

Addiction changes orbitofrontal gyrus function: involvement in response inhibition

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We used the Stroop task as a measure of the ability to inhibit a prepotent response tendency and examined its association with relative glucose metabolism in selected prefrontal brain regions in cocaine addicts, alcoholics, and controls (17 per group). Results revealed that for the substance abusers, higher orbitofrontal gyrus (OFG) activation was associated with lower conflict (higher score; $r = 0.32$, $p < 0.05$). For the controls,

higher OFG activation was associated with higher conflict (lower score; $r = -0.42$, $p < 0.05$). Thus, at baseline, increased relative activation of the OFG is associated with worse performance in controls and better performance in substance abusers on the Stroop task, suggesting reversal of the role of the OFG as a function of addiction. *NeuroReport* 12:2595–2599 © 2001 Lippincott Williams & Wilkins.

Key words: Alcohol; Anterior cingulate; Cocaine; Drug addiction; Orbitofrontal cortex; PET FDG; Stroop interference score

INTRODUCTION

One of the hallmarks of drug dependence is the compulsive drug self-administration that occurs in addicted individuals even when the drug is no longer perceived as pleasurable and in the presence of adverse physical reactions to the drug [1]. We have previously linked this phenomenon with inability to inhibit a prepotent response tendency [2], a behavior that is frequently studied in experimental (e.g. reversal, go–no go) paradigms, and suggested that it represents a disrupted function of the striato-thalamo-orbitofrontal circuit [3,4]. The present study directly investigated the association between inhibition and its underlying neural circuit in cocaine addicts, alcoholics, and controls. We used the Stroop task [5], which necessitates the inhibition of an automatic response (reading) in order to rapidly perform a controlled response (color naming). The Stroop task has been extensively used in normal and patient studies of cognitive interference and response inhibition. The Stroop task has also been recently adapted to neuroimaging environments with results pointing to the importance of reactivity of prefrontal regions such as the anterior cingulate, in resolving the conflict inherent in this task [6,7].

An interesting issue that remains unclear is whether baseline/resting values of these regions are associated with performance on the Stroop task and whether these associations are modified by drug addiction. Studying baseline (as compared to reactivity) metabolism in prefrontal regions has profound research and clinical significance as it could be used to predict the development of clinical states from very subtle and largely unobserved processes. Thus, although cocaine addicts were found to perform as well on

the Stroop task as controls [8,9] or even slightly (but non-significantly) better [10], the neural networks underlying this preserved performance may already have changed through an adaptation process to a chronic addiction state. While performance on this neuropsychological measure in a laboratory environment would still be preserved, this should not be used as indicative of preserved inhibitory control processes. The underlying pathological process might be better reflected in the changes in the neural networks at rest and in their association with task performance. Discovering such a modified association as a function of drug use would be even more meaningful if groups are equated on measures such as age, education, and IQ, that are known to be powerful modifiers of neurocognitive function.

This study therefore included controls and cocaine addicts matched for age, education, and estimates of verbal and non-verbal IQ. A group of alcoholics was also included so as to aid in interpretation of results; the results for the alcohol group would help determine whether the effect is cocaine specific or whether it can be attributed to a more general drug addiction process. We performed correlational analyses between measures of baseline regional and relative cerebral glucose metabolism obtained using PET with 2-deoxy-2-[¹⁸F]fluoro-D-glucose (FDG) and Stroop interference in 17 control subjects, 17 alcoholics, and 17 cocaine addicts. All were right-handed males. Five regions of interest (ROIs) were selected: the orbitofrontal gyrus (OFG), rectal gyrus, anterior cingulate gyrus (ACG), basal ganglia, and thalamus. These regions have been most frequently implicated in the long-lasting effects of chronic addiction to drugs on self-monitoring [2–4].

MATERIALS AND METHODS

The cocaine and alcohol subjects were recruited from the detoxification unit of the Northport Veterans Affairs Hospital. All had a DSM-III-R (before 1994) or DSM-IV (after 1994) diagnosis of cocaine or alcohol dependence, respectively. The cocaine subjects had used cocaine (freebase or crack), ≥ 4 g/week, for at least the preceding 6 months. For the alcoholics, the inclusion criteria were early onset of alcoholism that continued for ≥ 10 years, and at least one first-degree relative with a history of alcoholism. Exclusion criteria were current or past psychiatric (other than cocaine or alcohol dependence, respectively), neurological, cardiovascular, or endocrinological disease; history of hepatic encephalopathy or delirium tremens for alcoholics; history of head trauma; current medical illness; and dependence on any substance other than cocaine/alcohol, nicotine, or caffeine. Controls were screened for a lack of history of substance abuse (excluding caffeine/nicotine). Exclusion criteria were otherwise as for the drug dependent subjects. No subject was taking medications at the time of the study, and prescan urine tests were conducted to ensure absence of psychoactive drug at time of study. Written informed consent was obtained for all subjects after procedures were fully explained.

