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Anger and depression in cocaine addiction: association with the orbitofrontal cortex

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Abstract

The high prevalence of anger, impulsivity and violence in cocaine addiction implicates chronic cocaine use in the compromise of higher-order inhibitory control neurocognitive processes. We used the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) anger content scale as a personality measure of inhibitory control and examined its association with glucose metabolism in the lateral orbitofrontal gyrus (LOFG) at rest as measured by positron emission tomography with 2-deoxy-2[^{18}F]fluoro-D-glucose (PET ^{18}FDG) in 17 recently abstinent cocaine-dependent subjects and 16 comparison subjects. Three additional variables—the MMPI-2 depression content scale, metabolism in the medial orbitofrontal gyrus (MOFG) and the anterior cingulate (AC) gyrus—were inspected. When level of education was statistically controlled for, the LOFG was significantly associated with anger within the cocaine group. No other region was associated with anger within the cocaine-dependent group, and the LOFG did not correlate with depression within any of the study groups. The present study confirms earlier reports in demonstrating a positive association between relative metabolism at rest in the LOFG and cognitive-behavioral and personality measures of inhibitory control in drug addiction: the higher the metabolism, the better the inhibitory control.

Keywords: PET ^{18}FDG; MMPI-2; Anger; Depression; Drug abuse

1. Introduction

We recently implicated the lateral orbitofrontal gyrus (LOFG) in the core characteristics of drug addiction, emphasizing its role in the failure to properly inhibit excessive drug consumption and develop aversive/withdrawal reactions to potentially dangerous situations. We documented that higher relative LOFG glucose metabolism at rest, measured using positron emission tomography with 2-deoxy-2[^{18}F]fluoro-D-glucose (PET ^{18}FDG), was associated with *higher* inhibitory control as measured by the

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Stroop Color-Word test in cocaine-addicted subjects and alcoholics. In contrast, for comparison subjects matched on age, education, IQ and performance on the Stroop task, higher metabolism was associated with *lower* control (Goldstein et al., 2001). In a follow-up study, we used the Tellegen's Multidimensional Personality Questionnaire Harm Avoidance (Fear) scale and the Constraint superfactor as *personality* measures of inhibitory control. Results revealed that higher relative LOFG glucose metabolism at rest was associated with higher self-reported avoidance of potentially harmful situations and inhibitory constraint on inappropriate approach behaviors in recently abstinent methamphetamine-dependent subjects (Goldstein et al., 2002b).

The primary goal of the current report was to examine whether we could reliably replicate an association between metabolism in the LOFG and another personality measure of inhibitory control in drug addiction. We chose the anger content scale of the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) because anger has been suggested to serve as a cue to cease current behavior (Elliott et al., 2000b) and may serve as an indirect measure of inhibitory control. Indeed, the MMPI-2 anger content scale assesses external aggressive tendencies such as anger expression and anger control problems (Kawachi et al., 1996; Schill and Wang, 1990; Strassberg and Russell, 2000). Anger has also previously been suggested to be specifically associated with the lateral orbitofrontal cortex (see, for example, two PET $H_2^{15}O$ activation studies: Blair et al., 1999; Drexler et al., 2000; for review, see Murphy et al., 2003). For control purposes, we also inspected an MMPI-2 measure of *internal* (as compared with external) symptomatic behaviors, the depression content scale. The rectal gyrus (gyrus rectus), the medial orbitofrontal gyrus (MOFG), and the anterior cingulate (AC) gyrus were selected as the other regions of interest (ROIs). These regions form the corticolimbic brain reward circuit most frequently implicated in the neurobiology of drug addiction (Volkow et al., 2002), in higher order cognition (e.g., inhibitory control) and in emotion (e.g., depression) (see Goldstein and Volkow, 2002a; see also Mayberg et al., 1999; Bechara, 2003).

We had the following hypotheses: (1) increased control (lower scores on the MMPI-2 anger scale) will be associated with greater relative glucose metabolism in the LOFG for drug-dependent subjects; (2) reported symptoms of depression will not be associated with LOFG metabolism but will be associated with metabolism in the MOFG or the AC. To test these hypotheses, we performed correlational analyses between measures of absolute and relative glucose metabolism in the LOFG (left and right), MOFG and AC obtained at resting baseline using PET ^{18}FDG and MMPI-2 anger and depression content scales in 17 cocaine-dependent subjects and 16 controls.

