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Multimodal predictive modeling of individual treatment outcome in cocaine dependence with combined neuroimaging and behavioral predictors

Sean X. Luo*, Diana Martinez, Kenneth M. Carpenter, Mark Slifstein, Edward V. Nunes

Division of Substance Abuse, Department of Psychiatry, New York State Psychiatric Institute, Columbia University, Box 83, 1051 Riverside Drive, New York, NY 10032, USA

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ABSTRACT

Background: Developing personalized treatments for cocaine dependence remains a significant clinical challenge. Positron emission tomography (PET) has shown that the [^{11}C]raclopride signal in the ventral striatum is associated with treatment success in a positively reinforced contingency management program. The present study investigates whether this signal can be used to predict treatment outcome at an individual level.

Methods: Predictive models were developed using PET signals from 5 regions of the striatum and follow-up data in 24 patients, and evaluated using cross-validation.

Results: The ventral striatal PET signal alone can predict individual treatment response with a substantial degree of accuracy (cross-validated correct rate = 82%). Incorporating information from other regions-of-interest (ROIs) in the striatum does not improve predictive performance, except for a small improvement with adding the posterior caudate. The addition of baseline demographic variables, including baseline severity measures, does not improve predictive performance. On the other hand, early treatment response and motivation, reflected by cumulative clinic attendance, performs as well as the PET signal (83%) by week 3 in the 24-week study. The combined model with both PET signals and cumulative clinic attendance demonstrates a significant improvement of performance, peaking at 96% during week 3 of the trial.

Conclusions: These results suggest that a multimodal model can predict treatment success in cocaine dependence at an individual level, and pose hypotheses for the underlying neural circuitry mechanisms responsible for individual variations in treatment outcome.

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1. Introduction

Recovery from cocaine dependence is a complex, multifactorial phenomenon. Previous studies have identified a number of clinical predictors of treatment efficacy, such as baseline severity of use and duration of use (Poling et al., 2007), though prediction of treatment response at the individual level remains difficult. Striatal dopamine neurons may encode many cognitive signals, such as reward response (Volkow et al., 2009), reinforcement (Tobler et al., 2005), and prediction error (Schultz, 2007), and computational models suggest that these signals are mechanistically related to clinical phenotypes (Montague et al., 2012). Biomarkers based on striatal dopamine transmission may therefore hold promise in predicting individual treatment response.

Positron Emission Tomography (PET) imaging with the dopamine D2/D3 receptor antagonist radioligand [^{11}C]raclopride provides two quantitative indices that could serve as biomarkers (Breier et al., 1997; Laruelle, 2000). The baseline binding potential (BP_{ND}) is proportional to the product of D2/D3 receptor density and the affinity of the tracer for the receptors, and measures dopamine receptor availability (Volkow et al., 1994). Because endogenous dopamine and [^{11}C]raclopride compete for binding to D2/D3 receptors, BP_{ND} reacts to changes in synaptic dopamine levels: BP_{ND} decreases after administration of psychostimulants, such as methylphenidate or amphetamine (Laruelle, 2000; Volkow et al., 1997), which increase endogenous synaptic dopamine. The percent decrease in BP_{ND} following a stimulant challenge (ΔBP_{ND}) measures dopamine release capacity. Previous studies have shown that both baseline BP_{ND} and stimulant-induced ΔBP_{ND} are decreased in cocaine-dependent subjects compared with healthy controls (Martinez et al., 2003; Volkow et al., 1997). Additionally, cocaine abusers with lower BP_{ND} in the ventral striatum are more likely to

* Corresponding author. Tel.: +1 646 774 6144
E-mail address: xsl2101@columbia.edu (S.X. Luo).

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choose cocaine over money in a non-treatment laboratory model of cocaine-seeking behavior (self-administration; Martinez et al., 2007). Lower D2 receptors expression in the ventral striatum is associated with greater cue-induced craving for alcohol (Heinz et al., 2005, 2004). In the treatment setting, cocaine dependent subjects who responded to Community Reinforcement Approach (CRA) with a voucher reward (Higgins and Budney, 1993; Higgins et al., 2003; Sigmon and Higgins, 2006) have higher average measures of both BP_{ND} and ΔBP_{ND} in the striatum compared with non-responders (Martinez et al., 2011). Similar signals of lower dopamine neurotransmission in the striatum are shown to be associated with relapse in methamphetamine abusers (Wang et al., 2012). However, even though the average intergroup differences are significant in these studies, the power of a given individual subject's PET scan to predict his or her treatment response has not been assessed.

