

## **Supplemental Data**

### **Additional Methods**

The cocaine dependent subjects underwent the following procedures: 1) screening; 2) 14 days of abstinence; 3) an MRI for identification of the Regions of Interest; 4) the first PET imaging session (two scans with [<sup>11</sup>C]raclopride, before and after 60mg methylphenidate); 5) twelve weeks of behavioral treatment; 6) second PET session (two scans with [<sup>11</sup>C]raclopride, before and after 60mg methylphenidate); 7) an additional twelve weeks of treatment. Healthy control subjects underwent only screening, an MR scan, and a single PET session (two scans). Details regarding each of these procedures are below.

#### *Subject selection criteria:*

Study criteria for the cocaine dependent subjects included: 1) males or females between 21 and 45 years old; 2) fulfill Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (1) for cocaine dependence; 3) currently seeking treatment; 4) absence of DSM-IV Axis I disorder other than cocaine abuse or dependence, including abuse or dependence to other drugs and alcohol (nicotine dependence was acceptable); 5) no current (six months) use of opiates, sedative-hypnotics, and/or cannabis more than twice a week; 6) no current (six months) use of prescription medication; 7) no pregnancy; 8) absence of significant medical conditions; 9) no metal implants or paramagnetic objects within the body which may interfere with the MRI scan; 10) no exposure to radiation in the last year. Study criteria for control subjects included 1) males or females between 21 and 45 years old; 2) absence of DSM-IV Axis I disorder (nicotine dependence was acceptable); and criteria 6 to 10 above. Screening procedures included a psychiatric assessment, physical exam, twelve-lead electrocardiogram, and laboratory tests, including urine toxicology and pregnancy test. The psychiatric assessment included the Structured Clinical Interview for DSM disorders (2) a drug history questionnaire and general health questionnaire. These procedures were performed by or reviewed by the study physicians (DM and AB). The study was approved by the Columbia University/New York State Psychiatric Institute Institutional Review Board and the local Radiation Safety Committee. The demographic comparison of the cocaine dependent and control subjects is shown in table 1.

Table 1: Group demographic comparison of the Control and Cocaine Dependent Subjects

Parameter	Healthy Control		Cocaine Dependent		p
Age (mean $\pm$ SD, years)	mean 35.9	sd 5.9	mean 36.7	sd 6.6	0.66 <sup>a</sup>
Ethnicity	10 Caucasian 7 African American 6 Hispanic 1 Other		11 Caucasian 7 African American 6 Hispanic 1 Other		0.98 <sup>b</sup>
Smoking status	18 smokers 5 non-smokers 1 ex-smoker		20 smokers 5 non-smokers		0.60 <sup>b</sup>
Cigarettes per day (mean $\pm$ SD, in smokers)	mean 9	sd 6	mean 8	sd 6	0.45 <sup>a</sup>

Abbreviations: a: unpaired t test; b: chi-squares.

### *Monitoring of abstinence:*

The cocaine dependent subjects were actively using cocaine prior to study entry (spending \$337  $\pm$  204 weekly on cocaine) and had been using average of 14.3  $\pm$  7.2 years. In order to obtain 14 days of abstinence prior to the PET scans, each subject was allowed to choose between two options for obtaining abstinence: 1) admission to the inpatient research unit at the Irving Institute for Clinical and Translational Research; or 2) subjects could come to the imaging laboratory three days a week (Monday, Wednesday, Friday) and submit urine for drug testing. Volunteers who choose the outpatient option were still admitted to the Irving Institute the day before the PET scans and for one night following the scans. All subjects were reimbursed for the 14 day abstinence period. The inpatient subjects were paid for each hospital day (\$60/day) and the outpatient subjects earned \$25 for each drug-negative urine sample. Nine subjects chose the inpatient option and the rest chose the outpatient option.

The rationale for offering both options was to avoid a selection bias. Previous studies in our treatment clinic showed that most volunteers would not be able to enter the hospital for 14 days (largely due to employment), yet we did not want to exclude subjects who were unable to maintain abstinence on an outpatient basis. All subjects were informed of the two options at the beginning of the study and were informed that if that they could chose between the options. Subjects were also informed that the inpatient option was always available if they were unsuccessful at the outpatient option. Twenty seven cocaine dependent subjects entered the abstinence portion of the study, but 2 dropped out and never completed the scans or treatment phase. Of the remaining 23, two subjects started as outpatients but were unsuccessful at obtaining abstinence in this way and opted for the inpatient admission and completed the study.