2. Methods

2.1. Participants

Nineteen men who fulfilled DSM criteria for cocaine dependence and 16 healthy male volunteers had completed the MMPI-2 within 2 years of a PET ^{18}FDG study. Two cocaine-addicted subjects were excluded from analyses because of potentially invalid MMPI-2 profiles (F validity T score >99). The interval (in days) between the PET and the MMPI-2 did not differ significantly between the groups (controls: M=529.1, S.D.=245.5, range 5–769 days, data missing for five subjects; cocaine: M=375.6, S.D.=325.6, range 6–812 days, data missing for seven subjects).

The characteristics of the complete sample of cocaine-dependent subjects were previously described (Volkow et al., 1997a). In brief, the cocaine-dependent subjects were mostly recruited from the detoxification unit of the Northport Veterans Affairs Hospital and had been detoxified for at least 2 weeks before the study. All had used cocaine (freebase or crack), at least 4 g/week, for at least the preceding 6 months. We excluded cocaine-dependent subjects with a current or past history of dependence on alcohol or if their use of alcohol led to regular (once a week) inebriation. However, we did not exclude cocaine-dependent subjects who used alcohol to come down from a cocaine binge (three to four times a week). Twelve cocaine-dependent subjects reported current or past alcohol use (mean number of beer equivalent drinks[1] for this subgroup was 3.4±2.2 per day), while all

[1] Ounces of hard liquor or wine were converted to beer ounces (1 beer equivalent drink=12 ounces of beer=1.5 ounces of hard liquor=5 ounces of wine).

control subjects denied a history of regular alcohol or cocaine use (data missing for one subject).

Other exclusion criteria were current or past psychiatric (other than cocaine dependence), neurological, cardiovascular or endocrinological disease, history of head trauma, current medical illness and dependence on any substance other than cocaine, nicotine or caffeine. Controls were paid volunteers from the community, screened for a lack of history of substance dependence (excluding caffeine/nicotine). Exclusion criteria were otherwise as for the cocaine-dependent subjects. Inclusion/exclusion criteria were based on a psychiatric interview conducted by trained study personnel (participating physician). The validity of diagnosis was corroborated by concordance from two clinicians. No subject was taking medications at the time of the study. Pre-scan urine tests were conducted to ensure absence of psychoactive drugs at the time of study. Structural magnetic resonance imaging was performed to ensure lack of circumscribed brain damage or atrophy in all subjects. The study was approved by the Institutional Review Boards at both Brookhaven National Laboratory and the Northport Veterans Affairs Hospital. Written informed consent was obtained for all subjects after procedures were fully explained.

2.2. Personality assessment

The MMPI-2 is the most widely used and investigated personality inventory. It is a rationally developed and empirically validated instrument consisting of 567 true-false items (Greene, 1991); there are four standard validity scales and 10 clinical scales, which assess test-taking attitudes and major categories of psychopathology, respectively. Supplementary scales and 15 content scales help in the interpretation of the standard scales. For the purposes of the current report, we chose the Butcher content scales and not the clinical scales because the former were constructed to insure psychometric homogeneity (Greene, 1991). As a result, reliability is generally higher for the content than for the clinical scales (Spiro et al., 2000); for example, stability (test–retest) correlations were 0.77 and 0.82 (uncorrected) for the anger and depression scales, respectively, in 1072 men retested after 5 years (absolute stability). Moreover, 89% (anger) and 96% (depression) of these subjects maintained their placement category over the 5 years (differential stability). In terms of validity, it has been shown that the MMPI-2 content scales contribute to the differential diagnosis of major psychopathology (Ben-Porath et al., 1991) and add incrementally to the prediction of variance in other (extra-test) standard self-report measures of personality and psychopathology, above and beyond what is predicted by the clinical scales alone (Ben-Porath et al., 2000). For the two content scales includes in the current study, high indices of criterion-related, concurrent and discriminant validity were documented across studies. Thus, the anger content scale was the highest correlating MMPI-2 scale with trait anger of the State-Trait Anger Expression Inventory and the depression content scale was the highest correlating scale with the Beck Depression Inventory (Ben-Porath et al., 2000). The anger content scale also correlated highest with therapists' ratings of symptoms of open and uncontrolled anger (r=0.26), while the depression content scale correlated highest with therapists' ratings of symptoms of depression (r=0.37) (Butcher et al., 2000). Similar results were reported in another outpatient sample (Strassberg and Russell, 2000).

