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Medial orbitofrontal cortex gray matter is reduced in abstinent substance dependent individuals

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Abstract

Background—Chronic exposure to drugs of addiction induces cellular adaptations in orbitofrontal cortex (OFC) and associated limbic-prefrontal pathways that may underlie abuse-related behavior. A propensity to make risky decisions in spite of substantial negative consequences may be mediated by medial OFC dysfunction in substance dependent individuals (SDI). We tested the hypothesis that medial OFC gray matter (GM) volume would be lower in SDI compared to controls.

Methods—Nineteen SDI and 20 controls participated. SDI were dependent on 2 or more substances, most often cocaine, amphetamine, and alcohol with mean duration of abstinence 4.7, 2.4, and 3.2 years, respectively. High resolution T1 weighted Images were acquired on a 3T MR system. Image processing and analyses was conducted using voxel-based morphometry (VBM) implemented in SPM5. Differences in regional GM volume were tested using an analysis of covariance model, co-varying for global GM and age. Statistical maps were set at $p<.05$, corrected for multiple comparisons. Medial OFC GM volume was correlated with behavioral performance on a modified gambling task.

Results—There was lower GM volume specifically in bilateral medial OFC in SDI compared to controls. There was a small but significant correlation between medial OFC GM and persistence of playing high risk decks on a modified gambling task.

Conclusions—This is the first paper to use VBM with whole brain correction for multiple comparisons in SDI after prolonged abstinence. Reduced medial OFC GM may reflect long-term adaptations within the reward-learning circuit underlying pathological decision making in substance dependence.

Introduction

Substance dependence is characterized by abnormal goal directed behavior and has been conceptualized as a pathological usurpation of the cortico-striatal-limbic circuit mediating reward behavior (1,2,3,4). Long-term cellular changes in prefrontal cortex associated with

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repeated drug exposure are thought to mediate dysfunctional goal-directed behavior and impaired decisions that lead to end stage addiction.

Neuroimaging studies provide evidence of functional (5,6,7,8) and structural abnormalities in orbitofrontal cortex (OFC) in substance dependence. Liu et al. found smaller prefrontal, but not temporal cortex, in poly-substance abusers compared to controls (9). Studies using voxel based morphometry (VBM) have found reduced medial OFC, anterior cingulate, and insular gray matter in cocaine addicts (10) and prefrontal and temporal gray matter in opiate addicts (11). In a study of methamphetamine addiction and HIV infection, methamphetamine was associated with an increase in lentiform gray matter volume, but complicated by opposing effects of HIV infection on brain volume. A limitation of these studies has been the recency of illicit drug use compared to the time of MR scanning. This is important because a) some drug effects on neural substrate may be reversible as has been shown for alcohol (12,13,14) and b) the neural substrates involved in acute drug effects likely differ from those underlying end-stage addiction (2). Thus, the current study sought to determine the pattern of gray matter loss in substance dependent individuals (SDI) after prolonged abstinence.

The data used for this study were collected as part of a study in which we reported reduced prefrontal brain activity in SDI compared to controls during decision making (15). The task was a modified Iowa Gambling Task (IGT) which simulates uncertainty and reward of real-life decision making initially developed to test impaired decision making in patients with ventral medial prefrontal cortex lesions (16). We extend those results here by determining if the volume of medial OFC gray matter is lower in abstinent SDI compared to controls

Methods

Subjects

Thirty-nine subjects, including 20 controls (14 women/ 6men, 33 SD 11 yrs old) and 19 substance-dependent individuals (SDI) (9 women/10 men, 35 SD 7 yrs old) participated in this study. SDI were recruited from the University of Colorado School of Medicine Addiction Research and Treatment Service (ARTS), a long-term residential treatment service. Inclusion criteria included dependence on one or more illicit substances, using DSM-IV criteria. Inclusion criteria for the controls were no diagnosis of substance abuse or dependence. Exclusion criteria for all participants included neurological illness, schizophrenia or bipolar disorder, prior significant head trauma, positive HIV status, diabetes, Hepatitis C, or other major medical illness, and IQ less than 80. All participants provided written informed consent approved by the Colorado Multiple Institutional Review Board.