Subjects were included in the current analyses if they were right-handed, male, and had complete information on the Stroop interference task and PET FDG. There were 18 cocaine subjects who satisfied these criteria and they were matched with 18 healthy controls and 18 alcohol dependent subjects on age, education, and estimates of verbal and non-verbal IQ. Two subjects, one from the cocaine and one from the control group, were excluded due to unreasonably high scores on the Stroop interference condition. To equate the size of the groups, an additional subject from the alcohol group was excluded (the oldest subject).

The Stroop task used was the standardized Golden version [11]. In brief, subjects were asked to read color words (red, green, blue) printed in black ink (word), then name the color of XXXX printed in red, green, or blue ink (color), and finally to name the ink color of color words (e.g. naming the ink color of the word blue that is printed in red color; color-word). Each condition consisted of a separate page of 100 items and performance was timed for 45 s. Dependent variable is number of items completed within this time period. Stroop interference score was calculated by subtracting a predicted CW (predicted $CW = C \times W / (C + W)$) score from the raw CW score (interference score = raw CW - predicted CW). The higher the resultant score, the less susceptibility to interference. All scores were age-corrected as suggested in the manual [11]. The Stroop task was administered individually as part of a larger neuropsychological battery [8].

PET scans were performed with a CTI 931 scanner (Siemens, Knoxville, TN; 15 slices, spatial resolution $6 \times 6 \times 6.5$ mm full width at half maximum). Details on procedures for positioning, arterial and venous catheterization, quantification of radiotracer, and transmission and emission scans have been published [12]. Briefly, one 20 min emission scan was taken 35 min after an i.v. injection of 4–6 mCi FDG. During the study, subjects were kept lying in the PET camera with their eyes open; the room was dimly lit and 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 [12]. In brief, to minimize the contribution of partial volume effects on the metabolic values, we used small ROIs that averaged 0.7 cm^3 for the OFG, ACG, and thalamus and 1.2 cm^3 for the basal ganglia and rectal gyrus. 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 [13] by an experienced investigator (G.J.W). The ROIs corresponding to the same anatomical regions were averaged to obtain measures for the five composite brain regions and one for global metabolism (average metabolism in the 15 planes scanned). To minimize the variation 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.

Differences in age, education, and estimates of verbal and non-verbal IQ between the three groups were tested with MANOVA. A separate MANOVA was used to test differences in regional metabolism between the three groups. Repeated MANOVA was conducted to assess differences between the groups on the three Stroop conditions (W, C, CW). Differences in Stroop interference score were tested by an ANOVA. *Post-hoc* tests (LSD) were performed when the differences between the groups were significant. Pearson product-moment correlation analyses were conducted between Stroop interference scores and regional brain metabolic measures separately in the three groups. Correlations with relative regions were also examined. All correlations were one-tailed as we expected positive associations between the selected brain regions and Stroop interference scores (i.e. the higher the metabolism the better the inhibition).

RESULTS

Means and s.d. for selected demographic, neuropsychological, and regional brain metabolic measures for the three groups are presented in Table 1. The three groups were well matched on age, education, and measures of verbal and non-verbal IQ. Similarly, the groups performed equally well on all three Stroop conditions, and although the cocaine group had slightly lower interference scores (higher conflict), this difference was not statistically significant. The expected main effect for Stroop condition was evident ($F = 444.11$, $df = 1.74$ after Greenhouse-Geisser correction for violation of the sphericity assumption, $p < 0.0001$), with all groups performing in the expected direction ($W > C > CW$; see Table 1). For this selected subsample, the only difference between the three groups in regional metabolism was in the ACG, where the alcohol group displayed significantly lower values than the control group (LSD = 16.21, $p < 0.01$).

There was one significant correlation and one correlation approached significance between regional glucose metabolism and Stroop interference scores for the cocaine group. Examining the relative metabolism values revealed three additional significant correlations and another correlation approached significance (Table 2). Correlations with the basal ganglia and thalamus were not significant. Examining

Table 1. Means (\pm s.d.) for selected demographic, neuropsychological, and regional brain metabolic measures in right-handed male 17 control subjects, 17 alcoholics, and 17 cocaine addicts matched for age, education, and estimates of IQ.