More specifically, individuals with high scores on the MMPI-2 anger content scale report being irritable, being hotheaded and sometimes wanting to swear or smash things; they may lose self-control and report having been physically abusive toward people and objects (Greene, 1991). The depression content scale assesses depressive mood and depressive thoughts; individuals with high scores on this scale report feeling unhappy and lonely, they cry easily, and they are likely to be self-critical and to brood (Greene, 1991).

2.3. PET scanning

PET scans were performed with the CTI 931 (15 slices, spatial resolution: 6×6×6.5 mm full width at half maximum) scanner (Siemens, Knoxville, TN). Details on procedures for positioning, arterial and venous catheterization, quantification of radiotracer, and transmission and emission scans have been published (Wang et al., 1993). Briefly, one 20-min emission scan was taken 35 min after an intravenous injection of 4–6 mCi of ^{18}FDG. During the study, subjects were scanned with the PET camera while supine and with eyes open; the room was dimly lit and

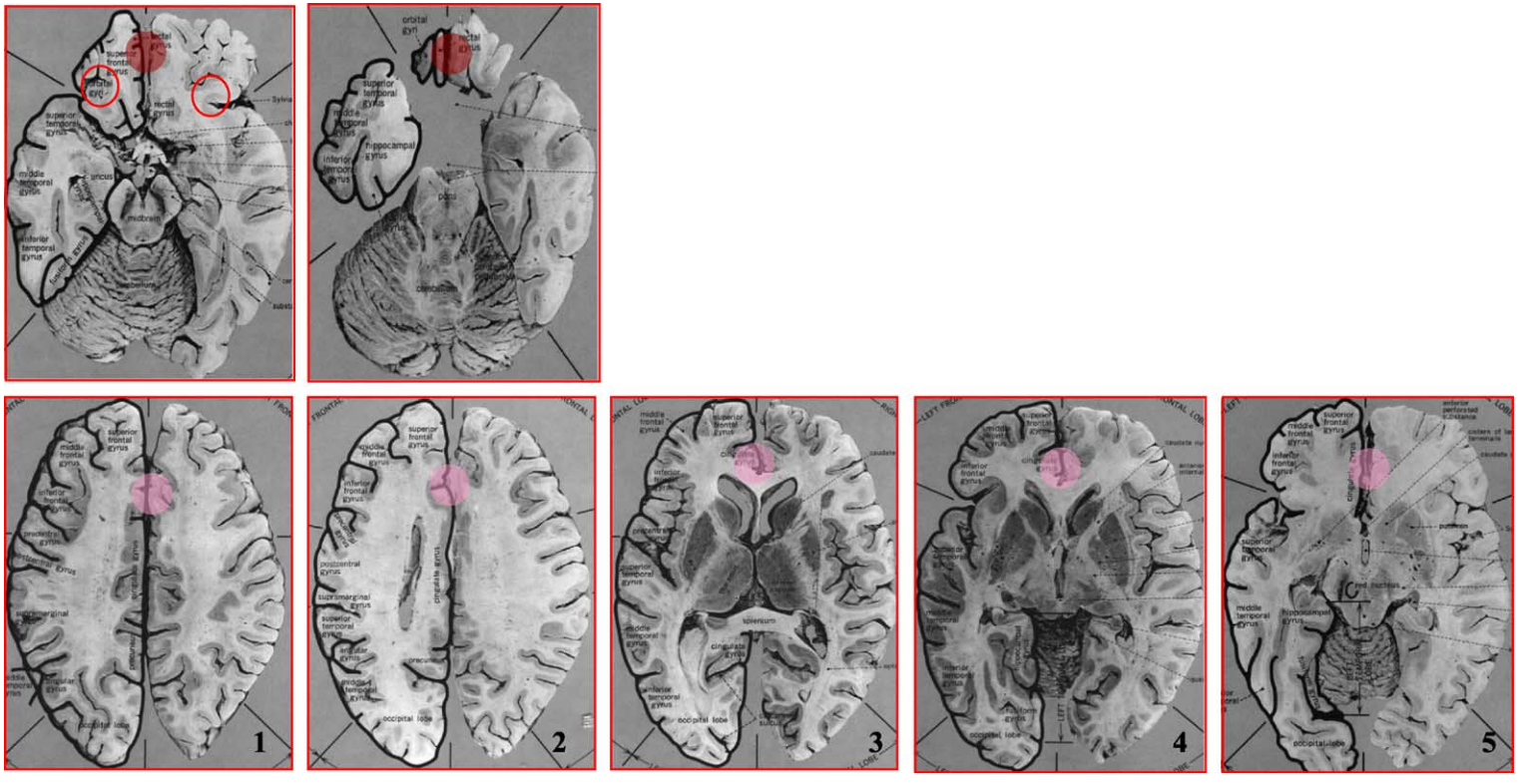

Fig. 1. Placement of the regions of interest in the current study. The lateral orbitofrontal gyrus (open circles) and medial orbitofrontal gyrus (closed circles) are shown in the top row; the anterior cingulate planes are shown in the bottom row. Planes shown are 1 through 5, where plane 1 corresponds to the dorsal (cognitive) division, while plane 5 corresponds to the ventral (affective) division (see Bush et al., 2000).

noise was kept to a minimum. A nurse remained with the subjects throughout the procedure to ensure that the subject did not fall asleep during the study.

Regions of interest were selected by using a previously published template that locates 115 non-overlapping ROIs (Wang et al., 1993). In brief, we used small ROIs to minimize the contribution of partial volume effects on the metabolic values. The LOFG averaged 0.7 cm^3, the MOFG averaged 1.2 cm^3 and the AC averaged 0.7 cm^3. The size and orientation of the ROIs were the same in all subjects. Placement of the regions was determined by reference to an atlas of axial tomographic anatomy (Matsui and Hirano, 1978) by an experienced investigator (G.J.W.). A total of seven ROIs in the frontal lobe 12 mm below an oblique plane, parallel to the canthomeatal line, were averaged to obtain measures for the LOFG (2 ROIs, left and right), the