Behavioral measures

In SDI, drug dependence was measured using the computerized Composite International Diagnostic Interview (CIDI)-Substance Abuse Module (SAM) (CIDI-SAM) (17). CIDI-SAM is a structured interview designed for trained, lay interviewers, and has been shown to have good test-retest and inter-rater reliability(18). For each drug, symptom count and date of last use were recorded. CIDI-SAM was not given to controls. Performance data on the modified gambling task were available for 34 (15 controls, 19 SDI) of the 39 subjects. We used a modification of the Iowa Gambling Task (IGT) adapted for an fMRI experiment (16). Details of the task have been previously described (15). There were 80 trials for which the subject chose “Play or Pass” and these were divided into 2 time blocks, early and late. The number of times an individual chose to play “bad” decks on early compared to late trials was totaled. Repeated measures analysis of variance (rmANOVA) using IQ, education, and age as covariates was performed in SPSS analyzing for effects of group by time interaction.

IQ was measured on the basis of the two-subtest Wechsler Abbreviated Scale of Intelligence in which Vocabulary and Matrix Reasoning subtests were administered.

MR Imaging

Images were acquired on a 3.0T whole body MR scanner (General Electric, Milwaukee, WI) using a standard quadrature head coil. A high resolution 3D T1-weighted SPGR-IR sequence used the following parameters: TR=45, TE=20, FA=45, 256^2 matrix, 240 mm^2 FOV (.9 × .9 mm^2 in-plane), 1.7 mm slice thickness, coronal plane. Scan time was 9′ 24″. A neuroradiologist (JT) evaluated anatomical images for motion artifact and the EPI T2* images for gross structural abnormalities, particularly encephalomalacia. No studies were excluded.

Image processing and statistics

Image processing was conducted using the Voxel-based morphometry toolbox (VBM5.1) (http://dbm.neuro.uni-jena.de/vbm/) implemented in SPM5 running on Matlab 7.5. VBM in SPM5 combines tissue segmentation, bias correction, and spatial normalization into a unified model (19). Hidden Markov Random Fields were applied to improve accuracy of tissue segmentation (medium HMRF 0.3). Otherwise, default parameters were used. Individual brains were normalized to tissue probability maps provided by International Consortium for Brain Mapping (ICBM). A 12 mm FWHM Gaussian kernel resulted in a final smoothing of $14 \times 15 \times 14$ mm^3. At the second level, whole brain data were modeled across the groups using analysis of covariance (ANCOVA) with total GM volume and age as covariates. The effects of total GM volume were removed to allow inferences about regional differences in GM volume. An absolute threshold mask of .1 was used. Statistical maps were set at a cluster-level threshold of $p<.05$, corrected for multiple comparisons using family-wise error (FWE), and a voxel-level threshold of $p<.005$. To ensure the validity of cluster-level statistics, a non-isotropic smoothness correction was applied (20).

Medial OFC region of interest (ROI)

To confirm whole brain analyses, an ROI analysis of right and left medial OFC was implemented using the Automated anatomic labeling (AAL) ROI library within Marsbar SPM toolbox (21,22).

Correlation between GM volume and decision making behavior

GM volume was obtained from the voxel corresponding to the global maxima of the group difference model which localized to medial OFC (-5, 53, -5, MNI) (Figure 1). Partial correlation between GM volume and behavioral data adjusted for IQ, education, and total GM was considered significant at $p<.05$, 1-tailed. A 1-tailed test was used because the hypothesis was that a higher GM would correlate with greater avoidance of “bad” cards.

