

Medial Orbitofrontal Cortex Gray Matter Is Reduced in Abstinent Substance-Dependent Individuals

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Background: Chronic exposure to drugs of addiction induces cellular adaptations in orbitofrontal cortex (OFC) and associated limbic-prefrontal pathways that might underlie abuse-related behavior. A propensity to make risky decisions in spite of substantial negative consequences might 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 with control subjects.

Methods: Nineteen SDI and 20 control subjects participated. The SDI were dependent on two 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 3-T magnetic resonance system. Image processing and analyses were conducted with voxel-based morphometry (VBM) implemented in Statistical Parametric Mapping (SPM) 5. Differences in regional GM volume were tested with 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 with control subjects. 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 study to use VBM with whole brain correction for multiple comparisons in SDI after prolonged abstinence. Reduced medial OFC GM might reflect long-term adaptations within the reward-learning circuit underlying pathological decision-making in substance dependence.

Key Words: Orbitofrontal cortex, substance dependence, voxel based morphometry

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 (1–4). Long-term cellular changes in prefrontal cortex associated with 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 (5–8) and structural abnormalities in orbitofrontal cortex (OFC) in substance dependence. Liu *et al.* (9) found smaller prefrontal but not temporal cortex in poly-substance abusers compared with control subjects. Studies using voxel-based morphometry (VBM) have found reduced medial OFC, anterior cingulate, and insular gray matter (GM) in cocaine addicts (10) and prefrontal and temporal GM in opiate addicts (11). In a study of methamphetamine addiction and human immunodeficiency virus (HIV) infection, methamphetamine was associated with an increase in lentiform GM 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 with the time of magnetic resonance (MR) scanning. This is important because: 1) some drug effects on neural substrate might be reversible, as has been shown for alcohol (12–14); and 2) 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 GM 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 with control subjects during decision-making (15). The task was a modified Iowa Gambling Task (IGT) that 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 whether the volume of medial OFC GM is lower in abstinent SDI compared with control subjects.

Methods and Materials

Subjects

Thirty-nine subjects, including 20 control subjects (14 women/6 men, 33 years old, SD 11 years) and 19 SDI (9 women/10 men, 35 years old, SD 7 years) participated in this study. The 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, with DSM-IV criteria. Inclusion criteria for the control subjects 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 < 80. All participants provided written informed consent approved by the Colorado Multiple Institutional Review Board.

Behavioral Measures

In SDI, drug dependence was measured with the computerized Composite International Diagnostic Interview Substance Abuse Module (CIDI-SAM) (17). The CIDI-SAM is a structured

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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. The CIDI-SAM was not given to control subjects. Performance data on the modified gambling task were available for 34 (15 control subjects, 19 SDI) of the 39 subjects. We used a modification of the IGT adapted for a functional magnetic resonance imaging (MRI) 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 two time blocks, early and late. The number of times an individual chose to play “bad” decks on early compared with late trials was totaled. Repeated measures analysis of variance (ANOVA) with IQ, education, and age as covariates was performed in SPSS (SPSS, Chicago, Illinois) analyzing for effects of group \times time interaction.

The 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-T whole body MR scanner (General Electric, Milwaukee, Wisconsin) with a standard quadrature head coil. A high-resolution three-dimensional T1-weighted spoiled gradient echo (SPGR)-IR sequence used the following parameters: repetition time = 45, echo time = 20, flip angle = 45°, 256² matrix, 240 mm² field-of-view (.9 \times .9 mm² in-plane), 1.7-mm thick slice, coronal plane. Scan time was 9 min 24 sec. A neuroradiologist (JT) evaluated anatomical images for motion artifact and the echo planar T2* images for gross structural abnormalities, particularly encephalomalacia. No studies were excluded.

Image Processing and Statistics

Image processing was conducted with the Voxel-based morphometry toolbox (VBM5.1) (<http://dbm.neuro.uni-jena.de/vbm/>) implemented in Statistical Parametric Mapping (SPM5) running on Matlab 7.5. The VBM in SPM5 combines tissue segmentation, bias correction, and spatial normalization into a unified model (19). Hidden Markov Random Fields (HMRF) were applied to improve accuracy of tissue segmentation (medium HMRF .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 full-width-at-half-maximal Gaussian kernel resulted in a final smoothing of 14 \times 15 \times 14 mm³. At the second level, whole

brain data were modeled across the groups with 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 with family-wise error (FWE), and a voxel-level threshold of $p < .005$. To ensure the validity of cluster-level statistics, a nonisotropic smoothness correction was applied (20).

