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Low Prefrontal Perfusion Linked to Depression Symptoms in Methadone-Maintained Opiate-Dependent Patients

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Abstract

Background—Clinically depressed patients without substance use disorders, compared to controls, exhibit significantly lower resting regional cerebral blood flow (rCBF) in the prefrontal cortex (PFC). In this study, we examined the link between resting rCBF in the PFC and current depressive symptoms in methadone-maintained opiate-dependent (MM) patients with or without major depression.

Methods—Arterial spin labeled perfusion fMRI at 3 Tesla was used to measure resting rCBF in 21 MM patients. Perfusion data were analyzed using SPM2. The relationship between Beck Depression Inventory (BDI) score and resting rCBF was examined in a single regression analysis.

Results—The BDI scores ranged between 0 and 18 ($m=7.0$, $s.d.=4.8$), and 30% of the sample had mild to moderate depression symptoms according to BDI scores. A negative correlation was observed between BDI scores and relative rCBF in the left and right ventrolateral prefrontal cortex, and left and right middle frontal gyrus.

Conclusions—The inverse relationship between prefrontal paralimbic rCBF and depression scores suggests an association between fronto-limbic dysfunction and depressive symptoms in MM patients. A significant subgroup of opiate-dependent patients has clinical and sub-clinical depression that are often undetected; our data identify brain substrates underlying depression symptoms that may be a potential marker of relapse in this population. Treatment strategies targeting these brain regions may improve depression symptoms in substance abusers.

Keywords

opiate dependence; depression; methadone-maintenance; affect regulation; comorbidity; prefrontal cortex

1. Introduction

Depressive symptoms are common in methadone-maintained opiate-dependent patients (MM) (Brienza et al., 2000; Kidorf et al., 2004; Nunes et al., 2004; Peles et al., 2007), such that 42%

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to 54% of MM patients experience clinically significant depression. Given that depression is an important dimension of relapse vulnerability in opiate addiction, an investigation of the relationship between depression and brain function in MM patients may provide an insight into the shared mechanism of affect dysregulation.

Recent neuroimaging studies report frontal abnormalities in both depression and opiate dependence. For example, non-opiate-dependent, clinically depressed individuals, when compared to non-depressed controls, have reduced resting regional cerebral blood flow (rCBF), metabolism or grey matter volume in the frontal paralimbic regions (Drevets, 2000; Goodwin, 1997), including the subgenual prefrontal cortex (Drevets et al., 1997), middle frontal (Bench et al., 1992; Chen et al., 2007), inferior frontal (Mayberg et al., 1994) and dorsomedial/lateral prefrontal cortex (Drevets, 1999; Mayberg et al., 1997). Abnormalities in the prefrontal regions, including reduced rCBF in the prefrontal cortex (Danos et al., 1998; Rose et al., 1996) and gray matter density in bilateral prefrontal cortex (Lyo et al., 2006) relative to healthy comparison controls, have also been associated with opiate dependence. Because of the high degree of connectivity between the paralimbic regions and the limbic system, the prefrontal paralimbic regions are thought to regulate emotions (Drevets, 1999, 2000; Ochsner et al., 2002; Ochsner et al., 2004) and motivation to seek drugs (Kalivas et al., 2005; Kalivas and Volkow, 2005).

Although both depression and opiate dependence are associated with prefrontal abnormalities, the functional neuroanatomy of the comorbid opiate dependence and depression is not well understood. Gerra et al. (1998) found that 4-month drug-free depressed opiate-dependent patients had lower perfusion in the right frontal and left temporal lobes, relative to both healthy controls and detoxified opiate-dependent patients without depression symptoms. In the study, depression symptoms were negatively correlated only with perfusion in the general areas of the left temporal lobe (Gerra et al., 1998). In MM patients, Galynker et al. (2007) also did not find a significant relationship between regional cerebral glucose metabolism and a measure of dysthymia. However, sampling limitations, such as Gerra et al.'s (1998) use of drug abstinent sample and Galynker et al.'s exclusion of depressed patients, could explain the non-significant findings. Therefore, based on the wealth of data demonstrating the link between depression and frontal abnormalities, we examined a sample of 21 MM patients to characterize the relationship between current depression symptoms and prefrontal functioning, using arterial spin labeled (ASL) perfusion fMRI. We hypothesized that the depressive symptoms in MM patients would be inversely related to the resting rCBF in the frontal regions of interest (ROIs) based on the literature on depression, consisting of the lateral, orbitofrontal and medial prefrontal cortex regions, and the anterior cingulate cortex.