	Controls	Alcoholics	Cocaine addicts
Age	35.1 \pm 7.5	38.7 \pm 6.3	35.8 \pm 5.1
Education	13.0 \pm 1.7	12.4 \pm 1	12.5 \pm 1.7
Verbal IQ	100.9 \pm 12.9	102.2 \pm 11.7	103.0 \pm 16.9
Non-verbal IQ	109.7 \pm 10.4	110.9 \pm 5.9	104.4 \pm 14.1
Stroop word	106.8 \pm 20.2	102.6 \pm 20	103.1 \pm 19.6
Stroop color	74.9 \pm 12	74.8 \pm 16.1	71.2 \pm 16.2
Stroop color-word	45.4 \pm 13.2	44.7 \pm 11.8	38.3 \pm 12.7
Stroop interference score	1.6 \pm 8.6	1.8 \pm 9.2	-3.5 \pm 9.9
Orbitofrontal gyrus	51.0 \pm 6.6	47.7 \pm 8.5	48.0 \pm 4.5
Rectal gyrus	47.9 \pm 6.9	45.2 \pm 8.3	45.5 \pm 6.5
Anterior cingulate gyrus*	49.0 \pm 6.3	42.8 \pm 8	47.1 \pm 5.7
Basal ganglia	47.5 \pm 5.9	45.3 \pm 7.4	46.2 \pm 5.4
Thalamus	47.9 \pm 8.2	48.0 \pm 7.4	48.4 \pm 5.6

* $p < 0.05$ **Table 2.** Correlations between Stroop interference and relative metabolism in selected prefrontal regions for right-handed male 17 control subjects, 17 alcoholics, and 17 cocaine addicts matched for age, education, and estimates of IQ.

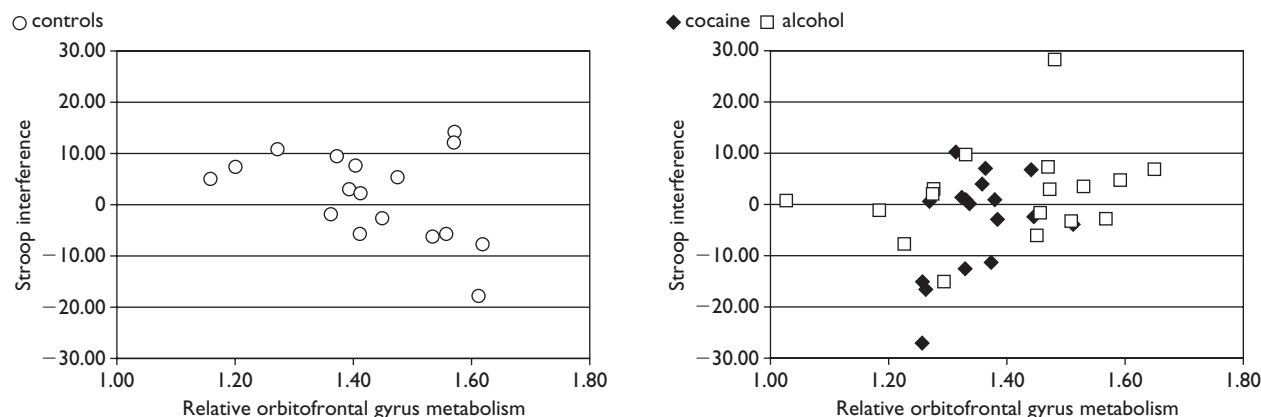
	Controls	Alcoholics	Cocaine addicts	Alcoholics and cocaine
Orbitofrontal gyrus	-0.42		(0.41)	0.32
Rectal gyrus		(0.41)		0.34
Anterior cingulate gyrus			0.49	

All $p < 0.05$ (in parentheses $p = 0.053$; 1-tailed).

the scatter plots demonstrated the double dissociation for the OFG between the controls and addicts: while the correlation of Stroop interference scores with the OFG was negative for the controls, it was positive for the cocaine addicts and alcoholics (Figure 1). Correlations were also examined with the ratio OFG/frontal relative metabolism: it was negative for controls ($r = -0.53$, $p < 0.05$) and positive for addicts ($r = 0.28$, $p < 0.06$).

DISCUSSION

This study documented different underlying neural networks associated with the ability to inhibit a prepotent response tendency in cocaine and alcohol dependent individuals as compared to normal controls, which cannot be attributed to differences in age, education, and general intellectual functioning, nor to observable behavioral changes on standard neuropsychological measures. Thus,

**Fig. 1.** Association between Stroop interference and relative orbital gyrus metabolism in right-handed male 17 control subjects, 17 alcoholics, and 17 cocaine addicts matched for age, education, and estimates of IQ.

while in the control group increased relative OFG metabolism was associated with lower interference scores, and hence with more conflict on the Stroop task, the opposite was true for both the drug groups. This suggests a modification of the role of this region by chronic use of drugs of abuse, implicating a general addiction process in this modification, and not any one drug in particular (cocaine, alcohol).