MOFG (1 ROI) and AC (5 ROIs, planes 3–5 correspond to ventral AC) (see Fig 1). To minimize the variable effect of whole brain metabolism on the regional measures, we computed the ratio of the regional to the global metabolic measures to obtain relative measures of metabolism. It has previously been shown that scaling the regional values to compensate for the effects of changes in whole brain metabolism provides a stable reflection of the metabolic characteristics of clinical as well as normal populations (Bartlett et al., 1991).

2.4. Statistical analyses

The cocaine-dependent subjects were compared with the controls on select variables. Group differences in continuous variables were examined using unpaired Student's *t*-tests (two-tailed). Levene's test for equality of variance was used and, whenever significant, the corrected *t*-statistic and degrees of freedom were used. For dichotomous variables, chi-square tests with Fisher's exact statistic were used. A 0.01 level was set to protect against type I error in all group comparisons (note that, for the subsequent correlational analyses, a 0.05 level was the nominal

Table 1
Frequencies or means and standard deviations for selected demographic variables, personality and resting glucose metabolism (μmol/100/min) in 17 cocaine-addicted and in 16 comparison men

	Cocaine	Controls
Demographics		
Race (% Caucasian)	53%	81%
Handedness (% right)	82%	100%
Age	36.7 (4.5)	35.6 (6.9)
Education	12.2 (1.6)‡	15.6 (2)
MMPI-2 scales		
L validity scale	50.3 (10.1)	53.4 (7)
F validity scale	58.9 (12.6)	48.6 (14.5)
K validity scale	46 (10.9)†	55.9 (9.5)
Anger content scale	60.9 (14.9)‡	43.9 (6.4)
Depression content scale	64 (13.4)	51.8 (14.5)
Glucose metabolism: absolute/relative		
Lateral orbitofrontal gyrus	47.4 (5)/1.3 (0.1)†	49.1 (5.4)/1.4 (0.1)
Left lateral orbitofrontal gyrus	47.4 (4.7)/1.3 (0.1)†	49.9 (5.6)/1.5 (0.1)
Right lateral orbitofrontal gyrus	47.3 (6.5)/1.3 (0.1)	48.2 (6.3)/1.4 (0.1)
Medial orbitofrontal gyrus	45.7 (6.9)/1.3 (0.1)	44.8 (4.8)/1.3 (0.1)
Anterior cingulate gyrus (third plane[a])	44 (6.3)/1.2 (0.1)	44 (7.3)/1.3 (0.2)

MMPI-2 = Minnesota Multiphasic Personality Inventory-2. The validity scales assess denial of symptoms (L, "faking-good"), over-endorsement of symptoms (F, "faking-bad") and defensiveness (K, self-disclosure vs. self-protection). The differences between the groups on MMPI-2 scales disappeared after correction for education (using regression analysis).