2. Method

2.1 Participants

The participants were 21 men (n=11) and women (n=10) who met the following inclusion criteria: 1) ages between 18 to 65 (inclusive); 2) DSM-IV criteria for lifetime diagnosis of opiate dependence; 3) enrolled in a methadone-maintenance treatment program; 4) speaks, understands, and prints in English; and 5) signs written informed consent. Each participant gave written consent to participate in the study after hearing and reading a description of the study procedures. This study was approved by the Institutional Review Board of the University of Pennsylvania.

Fourteen were right-handed, 3 left-handed, and 4 ambidextrous. The mean age of the participants was 35.52 (s.d.=10.77), and 19 (90.5%) were Caucasian. They had completed an average of 13.31 (s.d.= 2.42) years of education. All subjects were primarily heroin users with an average of 11.05 (s.d.=9.91) years of use. Their last heroin use occurred 15.58 (s.d.=15.34)

months prior to the study enrollment. No subject had used heroin or other illicit substances within 30 days prior to the study enrollment.

The subjects had been in methadone-maintained treatment for approximately 2.25 (s.d.=2.13) years in their lifetime. At the time of the initial screening, their average methadone dose was 100.24mg (s.d.=54.52). Their current abstinence from illicit drugs and compliance with methadone-maintenance treatment was confirmed by urine toxicology screen at study enrollment and before the imaging session. Ten patients smoked cigarettes regularly. None of the patients were prescribed with psychotropic medications at the time of the study. Eleven of 21 patients were diagnosed with major depressive episode (current or recurrent; 6 current) (DSM-IV) using the Mini International Neuropsychiatric Interview (Sheehan et al., 1998) at the time of the screening.

Individuals were excluded if they met any of the following conditions: 1) a diagnosis of current alcohol or other drug dependence; 2) psychiatric diagnoses other than depression; 3) clinically significant cardiovascular, hematologic, hepatic, renal, neurological or endocrinological abnormalities; 4) a history of serious head trauma or injury causing a loss of consciousness lasting more than 3 minutes; 5) a history of psychosis or organic brain syndrome unrelated to drug abuse; 6) a presence of magnetically active prosthetics, plates, pins, broken needles, permanent retainer, bullets, etc. in subject's body; and 7) claustrophobia or other medical conditions that would preclude a subject from lying in the MRI for approximately 60 minutes.

2.2 Procedure

On the day of the imaging session, a trained research technician administered self-report behavioral measures (see below). Prior to the resting perfusion sequence (see Acquisition Parameters section), the subjects were instructed to look directly at a black computer screen during the imaging session. Each MM subject was scanned 90 minutes prior to their daily methadone dose. This time point was roughly near the trough of methadone plasma level with once daily dosing (Dyer and White, 1997).

2.2.1 Behavioral Measures—The Beck Depression Inventory (BDI) (Beck et al., 1961) is a 21-item self-report questionnaire on depressive symptoms. Each item is scored between 0 (no symptom) and 3 (severe symptoms). Total score can range between 0 and 63. A score of 10–18 indicates mild to moderate depression, 19–29 moderate to severe depression, and 30–63 severe depression.

The Symptom Checklist-90-Revised (SCL-90-R) (Derogatis, 1977) is a 90-item self-report symptom inventory measuring the level of overall psychological distress during a previous 7-day period. Each item is rated on a 5-point scale, between 0 (“not at all”) and 4 (“extremely”). We used the Depression subscale (13 items) to assess dysphoric mood and affect, loss of interest, lack of motivation and energy, feelings of hopelessness, and thoughts of suicide.