Correlation between GM volume and CIDI symptom count

For each drug, CIDI-SAM generated a symptom count (11 total, from 7 dependence and 4 abuse symptoms). Partial correlation between symptom count and medial OFCGM volume was performed, adjusted for total GM, IQ, and age.

Effects of gender on GM volume and decision making behavior

A 2 × 2 (gender, group) ANOVA with covariates of age and total GM and multiple comparison correction was performed evaluating for a main effect of gender and gender by group interactions on GM volume and decision making behavior.

Results

There was no difference in age or gender between the groups. There were differences in education and IQ between the groups. IQ and education were correlated (p=.03). Table 1 shows the number of SDI meeting criteria for dependence or abuse. There was considerable variation in duration of abstinence across and within different drugs. Average abstinence from cocaine, alcohol, and amphetamine was 4.7, 3.2, and 2.4 years, respectively.

Whole brain analysis

Controls > SDI—Figure 1 is a color overlay and glass brain from a whole brain analysis using ANCOVA, adjusting for known confounds of age and global GM. There was significantly more GM specifically in bilateral medial OFC in controls compared to SDI. The most significant difference was right medial OFC ([-5, 53, -3], p<.004, corrected). Adding IQ as a covariate did not change the results. Since IQ and education were significantly correlated, we did not repeat the analysis with both covariates.

SDI > Controls—There were no significant regions of increased GM in SDI compared to controls using the same whole brain cluster-level correction for multiple comparisons.

ROI analysis

Medial left and right orbitofrontal regions confirmed the results from the whole brain analyses (control > SDI, Frontal_Med_Orb_Left, t=3.59, p=.001, Frontal_Med_Orb_Right, t=2.9, p=.006).

Behavioral

There was no main effect of time or group on selection of bad decks. Controls tended to avoid bad decks to a greater extent than SDI over time, but this interaction was not significant (Figure 2) (F=.88, p=.3).

Correlation between decision making performance and medial OFC gray matter volume

A small, significant negative correlation between medial OFC GM volume and avoidance of bad decks was observed across groups (r=-.39, p=.01,1-tail). After adjusting for age, education, and IQ, the correlation remained significant (r=-.35, p=.03, 1-tail). The correlation was higher in controls (r=-.37) than SDI (r=-.22) but due to small numbers was not significant within group (Figure 3).

Correlation between GM volume and CIDI symptom count

Among SDI there was no correlation between medial OFC GM volume and abuse and dependence symptom count (11 total, from 7 dependence and 4 abuse symptoms).

Effects of gender on GM volume and decision making behavior

There were no significant main effects of gender or gender by group interactions on GM volume in OFC. There was no difference in gender on performance.

Discussion

The finding of reduced medial orbital frontal cortex (OFC) gray matter (GM) in substance dependent individual (SDI) compared to controls is consistent with previous studies. Franklin et al. were the first to report lower GM in cocaine dependent subjects compared to controls using voxel-based morphometry (VBM) methods (10). They observed lower GM density in ventral medial OFC, anterior cingulate, and anterior insula. Lyoo et al. found lower GM in

bilateral medial OFC in opiate dependent subjects compared to controls (11). Less GM was also found in superior and middle frontal and anterior temporal lobes. In both of these studies subjects were using drugs close to or at the time of MR scanning. In Franklin et al., the average number of days cocaine was last used prior to imaging was 15. In the second paper, opiate-dependent persons were on methadone maintenance. Thus, a potentially important difference of the current study is the relatively prolonged abstinence. In this cohort of SDI abstinence averaged 2.4 years for amphetamine and longer for other drugs. Reversible effects of drugs on brain structure have been well documented for alcohol. Recovery of brain volume as assessed with MRI methods in alcoholics can be measured within a few weeks and may last months after sobriety (13,23,12). Such recovery appears to be impeded by relapse (13,14,23). While similar studies of reversible tissue loss have not been performed for illicit drugs, PET neuroimaging studies in methamphetamine abusers show a reduction in dopamine transporter availability that reverses with prolonged abstinence (24). These temporal changes associated with cessation and relapse underscore the importance of studying long-term as well as short-term changes. Thus, the prolonged abstinence in our population could account for relatively specific changes in medial OFC and suggests the possibility that differences in medial OFC reflect more persistent, enduring brain changes.