[a] Means for the other four AC planes are not provided as there were no significant correlations between any of these AC planes with the personality scales.

‡ Significantly different from controls by Student's *t*-test, $P<0.0001$ (two-tailed).

† Significantly different from controls by Student's *t*-test, $P<0.01$ (two-tailed).

significance level). Because there were significant differences between the study groups in years of education (Table 1), we corrected the MMPI-2 content scales for education by using regression analyses. The resulting standardized residuals were used in all subsequent analyses. Within each group, Pearson product-moment correlation analyses were then conducted between the two MMPI-2 content scales (corrected for education) and absolute and relative metabolism in the LOFG (left and right), MOFG and AC (five planes).

3. Results

There were no significant differences between the cocaine and control subjects in distributions of race and handedness, or in age (Table 1). All MMPI-2 scales are reported as *T* scores. There were significant differences between the cocaine and comparison subjects for the MMPI-2 K validity scale and the anger content scale: the scores on the former scale were lower [$t(31)=2.8$, $P<0.01$], while the scores on the latter scale were significantly higher [$t(22)_{corrected}=-4.3$, $P<0.0001$] in the cocaine-addicted subjects than in controls. These differences between the groups disappeared after correction for education (using regression analysis). The groups differed in relative metabolism in the LOFC [$t(31)=2.9$, $P<0.01$], driven mostly by a higher difference on the left side [cocaine<controls; $t(31)=3.3$, $P<0.01$].

Fig. 2 presents the correlations between the MMPI-2 content scales (corrected for education) and relative metabolism in the three ROIs. Consistent with our hypotheses, a negative association between anger and relative metabolism in the LOFG was documented for the cocaine-dependent subjects ($r=-0.53$, $P<0.05$). A similar pattern was observed for the right ($r=-0.44$) and left ($r=-0.41$) LOFG (and also for the absolute metabolism in these regions), but significance level was only reached for the averaged relative metabolism in the LOFG. These correlations were not significant for the control group. The LOFG was not associated with depression in any of the study groups. In contrast, depression in the cocaine group was significantly correlated with relative metabolism in the MOFG ($r=-0.55$, $P<0.05$) and AC (third plane) ($r=-0.54$ relative, $r=-0.56$ absolute, $P<0.05$). Finally, in the control group, the only association that reached significance was between anger and metabolism in the AC (absolute and relative, *r* values=0.63 and 0.65, respectively, $P<0.01$). The correlations with the AC were only significant for the third plane, which is at the level of the upper thalamus, just above the striatum, and corresponds to the affective (ventral, subgenual) division of the AC (Bush et al., 2000).