2.2.2 Acquisition Parameters—MR scanning was conducted on a Siemens 3.0 Tesla Trio whole-body scanner (Siemens AG, Erlangen, Germany), using a standard Transmit/Receive Brucker head coil. A 3-plane localizer scan and a T1-weighted high-resolution scan (approximately six minutes) were acquired before functional scanning. These scans served a dual purpose: they were used for subsequent anatomical co-registration and normalization of the functional images, and provided the subject with an introduction and habituation period to the MR environment. The 3-plane localizer scan (sagittal, axial and coronal) was acquired with FOV = 280 mm, TR/TE = 20/5ms, 192×144 matrix, and slice thickness 5mm. Acquisition parameters for the 3D high resolution MPRAGE structural in the axial plane were: FOV = 250 mm, TR/TE = 1620/3.87ms, 192×256 matrix, slice thickness 1 mm.

Immediately following the MPRAGE scan, an arterial spin labeling (ASL) perfusion fMRI (Wang et al., 2003b) sequence was used to measure resting CBF of the whole brain. Participants were administered a 3T optimized amplitude modulated continuous arterial spin labeling (CASL) perfusion imaging sequence (Wang et al., 2005): Interleaved images with and without labeling were acquired using a gradient echo echo-planar imaging sequence. A delay of 700 ms was inserted between the end of the labeling pulse and image acquisition to reduce transit artifact (Alsop and Detre, 1996). Acquisition parameters were: FOV=22cm, matrix=64×64, TR/TE = 3000/17ms, flip angle=90°. Fourteen slices (8mm thickness with 1.5mm gap) were acquired from inferior to superior in a sequential order. Each CASL scan with 100 acquisitions took 10 minutes. Each resting perfusion session was completed within the first 15 minutes of the scanning.

2.2.3 Pre-Processing and Image Analysis—Perfusion fMRI data were pre-processed and analyzed using the SPM2 software package (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK, <http://www.fil.ion.ucl.ac.uk>) and customized ASL processing software. The MR image series was first realigned to a reference volume to correct for head movements, co-registered with each subject's anatomical MRI, and spatially smoothed with an isotropic Gaussian kernel with FWHM (Full Width at Half Maximum) of 10mm. A perfusion weighted image series was generated using the sinc-subtraction method to counterbalance the acquisition time gap between the label and control images (Aguirre et al., 2002), followed by a conversion to absolute CBF image series based on a single compartment CASL perfusion model (Detre et al., 1992). Functional data were registered to Montreal Neurological Institute (MNI) 152 standard space template, and displayed on the single subject ("Colin") structural MRI template. Voxel-wise analyses of the CBF data were conducted on each subject, utilizing a general linear model (GLM) including the global time course as a covariate to reduce the effect of spatially coherent noise (first-level analysis) (Wang et al., 2003a). No temporal filtering or smoothing was involved.

Resting relative mean CBF images were then produced for across subject analysis. The relationship of the scan-day Beck Depression Inventory (BDI) score with resting relative rCBF was examined in a single (simple) regression analysis, and by Pearson's correlation coefficient (r). We included age, sex, handedness and smoking status variables as nuisance covariates in the analysis in order to correct for CBF variations with aging (Meltzer et al., 2000), sex (Parkes et al., 2004), handedness (Toga and Thompson, 2003) and smoking (Domino et al., 2000). The negative correlational relationships were identified using a cluster corrected whole brain analysis with a voxel probability of $p < 0.005$ and a cluster probability of $p < 0.05$.

3. Results

3.1 MM BDI Scores

The BDI scores ranged between 0 and 18, with a mean of 7.0 (s.d.=4.8). Approximately 33% of the sample had scores greater than 9, indicating that these patients experienced mild to moderate depression. No subjects had BDI scores indicating severe depression. Pearson's product-moment correlation and point biserial correlation were used to examine the relationship between BDI scores and other behavioral measures (e.g., cocaine use; overall psychological distress). The results of these analyses are shown in Table 1. At the initial screening, BDI scores were significantly correlated with SCL-90-R Depression subscale ($r=0.637$, $p=0.003$), and with the diagnosis of major depressive episode ($r=0.466$; $p=0.033$).