The orbitofrontal cortex has emerged as a potential neural substrate for an impaired ability to evaluate expected outcomes leading to poor decision making among SDI (8,2,4).Through its connections with the limbic system, OFC integrates associative information to produce a representation of expected outcomes. Chronic drug use results in adaptations in neural morphology and cell signaling that are thought to disrupt cognitive processes such as decision-making (8). Rats treated with cocaine show deficits in OFC-dependent functions such as reversal learning (4). In chronic cocaine users, metabolic abnormalities are relatively specific to frontal lobes (7). As noted above, some changes are transient, but others may persist long after drug exposure (2,25,26)

Our findings are consistent with behavioral studies showing decision-making deficits on the Iowa Gambling Task (IGT) in patients with ventral medial OFC lesions (16). Like patients with ventral medial frontal lesions, SDI are impaired on the IGT (27,28,29,30), although the impairments are less severe (30,28,31). This is consistent with our data suggesting that controls avoid “bad” decks over time more than SDI, but the differences were not significant. The negative correlation between medial OFC GM volume and decision to avoid bad cards is consistent with a role of OFC in evaluating expected outcomes. The correlation seemed mainly driven by controls, not SDI. We subsequently analyzed whether OFC GM correlated with abstinence, as such a relationship could suggest that chronic drug exposure influenced the OFC GM finding. However, there was no relationship between abstinence and morphology. On the other hand, the lack of a relationship does not imply a pre-morbid deficit as a number of other factors including severity of drug dependence, number or type of substances, and environmental factors could contribute to the findings. The possibilities of a pre-morbid condition, post-drug effect, or a combination remain equally likely.

We did not find regions of significantly increased GM in SDI compared to controls. One study using ROI methods found GM increases in striatum, accumbens and parietal cortex (32). Others have reported increases in striatal volume in cocaine abusers (33) and in thalamus and pre-central gyrus in marijuana users (34) compared to controls.

The major methodological difference between our study and previous ones using VBM is the use of the unified model that integrates segmentation, bias correction, and registration(19). Another technical difference is that MR images were acquired at 3T in this study compared to previous studies at 1.5T (10,11,35,14). Although this is not expected to significantly impact the results, it is worth noting that studies that have quantified gray matter-white matter contrast-

to-noise ratio (CNR) found higher CNR at 3T compared to 1.5 T when parameters are optimized (36,37). Higher gray matter-white matter CNR would be expected to result in better tissue segmentation and more accurate VBM results for a given spatial resolution and signal to noise ratio.

There are several limitations to this study. First, the sample size was modest (n=39) although in the range of similar studies. Second, subjects were dependent on multiple substances, precluding inferences about drug-specific effects on brain structure. Third, abstinence was based on self-report. SDI were remanded to residential treatment by the criminal justice system, either on diversion (instead of prison) or following a prison sentence, and before release to community probation. A minimum 2 months treatment compliance was required before they could participate in this study. Thus, the time in diversion or prison plus 2 months at ARTS resulted in relatively long abstinence. SDI were closely supervised and underwent frequent, observed urine drug tests. While self-report may be unreliable, it is highly unlikely that there were acute drug effects. Fourth, the findings of group differences and relationship between behavior and morphology are inconclusive about causality or predisposition. Finally, although a diagnosis of bipolar disorder was exclusionary, we did not specifically screen for major depression which has been shown to be associated with reduced OFC volume (38).