Medial OFC Region of Interest

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

Correlation Between GM Volume and Decision-Making Behavior

The GM volume was obtained from the voxel corresponding to the global maxima of the group difference model that localized to medial OFC (−5, 53, −5, Montreal Neurological Institute) (Figure 1). Partial correlation between GM volume and behavioral data adjusted for IQ, education, and total GM was considered significant at $p < .05$, one-tailed. A one-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 OFC GM volume was performed, adjusted for total GM, IQ, and age.

Effects of Gender on GM Volume and Decision-Making Behavior

A 2 \times 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 \times 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

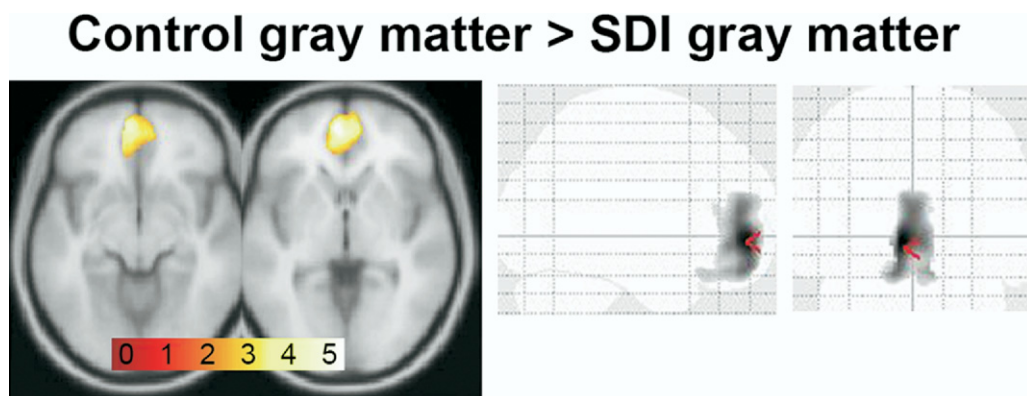


Figure 1. Color map and glass brain showing increased gray matter in orbitofrontal cortex (OFC) in control subjects compared with substance-dependent individuals (SDI), after co-varying for total gray matter and age (threshold $p < .05$, cluster-level, corrected for multiple comparisons family-wise error,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

Table 1. Demographic and Substance Dependence Variables for SDI and Control Samples

	Control Subjects (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)

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.

SDI, substance-dependent individuals.

* $p < .005$.

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

Control Subjects > SDI. Figure 1 is a color overlay and glass brain from a whole brain analysis with ANCOVA, adjusting for known confounds of age and global GM. There was significantly more GM specifically in bilateral medial OFC in control subjects compared with 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. Because IQ and education

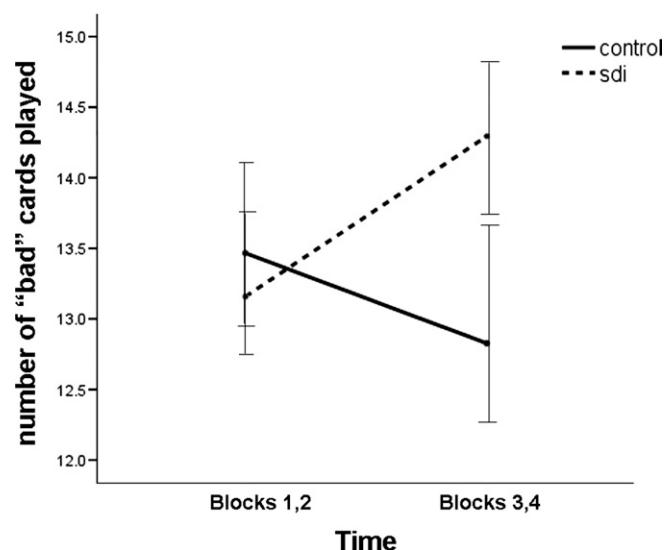


Figure 2. Estimated marginal mean of "bad" cards played over time for substance-dependent individuals (SDI) and control subjects, adjusted for education, IQ, and age. Over time control subjects played fewer "bad" cards than SDI, but the group \times time interaction was not significant due to high variability. Mean and SEM are shown.