The direction of the association between the Stroop interference scores and OFG was unexpected for the control group. We expected higher scores (less conflict) to be associated with higher metabolism while the reverse was true: more conflict was associated with higher OFG metabolism. Larger volumes of this same region were recently reported to be associated with worse task performance on working memory tasks in older adults [14], suggesting either neurodegenerative (i.e. hypertrophic) influences or relative preservation of a region as a sign of a neural communication breakdown. Our findings support the second hypothesis: the correlation between Stroop interference score and the ratio OFG/frontal relative metabolism was negative for controls and positive for the combined addict group. This implies that greater OFG metabolism relative to overall frontal metabolism is related to poorer inhibition in controls and vice versa for addicts.

It has recently been reported that higher activity of the ACG is associated with more interference [6] while higher prefrontal activity is associated with less interference [7] as measured by using a Stroop analogue in a functional MRI environment. Similarly, using a different paradigm to measure response inhibition (go-no go), better response inhibition (i.e. less interference) was associated with bigger volume of activation in the orbitofrontal cortex and a smaller magnitude of activation in the anterior cingulate cortex [15]. Despite seemingly reverse associations, our results are not inconsistent with these studies: an individual with higher baseline activity in the ACG would be expected to monitor conflict and resolve it successfully. This same individual may still exhibit less ACG activation while performing a high conflict task relative to a lower conflict task. In terms of the OFG, the association might be curvilinear, with too high or too low baseline values being related to a sub-optimal inhibitory control. Our sample size was too small to test for this assumption.

Alternatively, the association between increased relative OFG metabolism and worse performance on the Stroop in controls may be related to an evaluative process such that the worse the performance, the greater the adaptation to it (recognition of failure, increased frustration, increased awareness of a need to increased effort, etc.) in controls but not in addicts. This interpretation, although speculative, is consistent with the role of the orbitofrontal cortex in evaluative and emotional processes [16] and with the detrimental effect of chronic addiction to drugs and alcohol on this region [17,18]. As with the explanation for the ACG, an individual with high baseline OFG metabolism may still exhibit more OFG activation while performing successfully on a high conflict task.

To our knowledge, this study is the first to demonstrate a reverse association between brain glucose metabolism and a behavioral measure of inhibition as a function of drug addiction. The significance of this finding lies in the

chronic changes to brain function and in the associated behavioral changes accompanying chronic dependence on drugs [4]. More specifically, it is possible that as addiction progresses, certain areas of the brain assume secondary roles either because of their own down regulation or because of the down regulation of other areas, hindering their participation in their primary roles. In this case, the OFG would assume a new role, and will be recruited for bottom-up (conflict monitoring) instead of the top-down (effort, awareness, and evaluation) processes. This may result in temporary better performance on the task that recruits this area, but may lead to more pronounced deficits later on in the addiction process or to a failure of this network to support performance on more complex tasks as resources become limited.

The OFG has not only been implicated in inhibitory control but has also been shown to be important in providing the salience value of a reinforcer as a function of the context, satiety and competing stimuli [19]. Thus the disrupted activity of the OFG in the drug addicted subjects could result both in a disrupted ability to modify the reinforcing effects of the drug as a function of satiety or other competing stimuli as well as a failure to properly inhibit tendencies to interrupt the consumption of the drugs when exposed to the drug or to drug-associated stimuli. Since both the compulsive drug administration as well as the inability to refrain from using it once the drug becomes available are hallmarks of drug addiction this places the OFG at a critical role in the addictive process.

CONCLUSION

Our findings suggest a change in the role of the OFG as a function of addiction to drugs: while higher relative values were associated with worse conflict monitoring in non-addicted individuals, they were associated with better conflict monitoring in addicted individuals. In addition to the possible effect of addiction on the function of this region and others in the network that underlie response inhibition, our results point to the importance of measuring relative glucose baseline values and examining not only the differences in activation associated with different neuropsychological/cognitive tasks but also the individual differences in the neural networks underlying performance on these tasks at resting states. We suggest that reactivity to a task in a certain region/network will depend on the baseline values of this network, and will differ as a function of the magnitude and pattern of these values. For example, we predict that high ACG baseline values will be associated with lower reactivity during an inhibition task and with better task performance. The reverse should be observed for the OFG for non-drug-dependent individuals. Dividing individuals to low vs. high reactors might also shed light on the network involved in response inhibition and its modification by drug addiction.

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