3.2 Relationship between BDI and rCBF

Anatomical coordinates of all significant regions are listed in Table 2 (Lancaster et al., 2000; Talairach and Tournoux, 1988).

Regression analyses with age, sex, handedness and smoking status as nuisance covariates (cluster corrected whole brain analysis) showed a significant relationship between increased BDI scores and reduced resting relative rCBF in the following ROIs: Right ventrolateral prefrontal cortex (VLPFC) (MNI coordinates: 12, 52, -12; $r = -0.7898$; $p = 0.0001$) (Figure 1, A and B); left VLPFC (MNI coordinates: -16, 48, -6; $r = -0.7104$; $p = 0.0003$) (Figure 1, C and D); right middle frontal gyrus (MNI coordinates: 42, 26, 27; $r = -0.7527$; $p < 0.0001$) (not shown); and left middle frontal gyrus (MNI coordinates: -40, 10, 57; $r = -0.7804$; $p < 0.0001$) (not shown).

Although not a priori ROI in the present study, we found that reduced baseline perfusion in the left inferior parietal lobe correlated with higher BDI scores (MNI coordinates: -40, -40, 30; $r = -0.7589$, $p < 0.0001$). We did not find a significant relationship between temporal lobe regions and BDI scores.

4. Discussion

Previously, reduced perfusion in the prefrontal cortex has been observed in both clinically depressed (Drevets, 2000) and opiate-dependent individuals (Danos et al., 1998; Rose et al., 1996). In this study, we examined the relationship between baseline rCBF and depressive symptoms in MM patients, who met or did not meet the diagnosis of major depression. We found that reduced baseline rCBF in the bilateral VLPFC and middle frontal regions were linked to higher depression scores on the BDI, a continuous measure of depression symptoms. These findings suggest that frontal paralimbic dysfunction may be linked to depressive symptoms in patients with and without opiate dependence.

Because opiate-dependent patients report fewer depressive symptoms over the course of methadone treatment (Hesse, 2006), our patient sample, whose methadone treatment averaged 2.25 years, had a low, narrow range of depressive symptoms and did not meet the BDI score criterion for major depression of 21 as suggested by Geisser et al. (1997). Despite this limited range, the inverse relationship between rCBF and depression scores was robust.

In a sample of abstinent opiate abusers, Gerra et al (1998) showed a significant negative correlation between depression symptoms and perfusion in the left temporal lobe, and near significant negative correlation in the frontal lobe. Our voxel-based fMRI approach, which provides more localized results, demonstrates the inverse relationship between frontal perfusion and depression symptoms. Interestingly, perfusion in the temporal lobe region was not inversely associated with depression symptoms in our study. This lack of consistency between our results and Gerra et al's (1998) may be due to the differences in participant samples. First, Gerra et al.'s (1998) patients were former opiate-dependent patients who had been abstinent for 4 months. Additionally, using a sample of patients who entered a voluntary therapeutic community and did not seek methadone-maintenance treatment may help explain the differences in results. Alternatively, the relationship between perfusion in the temporal lobe and depression symptoms is demonstrably different in men and women (Videbech et al., 2002), suggesting that the differences in sex distribution of the samples may help explain the discrepancy between the results.

Our findings are in agreement with two previous investigations that reported a negative correlation between depression symptoms as measured by BDI, and frontal brain metabolism (Dunn et al., 2002) or rCBF (Bench et al., 1993) in clinically depressed patients. However, two studies using Hamilton Rating Scale for Depression scores (HRSD) reported no association (Milak et al., 2005) or a positive association (Graff-Guerrero et al., 2004). The inconsistent results may reflect that BDI and HRSD, in part, assess different dimensions of depression; the BDI captures cognitive and affective dimensions whereas the HRSD captures somatic and