In conclusion, we found robust reductions in GM volume limited to bilateral medial OFC in abstinent substance dependent individuals compared to controls. This is the first paper reporting lower GM volume in this population *specific* to the medial OFC using whole-brain correction for multiple comparisons. Since abstinence was prolonged, the reduced medial OFC GM may reflect long-term adaptations within the reward-learning circuit underlying pathological decision making behavior in substance dependence.

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Reference List

1. Volkow ND, Li TK. Drug addiction: the neurobiology of behaviour gone awry. Nat Rev Neurosci 2004;5:963–970. [PubMed: 15550951]
2. Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. Am J Psychiatry 2005;162:1403–1413. [PubMed: 16055761]
3. Jentsch JD, Taylor JR. Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. Psychopharmacology (Berl) 1999;146:373–390. [PubMed: 10550488]
4. Schoenbaum G, Roesch MR, Stalnaker TA. Orbitofrontal cortex, decision-making and drug addiction. Trends Neurosci 2006;29:116–124. [PubMed: 16406092]
5. Stapleton JM, Morgan MJ, Phillips RL, Wong DF, Yung BC, Shaya EK, et al. Cerebral glucose utilization in polysubstance abuse. Neuropsychopharmacology 1995;13:21–31. [PubMed: 8526968]
6. London ED, Ernst M, Grant S, Bonson K, Weinstein A. Orbitofrontal cortex and human drug abuse: functional imaging. Cereb Cortex 2000;10:334–342. [PubMed: 10731228]
7. Volkow ND, Hitzemann R, Wang GJ, Fowler JS, Wolf AP, Dewey SL, et al. Long-term frontal brain metabolic changes in cocaine abusers. Synapse 1992;11:184–190. [PubMed: 1636149]
8. Volkow ND, Fowler JS. Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. Cereb Cortex 2000;10:318–325. [PubMed: 10731226]