While PET imaging can elucidate brain mechanisms of treatment response variations, it is expensive and burdensome to conduct. A simpler clinical variable may serve as a proxy or be used in conjunction. A parallel line of inquiry finds that early treatment success, as a behavioral metric, is also a good predictor of treatment outcome at the group level. For instance, cessation of drug use during lead-in periods or abstinence at the time of randomization have been shown to be strong predictors of abstinence outcome in clinical trials (Bisaga et al., 2010, 2006, 2005; Brensilver et al., 2012; Kampman et al., 1996, 2001). Even a delay to the first clinic visit may be predictive of treatment attrition (Chawdhary et al., 2007). Early response to treatment (early abstinence or treatment attendance) might indicate motivation or sensitivity to reinforcement that is reflected in the PET signal of dopamine transmission. The potential for such a behavioral signal to predict individual outcome, both alone and in combination with the PET signal, needs to be assessed.

We, therefore, set out to quantify our ability to predict individual response to treatment using a subject's PET scan, her early cumulative clinic attendance, or both, in a study of behavioral treatment for cocaine dependence. Our hypotheses are: (1) the ventral striatal PET signal is a good predictor for treatment responses at an individual level; (1a) combining the PET signals from other regions-of-interest improves predictive performance; (1b) adding other demographic and clinical predictors, including baseline severity measures, improves predictive performance; (2) early clinic attendance alone is a good predictor of eventual treatment responses; and (3) while the PET signals and early clinic attendance may share some common variance, combining these variables in a multimodal model improves predictive performance.

2. Methods

2.1. Subjects and procedure

Details of the procedures were previously published (Martinez et al., 2011). All participants were active cocaine users recruited from the community as an independent study, approved by the IRB of the New York State Psychiatric Institute. The screening evaluation included the Structured Clinical Interview for DSM-IV disorders (SCID-IV), an independent psychiatric evaluation, and a medical exam. Individuals were eligible to participate if they were between the ages of 21 and 45 and met criteria for a current DSM-IV diagnosis of cocaine dependence. Exclusion criteria were: currently meeting criteria for other Axis I DSM-IV disorders, lifetime criteria for dependence on a psychostimulant other than cocaine, reporting the current use of psychotropic medication or the use of opiates, sedative-hypnotics, or cannabis more than twice per week, and/or the presence of severe medical (e.g., hypertension, active hepatitis) or neurological illnesses. Twenty-five participants completed a baseline assessment session, met inclusion criteria, and gave informed consent to participate in the study. The sample average age was 37, predominantly male and was racially mixed. For further details of the demographic characteristics, see (Martinez et al., 2011).

2.2. PET and MRI scanning

PET scans were obtained on the ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, Tenn.) in three-dimensional mode over 60 min. For each subject, [^{11}C]raclopride was administered as a bolus and participants underwent two PET scans: one at baseline and one following oral methylphenidate (60 mg) administration (Martinez et al., 2003). The PET data were analyzed using Simplified Reference Tissue Modeling (Martinez et al., 2009a, 2009b), with cerebellum as a reference tissue. Binding potential (BP_{ND}) was defined as:

$$BP_{ND} = f_{ND} \times \frac{B_{AVAIL}}{K_D}$$

where the subscript ND indicates the measurement with respect to the non-displaceable concentration of [^{11}C]raclopride in brain tissue (free plus non-specifically bound), f_{ND} was the free fraction of the non-displaceable tracer concentration, B_{AVAIL} was the concentration of D2/D3 receptors available for the tracer to bind to (pmoles per cm^3 of tissue), and KD (pmoles per cm^3 of tissue) was the inverse of the affinity of the radiotracer for the receptor. The relative change in [^{11}C]raclopride BP_{ND} (ΔBP_{ND}) following methylphenidate administration was calculated as

$$\Delta BP_{ND} = 100\% \times (BP_{ND}\ \text{baseline} - BP_{ND}\ \text{methylphenidate})/BP_{ND}\ \text{baseline}.$$

