dependence level, which is consistent with previous findings of increased striatal tissue volume or higher volumes in different subsets of the striatum involved in drug addiction (Ersche et al., 2012; Jacobsen et al., 2001; Jan et al., 2012). Tissue volume in the subgenual ACC was also positively correlated to drug dependence level. The subgenual ACC plays an important role in emotion and reward anticipation (Botvinick et al., 2001). The positive relation of subgenual ACC volume to drug dependence level may reflect an elevated drug-related reward anticipation or emotional functional activity in the drug-dependent brain. However, this relationship does not necessarily imply greater ACC volume in drug dependent-brains as compared to controls. Actually, grey matter volume in different brain regions has been shown to be both positively and negatively related to impulsivity by Crunelle et al. (Crunelle et al., 2014).

Both the cross-sectional brain difference between cocaine patients and controls, and the imaging vs behavior relations suggest that the multi-modal data provides distinct information about the brain, though the positive inter-modality correlations suggest that they may still be coupled to some extent. Tissue volume showed positive correlation to both CBF and BEN in PFC, meaning that higher tissue volumes in the PFC requires an increase in CBF and a larger dynamic functional capacity, which is consistent with the high cognitive functions governed by the PFC. The negative correlations of tissue volume to CBF and to BEN indicate a structure-function decoupling. BEN and CBF were positively correlated in frontal, temporal, and subcortical area, suggesting a strong coupling between these two functional modalities in those regions.

Combining all modalities provided the highest patient vs control brain classification accuracy than any other combinations of the three modalities, further indicating that different modality does provide distinct information related to addiction. We also observed that tissue volume and CBF did not substantially add to the accuracy of BEN alone. One possible reason could be that cocaine addiction causes phasic alterations (as measured by BEN) more homogeneously across patients than the static (tissue volume) and tonic brain function (CBF) alterations. Certainly, this possibility should be further evaluated in future studies.

Mainly used to demonstrate the overlapping and distinct features between different modalities in different areas of the brain, these observed inter-modality correlation patterns will certainly need future large-sample size studies to be verified and further explored. Nevertheless, these results proved that the different modalities provide common and distinct information about the brain. Combining them may lead to a better understanding of brain mechanism. In this paper, we clearly showed that combining the 3 modalities improved brain classification accuracy.

One limitation of the current study is the small sample size which can be attributed to the small number of controls in our currently available neuroimaging datasets. The clinical meanings of the multi-model imaging measures will need to be further evaluated with a large cohort of patients in a future study. BEN remains new to cocaine addiction studies. It should be noted that BEN is different from the inter-regional functional connectivity (FC) that is widely used in rsfMRI studies and has been priorly used in cocaine-addiction studies (Gu et al., 2010). BEN measures irregularity of each voxel independently so it can directly characterize regional brain activity, while FC is an indirect measure of local voxels since it needs a reference either from one or several seed regions. Inappropriate seed determinations will inevitably affect the FC analysis results.

In summary, by proving the three hypotheses about the multi-modal brain alterations in cocaine addiction, we have demonstrated for the first time, a comprehensive hypo-status in the cocaine-addicted brain using multi-modal MRI, which were related to drug dependence or craving for drug. We also showed that combining multi-modal imaging data can improve sensitivity for discriminating drug-addicted brain from non-drug dependent brain, suggesting that combining multi-modalities may provide a better approach for predicting disease progression or relapse to drug use. The imaging findings confirmed the sporadic tissue atrophy and functional hypo-status reported in the literature based on different single-modal imaging. The findings highlight the mesocortico limbic area and prefrontal brain in cocaine addiction.

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Fig. 1.

Brain difference between cocaine patients and age-matched controls. Hot, violet, and green colors means atrophy, hypoperfusion, and hypo-BEN in cocaine patients, respectively. The left side of the image is the left side of the brain. The numbers above each slice indicates the spatial location of the slice in the MNI space.

Fig. 2. Correlations of GM tissue volume a) and CBF b) to cocaine dependence level. Violet and green mean positive and negative relation between GM volume and drug dependence level, respectively. Cool color means negative correlation between CBF and drug dependence level. The left side of the image is the left side of the brain. The numbers above each slice indicates the spatial location of the slice in the MNI space.

Fig. 3.
Correlations of grey matter volume, CBF, BEN to drug craving scores. Violet, blue, and green colors mean negative correlation between craving score and grey matter volume, CBF, and BEN, respectively. The left side of the image is the left side of the brain. The numbers above each slice indicates the spatial location of the slice in the MNI space.

Fig. 4.

Voxel-wise inter-imaging modality correlations. A) Tissue volume vs CBF, B) Tissue volume vs BEN, C) BEN vs CBF correlations. Hot color and green mean positive and negative correlation, respectively. Color bars indicate the display window for the correlation coefficients. The left side of the image is the left side of the brain. The numbers above each slice indicates the spatial location of the slice in the MNI space.

Table 1

Demographic data for participants.

	Patients (n=20)	Controls (n=19)
Age (yrs) ¹	42.15±4.3	39.9±4.5
Education (yrs) ²	12.07±1.7	14.9±2.9
Gender	20 males	19 males
Cocaine dependence severity ³	7.26±1.76	0
Cocaine use years	17.10±7.47	0
Cocaine use days in the last 30 days	17.88±7.01	0
Alcohol dependence severity	2.74±2.54	0
Marijuana dependence or abuse	4	0
Drug craving score	0~3, 0.39±0.89	0
Cigarette per day	7.67±6.0	0
Smoking duration (yrs)	15.61±12.1	0

¹ p=0.13 for the two group age difference;² p=0.0006 for the education difference between patients and control;³ Severity of drug dependence (days of the past 30) was assessed using the Addiction Severity Index (ASI) (McLellan et al., 1980).

Table 2

Patient vs control classification accuracy using different combinations of the 3 modality data.

Imaging data	Accuracy (%)
Tissue	43.59
CBF	48.72
BEN	79.49
Tissue + CBF	46.15
Tissue + BEN	56.41
CBF + BEN	82.05
Tissue+CBF+BEN	84.62