9. Liu X, Matochik JA, Cadet JL, London ED. Smaller volume of prefrontal lobe in polysubstance abusers: a magnetic resonance imaging study. Neuropsychopharmacology 1998;18:243–252. [PubMed: 9509492]
10. Franklin TR, Acton PD, Maldjian JA, Gray JD, Croft JR, Dackis CA, et al. Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. Biol Psychiatry 2002;51:134–142. [PubMed: 11822992]
11. Lyoo IK, Pollack MH, Silveri MM, Ahn KH, Diaz CI, Hwang J, et al. Prefrontal and temporal gray matter density decreases in opiate dependence. Psychopharmacology (Berl) 2006;184:139–144. [PubMed: 16369836]
12. Pfefferbaum A, Sullivan EV, Rosenbloom MJ, Mathalon DH, Lim KO. A controlled study of cortical gray matter and ventricular changes in alcoholic men over a 5-year interval. Arch Gen Psychiatry 1998;55:905–912. [PubMed: 9783561]
13. Gazdzinski S, Durazzo TC, Meyerhoff DJ. Temporal dynamics and determinants of whole brain tissue volume changes during recovery from alcohol dependence. Drug Alcohol Depend 2005;78:263–273. [PubMed: 15893157]
14. Cardenas VA, Studholme C, Gazdzinski S, Durazzo TC, Meyerhoff DJ. Deformation-based morphometry of brain changes in alcohol dependence and abstinence. Neuroimage 2007;34:879–887. [PubMed: 17127079]
15. Tanabe J, Thompson LL, Claus ED, Dalwani M, Hutchison KE, Banich M. Prefrontal cortex activity is reduced in gambling and non-gambling substance abusers during decision-making. Human Brain Mapping 2007;28:1276–1286. [PubMed: 17274020]
16. Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. Cognition 1994;50:7–15. [PubMed: 8039375]
17. Cottler LB, Schuckit MA, Helzer JE, Crowley T, Woody G, Nathan P, et al. The DSM-IV field trial for substance use disorders: major results. Drug Alcohol Depend 1995;38:59–69. [PubMed: 7648998]
18. Compton WM, Cottler LB, Dorsey KB, Spitznagel EL, Mager DE. Comparing assessments of DSM-IV substance dependence disorders using CIDI-SAM and SCAN. Drug Alcohol Depend 1996;41:179–187. [PubMed: 8842630]
19. Ashburner J, Friston KJ. Unified segmentation. NeuroImage 2005;26:839–851. [PubMed: 15955494]
20. Hayasaka S, Phan KL, Liberzon I, Worsley KJ, Nichols TE. Nonstationary cluster-size inference with random field and permutation methods. NeuroImage 2004;22:676–687. [PubMed: 15193596]
21. Brett, M.; Anton, J.; Valabregue, R.; Poline, J. Region of interest analysis using an SPM toolbox. Eighth International Conference on Human Brain Mapping; Sendai, Japan. 2002.
22. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 2002;15:273–289. [PubMed: 11771995]
23. Pfefferbaum A, Sullivan EV, Mathalon DH, Shear PK, Rosenbloom MJ, Lim KO. Longitudinal changes in magnetic resonance imaging brain volumes in abstinent and relapsed alcoholics. Alcohol Clin Exp Res 1995;19:1177–1191. [PubMed: 8561288]
24. Volkow ND, Chang L, Wang GJ, Fowler JS, Franceschi D, Sedler M, et al. Loss of dopamine transporters in methamphetamine abusers recovers with protracted abstinence. J Neurosci 2001;21:9414–9418. [PubMed: 11717374]
25. Porrino LJ, Lyons D. Orbital and medial prefrontal cortex and psychostimulant abuse: studies in animal models. Cereb Cortex 2000;10:326–333. [PubMed: 10731227]
26. Jentsch JD, Redmond DE Jr, Elsworth JD, Taylor JR, Youngren KD, Roth RH. Enduring cognitive deficits and cortical dopamine dysfunction in monkeys after long-term administration of phencyclidine. Science 1997;277:953–955. [PubMed: 9252326]
27. Petry NM, Bickel WK, Arnett M. Shortened time horizons and insensitivity to future consequences in heroin addicts. Addiction 1998;93:729–738. [PubMed: 9692271]
28. Grant S, Contoreggi C, London ED. Drug abusers show impaired performance in a laboratory test of decision making. Neuropsychologia 2000;38:1180–1187. [PubMed: 10838152]
29. Mazas CA, Finn PR, Steinmetz JE. Decision-making biases, antisocial personality, and early-onset alcoholism. Alcohol Clin Exp Res 2000;24:1036–1040. [PubMed: 10924007]

30. Bechara A, Dolan S, Denburg N, Hindes A, Anderson SW, Nathan PE. Decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. Neuropsychologia 2001;39:376–389. [PubMed: 11164876]

31. Petry NM. Substance abuse, pathological gambling, and impulsiveness. Drug Alcohol Depend 2001;63:29–38. [PubMed: 11297829]

32. Jernigan TL, Gamst AC, Archibald SL, Fennema-Notestine C, Mindt MR, Marcotte TD, et al. Effects of methamphetamine dependence and HIV infection on cerebral morphology. Am J Psychiatry 2005;162:1461–1472. [PubMed: 16055767]

33. Jacobsen LK, Giedd JN, Gottschalk C, Kosten TR, Krystal JH. Quantitative morphology of the caudate and putamen in patients with cocaine dependence. Am J Psychiatry 2001;158:486–489. [PubMed: 11229995]

34. Matochik JA, Eldreth DA, Cadet JL, Bolla KI. Altered brain tissue composition in heavy marijuana users. Drug Alcohol Depend 2005;77:23–30. [PubMed: 15607838]

35. Fein G, Landman B, Tran H, McGillivray S, Finn P, Barakos J, et al. Brain atrophy in long-term abstinent alcoholics who demonstrate impairment on a simulated gambling task. Neuroimage 2006;32:1465–1471. [PubMed: 16872844]