Data were analyzed in regions-of-interest (ROI), using each subject's magnetic resonance imaging (MRI) scan (GE Signa EXCITE 3 T/94 cm scanner, GE Medical Systems, Milwaukee, Wis.) to determine the subdivisions of the striatum. These included the ventral (limbic) striatum (VST), the anterior and posterior caudate (DCA and PCA) and the anterior and posterior putamen (ANP and POP) (Fig. 1A). Regional values were expressed as BP_{ND}-ROI or ΔBP_{ND}-ROI (e.g. BP_{ND}-VST, ΔBP_{ND}-VST).

2.3. Treatment

The cocaine-dependent subjects were enrolled in treatment consisting of contingency management with the Community Reinforcement Approach (CRA; Higgins and Budney, 1993; Higgins et al., 2003), using a standard manual (Budney and Higgins, 1998). Each patient received twice weekly, supervised therapy, and obtained voucher points for each negative urine sample. They had three clinic visits per week. The voucher points (worth $0.25 each) were escalated starting at 10 points for the first cocaine negative sample, with each subsequent negative sample increasing the voucher value by 5 points. Extra points were given for three consecutive cocaine-free urine samples. A urine test positive for cocaine metabolites would reset the escalating schedule to the starting point (i.e., $0.25). Patients did not lose any of the voucher points earned prior to a positive cocaine urinalysis (UA). All patients were followed through the end of the study, but missed appointments were recorded as positive UAs and reset the escalating schedule. In the first 12 weeks, the voucher reward was escalated and the total maximum amount that could be earned over that period was $997.50, which reflected complete abstinence and perfect attendance. In weeks 13–24, subjects earned a lottery ticket for each cocaine free UA, an incentive system developed to maintain gains and fade out the high magnitude reinforcements put in place at the beginning of treatment. Treatment response was dichotomized into "responders" and "non-responders" by the end of 12 weeks using a threshold of voucher money earned ($163), based on the observation that voucher earnings appeared bimodal. This threshold also defined the patients with a month of abstinence versus those demonstrating less than a month of abstinence. Of the 15 non-responders, 10 earned less than $100 of vouchers and five between 100 and 163 (Martinez et al., 2009a).

2.4. Construction of predictive models

In the original study (Martinez et al., 2011), the ΔBP_{ND} signal in the ventral striatum (ΔBP_{ND}-VST) was significantly higher in the treatment responders group compared with the non-responders group. ΔBP_{ND} in the posterior caudate (ΔBP_{ND}-PCA) and baseline BP_{ND} in the ventral striatum (BP_{ND}-VST) and anterior putamen (BP_{ND}-POP) also trended toward significance. A quick calculation shows that the intergroup difference in ΔBP_{ND}-VST remains significant when it is adjusted for ΔBP_{ND} and baseline BP_{ND} in other ROIs (ANCOVA, $p < 0.001$). There is also a significant difference between responders and non-responders across all ROIs in the striatum (MANOVA, $p < 0.001$).

We evaluated the capacity for ΔBP_{ND}-VST as a predictor for individual treatment response using predictive models with logistic regression. The univariate model with ΔBP_{ND}-VST as the sole predictor was

$$\text{Log(odds)}_R = \beta_1(\Delta BP_{ND} - \text{VST}) + \beta_2(\Delta BP_{ND} - \text{DCA}) + \varepsilon$$

where R was treatment response and ε an error term. The regression coefficient β_1 was obtained from standard maximum likelihood procedures. Adding a second predictor, for example ΔBP_{ND}-DCA, to the model led to

$$\text{Log(odds)}_R = \beta_1(\Delta BP_{ND}\text{-VST}) + \beta_2(\Delta BP_{ND} - \text{DCA}) + \varepsilon$$

Neuroimaging, demographic or behavioral predictors were added in this way. We visualized a model with two predictors by plotting the line that divided the