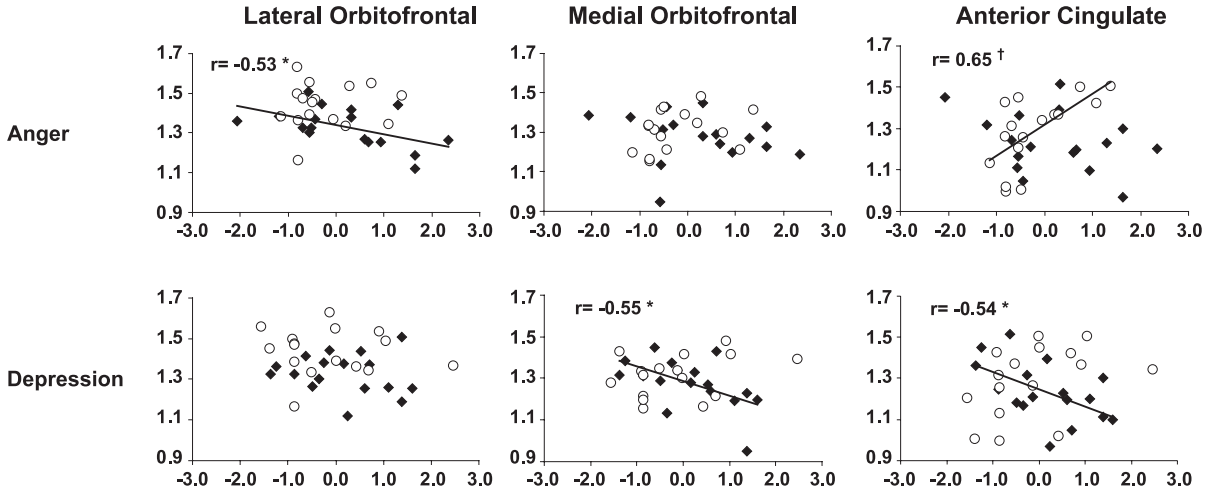

Fig. 2. Association between MMPI-2 Anger and Depression content scales (corrected for education) with relative resting glucose metabolism in the lateral orbitofrontal gyrus, medial orbitofrontal gyrus, and anterior cingulate in 17 cocaine dependent (♦) and 16 comparison subjects (○). Note: Anterior cingulate 3 is the third plane of the anterior cingulate (see Fig. 1). *Significant Pearson correlation at $P<0.05$ (two-tailed). †Significant Pearson correlation at $P<0.01$ (two-tailed).

There were no significant correlations between MMPI-2 K scale and metabolism (absolute or relative) in any of the inspected ROIs. Removing one cocaine subject with very low relative metabolism in the MOFG did not change the above results, except for attenuating the correlation between depression and MOFG ($r=-0.46$, $P=0.076$).

All three ROIs (relative metabolism) were then entered into two separate stepwise forward regression analyses with the MMPI-2 scales as dependent variables (these analyses were also conducted with one outlier removed). The MMPI-2 anger content scale was significantly predicted by relative metabolism in the LOFG in the cocaine-dependent group ($R^2=0.29$, $F=6$, $df=1,15$, $\beta=-0.53$, $P<0.05$) but not in the comparison group, where relative metabolism in the AC was the sole predictor ($R^2=0.42$, $F=10.2$, $df=1,14$, $\beta=0.65$, $P<0.01$). The MMPI-2 depression scale was significantly predicted by relative metabolism in the MOFG ($R^2=0.3$, $F=6.5$, $df=1,15$, $\beta=-0.55$, $P<0.05$) or AC (when the outlier was removed; $R^2=0.25$, $F=4.7$, $df=1,14$, $\beta=-0.50$, $P<0.05$) in the cocaine-dependent group but not in the comparison group.

4. Discussion

The results in this report provide preliminary evidence supporting both our hypotheses. Controlling for education, (1) increased inhibitory control, as indicated by lower scores on the MMPI-2 anger scale, was associated with greater relative resting glucose metabolism in the LOFG for the cocaine-dependent subjects. For the comparison subjects, anger correlated instead with AC metabolism (absolute and relative); and (2) self-reported symptoms of depression were not associated with metabolism in the LOFG. Rather, they correlated significantly with metabolism in the AC (absolute and relative) in the cocaine group (a significant correlation with relative metabolism in the MOFG disappeared after exclusion of one outlier). Results of multiple regression analyses confirmed this dissociation: the LOFG was solely predictive of anger within the cocaine group. No other ROI predicted anger within the cocaine group, and the LOFG was not predictive of depression within any of the study groups.

Although a direct comparison with our results is impossible, several studies provide evidence supporting this unique association of the LOFG with anger. A recent PET $H_2^{15}O$ study documented decreased regional cerebral blood flow in the right lateral orbitofrontal cortex during mental imagery of a personal anger-associated scene as compared with an emotionally neutral scene in 10 inpatient cocaine-dependent subjects but not in 11 nicotine-dependent subjects (Drexler et al., 2000). In another PET $H_2^{15}O$ study, angry but not sad faces specifically activated the right LOFG, proportionally with the increasing intensity of the emotion (Blair et al., 1999). In contrast, the AC was coactivated by both sad and angry facial expressions, similarly to the association of the AC with both depression (in the cocaine-dependent subjects) and anger (in the controls) in our study. The MOFG, which has its strongest connections with the cingulate (Elliott et al., 2000a), displayed similar associations. Of note is the fact that, in contrast to these two studies, we did not observe differential correlations for the right vs. left LOFG. The distinct analytical methodologies used in these studies (pixel-by-pixel vs. ROI analyses in the current study) may account for this discrepancy (activations on the left side may have been smaller in intensity or extent and therefore not visible using the set threshold). The association of the mesial aspects of the prefrontal cortex with depression may involve serotonin; in a recent PET study, a decrease in $5HT_2$ binding potential in the right mesial frontal region was associated with decreased depression with anger attacks after 6 weeks of treatment with nefazodone in 16 outpatients (Mischoulon et al., 2002).