36. Fushimi Y, Miki Y, Urayama S, Okada T, Mori N, Hanakawa T, et al. Gray matter-white matter contrast on spin-echo T1-weighted images at 3 T and 1.5 T: a quantitative comparison study. Eur Radiol 2007;17:2921–2925. [PubMed: 17619195]

37. Lu H, Nagae-Poetscher LM, Golay X, Lin D, Pomper M, van Zijl PC. Routine clinical brain MRI sequences for use at 3.0 Tesla. J Magn Reson Imaging 2005;22:13–22. [PubMed: 15971174]

38. Lacerda AL, Keshavan MS, Hardan AY, Yorbik O, Brambilla P, Sassi RB, et al. Anatomic evaluation of the orbitofrontal cortex in major depressive disorder. Biol Psychiatry 2004;55:353–358. [PubMed: 14960287]

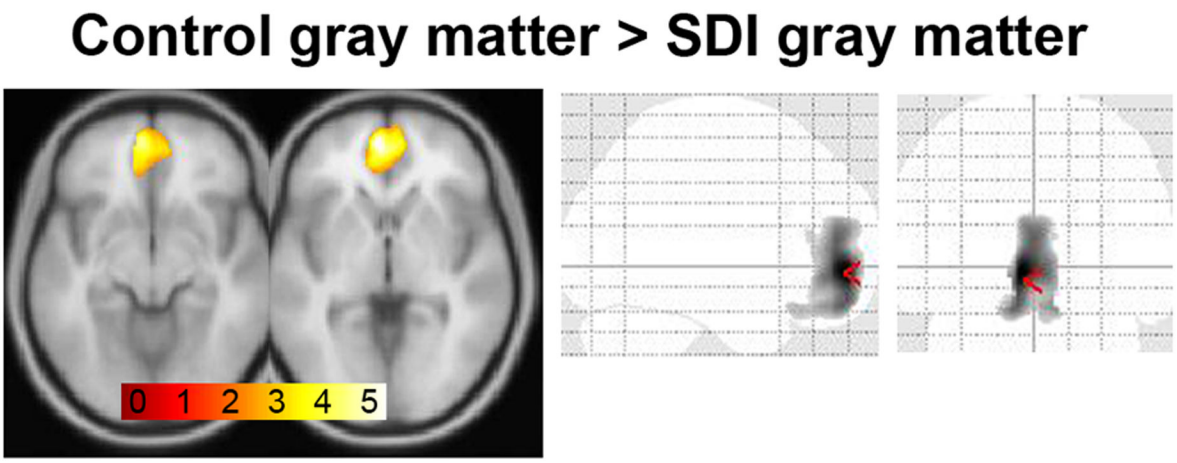

Figure 1.
Color map and glass brain showing increased gray matter in OFC in controls compared to substance dependent individuals (SDI), after co-varying for total GM and age (threshold p<.05, cluster-level, corrected for multiple comparisons family-wise error, voxel level, p<.005). Color bar represents t-values. Color map is overlaid on canonical avg152T1 template.