behavioral dimensions (Brown et al., 1995). Using cluster factors offered by Brown et al (Brown et al., 1995), 70% of the total BDI scores from our sample derive from items that measure negative affect and cognition. Given that different depression subtypes show unique brain perfusion patterns (Fountoulakis et al., 2004), our results may be most applicable to patients exhibiting a specific subset of depression symptoms. For example, in the present study, we used the BDI, a well-validated, stand-alone assessment tool with excellent psychometric properties, to measure severity of depression symptoms. An informal analysis between perfusion and SCL-90-R Depression subscale scores, which measure nonspecific depressive symptoms (Bonyng, 1993; Clark et al., 1983; Rauter et al., 1998) and accounted for only 41% of the variance with our BDI scores, yielded non-significant findings. Future neuroimaging investigations on depression should consider using a specific depression scale relevant to a depression subtype of interest.

In addition to the frontal resting perfusion findings from the aforementioned studies, the VLPFC and medial frontal regions have been observed to be crucial in emotional regulation (Grimm et al., 2006; Ochsner et al., 2002; Ochsner et al., 2004). For example, performing a task to regulate emotions was associated with increased activities in the VLPFC and middle frontal regions in healthy subjects. Given that depressed patients are poor affect regulators (Forbes et al., 2005; Garber et al., 1995), our results suggest that a similar relationship between poor affect regulation and frontal dysfunction is also present in our MM patients.

Though not a priori ROI in our study, perfusion in the left inferior parietal lobe was also negatively correlated with BDI scores. Two studies have reported reduced perfusion (Galynker et al., 1998) or glucose metabolism (Biver et al., 1994) in the parietal regions in depressed patients compared to normal controls, although its correlational relationship with depressive symptoms was not significant. This region has been associated with opiate withdrawal (Rose et al., 1996) and levomethadone dosage (Danos et al., 1998) in MM patients. Based on our results, it is possible the previous findings from Rose et al. (1996) and Danos et al. (1998) might be a result of withdrawal symptoms secondary to depressive symptoms. A further examination of the region's role in depressive symptoms for MM patients is warranted.

Resting rCBF in the anterior cingulate, an a priori ROI, was not significantly related to the depressive symptoms in our MM sample. Previous studies have reported abnormalities in the anterior cingulate regions in opiate-dependent patients (Forman et al., 2004; Lee et al., 2005; Yucel et al., 2007). In particular, Yucel et al. (2007) recently demonstrated that opiate-dependent patients had significantly lower concentrations of N-acetylaspartate (NAA), a marker of neuronal integrity, in the anterior cingulate when compared to healthy controls. Galynker et al. (2007) previously found a significant association between cerebral glucose metabolism in the left perigenual anterior cingulate and dysthymic scores, although the participants engaged in an attention task. Given the existing evidence for the association between depressive symptoms and brain dysfunction in this region, a further examination of the anterior cingulate's role in depressive symptoms for MM patients is warranted.

Our study has several limitations. First, our results do not explain whether dysfunction in the fronto-limbic systems and depressive symptoms contribute to the initiation/maintenance (e.g., relapse) of substance addiction, as compared to being a consequence of chronic drug use. One challenging task would be to investigate the relationship between depression (i.e., affect regulation) and addiction prospectively, with particular emphasis on neural mechanisms. Second, we used the BDI scores to assess the relationship between affect regulation and addiction. This relationship should be examined with a behavioral probe that can more directly measure the construct of affect regulation. Third, due to lack of comparable data from a matched cohort, we were not able to compare our present data to a healthy control group. Galynker et al. (2007) recently reported that self-reported dysthymic scores were negatively correlated with

cerebral glucose metabolism levels in the right perigenual anterior cingulate in controls. Comparing our present data to a healthy control group would be helpful in understanding the relationship between brain perfusion and depressive symptoms in MM patients, especially the unique ways in which MM patients process negative affect. Furthermore, the present study explicitly attempted to measure individual variations in mental or emotional activity during resting state and their functional relationship to brain perfusion at rest, and to relate them to the self-reported, depressive symptoms. Because our research depends on the natural, spontaneous variations in mental or emotional states during the resting condition, no explicit attempt was made to control for internal states during resting scans.