### *Demographic data: treatment responders and non-responders*

The comparison of the demographic data of the treatment responders and non-responders is shown below. The treatment responders included all 3 female subjects and included three non-smokers (the other two non-smokers were in the non-responders group). In addition, there was a difference in the time they remained in treatment. The responders attended an average of 32.9  $\pm$  3.9 visits (out a maximum possible of 36 visits) while the non-responders attended an average of 14.3  $\pm$  8.7 visits ( $p < 0.0001$ ).

Table 2: Group demographic comparison of the treatment responders and non-responders

Parameter	Responders		Non-responders		p
	mean	sd	mean	sd	
Age (mean $\pm$ SD, years)	34.4	7.2	38.3	6.0	0.20
Reported cocaine use	289.5	183.6	368.5	216.2	0.40
Years of cocaine use	10.5	5.5	16.8	7.2	0.03
Cigarettes per day (mean $\pm$ SD, in smokers)	8	5	8	6	0.84

*Additional data regarding the behavioral treatment:*

As described in the manuscript, the behavioral treatment consisted of Contingency Management/Community Reinforcement Approach (CM-CRA), as previously described by Higgins et al (3, 4). Participants were scheduled to attend the clinic three days a week. On two of the clinic visits, the participants received psychotherapy, using CRA, which seeks to develop cocaine avoidance strategies and promote lifestyle changes, such as improving relationships and vocational skills. The contingency management was also performed as previously described (3, 4). The subjects' urine was tested for the cocaine metabolite benzoylecgonine on each of the three visits per week. Participants received voucher points for cocaine-negative urine. The points were acquired on an escalating schedule as follows: voucher points (\$0.25) started at 10 points for first cocaine-free sample, and each subsequent cocaine-free sample increased the voucher value by 5 points, such that the second consecutive cocaine free urine earned 15 points (\$3.75) and the third 20 points (\$5.00), etc. Participants also received a bonus of 40 points (\$10.00) for every three consecutive cocaine free urine samples (equivalent to a week of abstinence). Abstinence from cocaine was confirmed by on-site urine testing (Abuscreen On-Trak system, Roche Diagnostics) and all urine specimens were sent to the hospital laboratory for confirmation. Missed clinic appointments and cocaine positive urine samples reset the voucher points to the starting value of 10 points, although participants did not lose the amount of points they earned prior to the time of the value reset. Participants could readjust their voucher points to the maximum amount they had earned prior to the reset by providing 5 consecutive cocaine free urines. The money earned was provided in the form of credit card gift cards, and the use of this money was discussed with the therapist. Following the 12 weeks of intensive therapy, the cocaine dependent subjects were offered an additional 12 weeks of treatment, in which they were seen in the clinic twice a week, but the voucher system was discontinued.

*Additional PET Scan Results:*

No significant difference was seen between groups or between conditions for injected dose of [<sup>11</sup>C]raclopride, specific activity, methylphenidate plasma level, or mass dose of raclopride (all  $p > 0.2$ , analysis performed with a two tailed t test for across group and condition, data not shown). No difference was seen between groups with respect to the volume of the ROIs (all  $p > 0.1$ , data not shown). Similarly, no differences in the PET scan parameters, methylphenidate level, or

volume of the ROIs was seen between the treatment responders and non-responders (all  $p > 0.1$ , data not shown).

## References

1. Association AP: DSM-IV : Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC, 2000
2. First MB, Spitzer RL, Gibbon M, Williams JBW, Benjamin L: Structured Clinical Interview for DSM-IV Axis II personality disorders (SCID-II, Version 2.0). Biometrics Research Department, New York State Psychiatric Department 1994
3. Higgins ST, Budney AJ, Bickel WK, Foerg FE, Donham R, Badger GJ: Incentives improve outcome in outpatient behavioral treatment of cocaine dependence. Arch Gen Psychiatry 1994; 51(7):568-76
4. Higgins ST, Sigmon SC, Wong CJ, Heil SH, Badger GJ, Donham R, Dantona RL, Anthony S: Community reinforcement therapy for cocaine-dependent outpatients. Arch Gen Psychiatry 2003; 60(10):1043-52