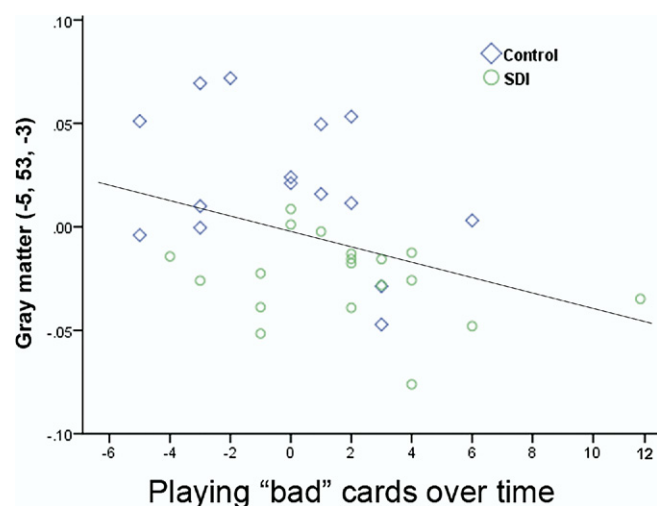


Figure 3. Scatterplot of medial orbitofrontal cortex gray matter volume (at $-5, 53, -3$), adjusted for total gray matter and age, and persistence in playing "bad" cards. A significant negative correlation was observed ($r = -.39, p = .01$ without controlling for IQ and education) ($r = -.35, p = .03$, after controlling for IQ and education). SDI, substance-dependent individuals.

were significantly correlated, we did not repeat the analysis with both covariates.

SDI > Control Subjects. There were no significant regions of increased GM in SDI compared with control subjects with the same whole brain cluster-level correction for multiple comparisons.

ROI Analysis

Left and right medial 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. Control subjects 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 GM Volume

A small, significant negative correlation between medial OFC GM volume and avoidance of bad decks was observed across groups ($r = -.39, p = .01$, one-tail). After adjusting for age, education, and IQ, the correlation remained significant ($r = -.35, p = .03$, one-tail). The correlation was higher in control subjects ($r = -.37$) 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 \times group interactions on GM volume in OFC. There was no difference in gender on performance.

Discussion

The finding of reduced medial OFC GM in SDI compared with control subjects is consistent with previous studies. Franklin *et al.* (10) were the first to report lower GM in cocaine-dependent subjects compared with control subjects with VBM methods. They observed lower GM density in ventral medial OFC, anterior cingulate, and anterior insula. Lyoo *et al.* (11) found lower GM in bilateral medial OFC in opiate-dependent subjects compared with control subjects. 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 that cocaine was last used before imaging was 15. In the second study, opiate-dependent persons were receiving 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 alcoholic subjects can be measured within a few weeks and might last months after sobriety (12,13,23). Such recovery seems to be impeded by relapse (13,14,23). Whereas similar studies of reversible tissue loss have not been performed for illicit drugs, positron emission tomography 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 OFC has emerged as a potential neural substrate for an impaired ability to evaluate expected outcomes leading to poor decision-making among SDI (2,4,8). 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 earlier, some changes are transient, but others might persist long after drug exposure (2,25,26).

Our findings are consistent with behavioral studies showing decision-making deficits on the IGT in patients with ventral medial OFC lesions (16). Like patients with ventral medial frontal lesions, SDI are impaired on the IGT (27–30), although the impairments are less severe (28,30,31). This is consistent with our data suggesting that control subjects 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 control subjects and not by SDI. We subsequently analyzed whether OFC GM correlated with abstinence, because such a relationship could suggest that chronic drug exposure influenced the OFC GM finding. However, there was no relationship between abstinence and morphology. In contrast, the lack of a relationship does not imply a pre-morbid deficit, because 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 with control subjects. 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 with control subjects.

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 3-T in this study compared with previous studies at 1.5-T (10,11,14,35). Although this is not expected to significantly impact the results, it is worth noting that studies that have quantified GM–white matter contrast/noise ratio (CNR) found higher CNR at 3-T compared with 1.5-T when parameters are optimized (36,37). Higher GM–white matter CNR would be expected to result in better tissue segmentation and more accurate VBM results for a given spatial resolution and signal/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. The 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-month 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. The SDI were closely supervised and underwent frequent, observed urine drug tests. Although self-report might 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 SDI compared with control subjects. This is the first article reporting lower GM volume in this population specific to the medial OFC with whole-brain correction for multiple comparisons. Because abstinence was prolonged, the reduced medial OFC GM might reflect long-term adaptations within the reward-learning circuit underlying pathological decision-making behavior in substance dependence.

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