Lastly, future research should examine the relationship between the rCBF and gray matter concentration in the PFC regions. Lyoo et al. (2006) reported that opiate-dependent patients have decreased gray matter density in the PFC. Further, Drevets et al. (1997) found that decreased activity in the anterior cingulate in depressed individuals is partially due to a grey matter volume reduction in the PFC area. It would be important to explore this particular relationship in MM patients, to determine whether the observed rCBF abnormalities reflect functional and/or structural differences, and extend our current understanding of the relationship between the PFC and depression symptoms in opiate addiction.

In conclusion, our findings showed an inverse relationship between rCBF in the bilateral VLPFC and middle frontal regions, and depressive symptoms, suggesting that frontal paralimbic dysfunction contributes to depressive symptoms in MM patients with or without a diagnosis of major depression. A significant subgroup of MM patients has clinical and sub-clinical depression; our data identify brain substrates underlying these symptoms. Additionally, affect dysregulation is an important risk factor for addiction (Tarter et al., 1995; Tarter et al., 1999). Future investigations of affect dysregulation in addiction may enhance our understanding of the substance dependence and depression comorbidity. Finally, depressive mood and symptoms are significantly correlated with escalations in drug craving, opiate use and treatment attrition (Childress et al., 1994; Hasin et al., 2002; Havard et al., 2006; Hesse, 2006; Kosten et al., 2004; Nunes et al., 2004; Zilberman et al., 2007). Treatment strategies, such as psychopharmacological or psychotherapeutic interventions, targeting these brain regions may improve the depression symptoms in addicted individuals.

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Figure 1.

Regions showing a significant negative correlation between baseline VLPFC rCBF and BDI scores with age, sex, handedness and smoking status as nuisance covariates (cluster corrected whole brain analysis). (A) Right VLPFC (MNI: 12, 52, -12; $z = -3.90$); (B) Scatter plot of the resting perfusion in the right VLPFC as a function of BDI scores ($r = -0.7898$; $p = 0.0001$) with regression line; (C) Left VLPFC (MNI: -16, 48, -6; $z = -3.30$); (D) Scatter plot of the resting perfusion in the left VLPFC as a function of BDI scores ($r = -0.7104$; $p = 0.0003$) with regression line. Images are displayed at $P_{\text{uncorrected}} \leq 0.005$; cluster size 20 or more contiguous voxels. Results are displayed on MNI single subject structural MRI template in neurological convention, with right side corresponding to right hemisphere.

Table 1
Correlation coefficients between Beck Depression Inventory (BDI) and other behavioral measures (n=21).

	SCL-90-R (Depression Subscale)	Major Depressive Episode ^a	Years of Lifetime Opiate Use	Months Since Last Opiate Use	Years of Methadone Use	Methadone Dose
BDI	0.637 *	0.466 **	-0.374	-0.269	-0.235	0.274

* p<0.01
** p<0.05

^aPoint biserial correlation

Anatomical coordinates of regions in significant negative correlations between resting perfusion and Beck Depression Inventory scores.

Table 2

Region of Interest (Brodmann area)	Cluster size (voxels)	MINI Coordinates			Peak T score	Peak Z score
		x	y	z		
<u>Frontal Lobe</u>						
- Ventrolateral frontal gyrus (BA 10/11), R	108	12	52	-12	-5.15	-3.90
- Ventrolateral frontal gyrus (BA 10), L	35	-16	48	-6	-4.04	-3.30
- Middle frontal gyrus (BA 10), R	107	42	26	27	-4.57	-3.60
- Middle frontal gyrus (BA 6), L	171	-40	10	57	-4.99	-3.82
<u>Parietal Lobe</u>						
- Inferior parietal lobe (BA 40), L	123	-40	-40	30	-4.66	-3.65

The x, y, z coordinates are given in peak MNI coordinates. L and R denote left and right, respectively. The Brodmann's areas (BA) were identified using Wake Forest University Pick Atlas software (Lancaster et al., 2000) and the atlas of Talairach and Tournoux (Talairach and Tournoux, 1988)