



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-[¹⁸F]fluoro-D-glucose (PET ¹⁸FDG) 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. © 2004 Elsevier Ireland Ltd. All rights reserved.

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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-[¹⁸F]fluoro-D-glucose (PET ¹⁸FDG), 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 H₂¹⁵O 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 ¹⁸FDG 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 ¹⁸FDG 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 drinks¹ 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).

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