More recent neuroimaging studies employing the higher resolution functional magnetic resonance imaging blood oxygenation level-dependent technique highlight these functional dissociations between the medial and lateral portions of the orbitofrontal cortex (Gottfried et al., 2002). Medial orbitofrontal cortex activity correlates with numerous measures of pleasantness such as monetary reinforcers (O'Doherty et al., 2001), odors (Gottfried et al., 2002) and facial attractiveness (O'Doherty et al., 2001), and possibly has a role in making associations between stimuli and correct or rewarded responses (reviewed in Elliott et al., 2000a). In contrast, the lateral orbitofrontal cortex is

more aligned with the negative or punishing aspects of reinforcers (Gottfried et al., 2002), and possibly has a role in the suppression of previously rewarded responses (reviewed in Elliott et al., 2000a).

A major limitation of this study is our inability to control for the period between the MMPI-2 and PET studies. Although our analyses indicated that this time interval did not differ between the groups, the effect of drug-use factors (e.g., length of abstinence, severity of relapse, neurological and health complications, learned compensatory mechanisms) on self-reported measures of personality remains unclear. For example, it is quite likely that the effect of drug use on cognition (and consequently on measures of affect and personality) differs as a function of length of abstinence (e.g., Selby and Azrin, 1998). Nonetheless, many reviews of the literature have concluded that personality traits show considerable differential *stability* (i.e., consistency in one's relative rank order in the distribution of a variable across occasions) and many others argue that once maturity is reached, absolute stability (constancy or change in means) is the norm (Spiro et al., 2000). Moreover, test–retest studies of human volunteers have found good reliability and low intrasubject variability in metabolism of regional cerebral metabolic rate of glucose as measured with PET FDG (reviewed in Schaefer et al., 2000); this was documented for short (e.g., 24 h) or longer (e.g., after 6 months) intervals, at both rest and active states, for cortical and subcortical regions. Moreover, the common practice of normalizing regional activity to global cerebral metabolic rate, which has been undertaken in the current report, has been shown to substantially reduce intrasubject and intersubject variance in PET FDG (Bartlett et al., 1991).

Two additional issues remain to be mentioned. First, the MMPI-2 anger content scale measures mostly anger control and expression problems, while the broader experience of anger encompasses several interrelated yet distinct affective, behavioral and cognitive factors (Linden et al., 2003). Similarly, the putative inhibitory control mechanisms are not unitary: functional neuroimaging and lesion studies suggest several different substrates of inhibitory control that can be measured by different batteries of tests and linked to different regions of the prefrontal cortex, including the LOFG and the AC (see Bechara, 2003). Indeed, the MMPI-2 anger scale may be measuring somewhat different inhibitory control processes in our two study groups: cognitive/affective flexibility in the cocaine-dependent subjects (association is with the LOFG) and behavioral/non-affective flexibility in the controls (association is with the AC). Thus, the full characterization of the construct of anger and its underlying cognitive-behavioral and neurobiological mechanisms, in addiction and in non-addictive states, remains to be fully delineated. Nevertheless, it is of interest to note the following: similar to the positive correlation between anger and AC in the controls in the current study is the reduction in self-reported anger after cingulotomy for intractable pain (Cohen et al., 2001), and similar to the negative correlation between anger and LOFG in the cocaine-dependent subjects in the current study is the increase in aggressiveness after OFC lesions in the rat (Fuster, 1997).

Of final note is that our current study design does not allow us to ascertain whether the pattern of associations observed for the cocaine-dependent subjects is the result of drug addiction or whether it predisposes to addiction. In previous studies from our laboratory, we have tackled this question mostly through studying subjects at-risk (i.e., positive family history) for developing drug addiction (see Volkow et al., 1997b). However, longitudinal studies using non-invasive imaging techniques (e.g., magnetic resonance imaging) of prepubescent adolescents may also elucidate this question.

Taken together with our previous findings, we have now repeatedly documented a positive association between relative metabolism in the lateral orbitofrontal gyrus and measures of inhibitory control in drug addiction. Lower scores on the MMPI-2 anger scale (present findings) and higher scores on the Stroop Color-Word Test (Goldstein et al., 2001) and on Tellegen's Multidimensional Personality Questionnaire's Harm Avoidance/Fear Scale (Goldstein et al., 2002b) are associated with *greater* relative resting glucose metabolism in the LOFG in subjects with drug (cocaine, alcohol or methamphetamine) addiction.

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