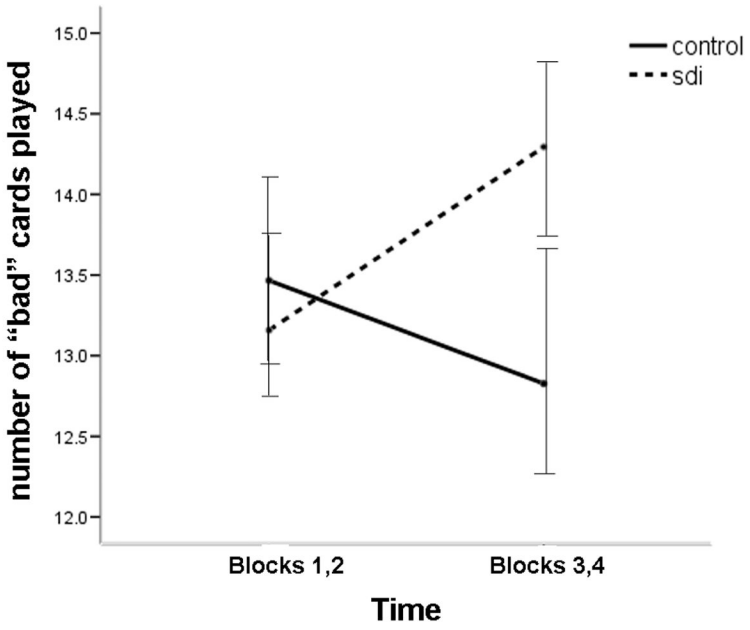

Figure 2.
Estimated marginal mean of "bad" cards played over time for SDI and controls, adjusted for education, IQ, and age. Over time controls played fewer "bad" cards than SDI, but the group by time interaction was not significant due to high variability. Mean and SEM are shown.

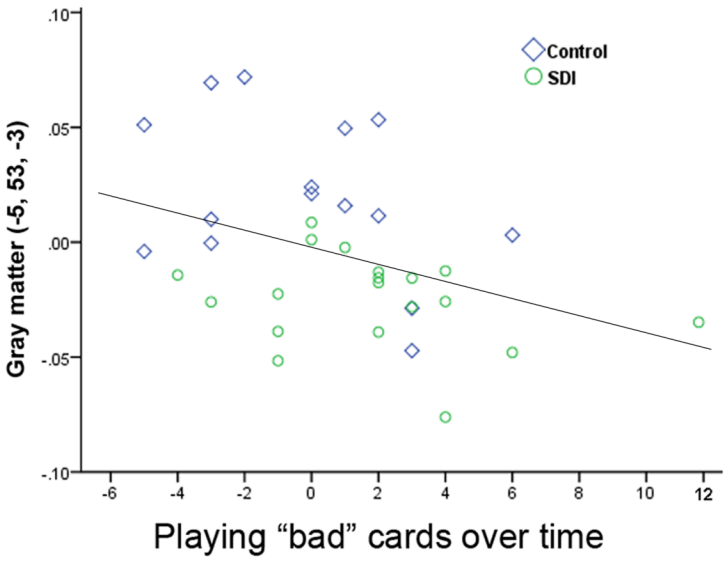

Figure 3.

Scatterplot of medial OFC gray matter volume (at -5, 53, -3), adjusted for total GM and age, and persistence in playing “bad” cards. A significant negative correlation was observed (r=-.39, p=.01 without controlling for IQ and education)(r=-.35, p=.03, after controlling for IQ and education).

Table 1

Demographic and substance dependence variables for SDI and control samples. Dependence = number of subjects meeting DSM-IV criteria for dependence; abuse=number of subjects meeting DSM-IV criteria for abuse. Mean ± SD (range) are shown. *p<.005.

	Controls (20)	SDI (19)	
Demographic			
Age	33 ± 11 (23-50)	35 ± 7 (21-47)	
Gender	6 M / 14 F	10 M / 9 F	
IQ	*112 ± 8 (91-130)	103 ±12 (80-121)	
Education	*14 ± 2 (12-19)	12 ± 3 (6-16)	
Drug		Dependence/abuse	Last use (yrs)
Cocaine	N/A	14 / 3	4.7 ± 4.8 (.2-18)
Alcohol	N/A	13 / 2	3.2 ± 8.3 (.8-9)
Amphetamine	N/A	12 / 2	2.4 ± 2.1 (1-8)
Cannabis	N/A	11 /4	4.4 ± 4.6 (.2-16)
Opiate	N/A	5 / 2	6.4 ± 7.4 (.2-22)
Club drugs	N/A	1 / 2	5.3 ± 5.9 (1-18)
Hallucinogens	N/A	1 / 9	8.0 ± 6.3 (.3-22)
Sedative	N/A	1 / 4	5.7 ± 6.5 (.3-22)