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Value and Risk Processing in Cocaine Addiction: Relationship to Brain Function, Structure, and Connectivity

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Abstract of the Dissertation

Value and Risk Processing in Cocaine Addiction: Relationship to Brain Function, Structure, and Connectivity

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Cocaine addiction is a chronically relapsing disorder characterized by a compulsive drive to seek and ingest cocaine, often at the expense of negative personal or social consequences and other rewarding outcomes. As such, it has been hypothesized that addiction impacts the brain circuits necessary for exerting self-control and those involved in processing the incentive value of environmental stimuli. The present set of studies aims to explore the effects of chronic cocaine use on these functions, and the brain systems supporting them, using multimodal neuroimaging and behavioral assessments and the highly generalizable reinforcer, money. *Study 1* examines the interplay between brain structure and reward value-related function using structural and functional magnetic resonance imaging (fMRI) in healthy individuals and individuals with cocaine use disorders (CUD). To determine the specificity of dysfunction to value, and translation to actual decision making behavior, *Study 2* uses behavioral economics to examine the influence of value and risk on decision-making in a second group of healthy individuals and individuals with CUD. Lastly, *Study 3* examines the crosstalk between brain regions involved in value and risk processing during a task-independent state (i.e., during resting-state) using functional connectivity MRI and tests whether a stimulant drug with a similar mechanism of action to cocaine but with lower abuse potential (i.e., methylphenidate) can modify these connections in a third group of individuals with CUD. Results will be discussed in the context of the impact of chronic cocaine use on frontostriatal brain circuits, and potential amelioration with short-term methylphenidate. Individual differences (e.g., disease severity, impulsivity) will also be discussed in the ways in which they may influence the relationship between brain and behavior. Together, these studies should strengthen our understanding of the impact of chronic cocaine use on value and risk assessment and may serve as an empirical foundation for the development of interventions targeting frontostriatal circuit dysfunction in cocaine addiction.

Dedication Page

This dissertation is dedicated to my family. To my parents, my husband, my two cats, and all other immediate and distant family members abroad, who supported me every step of the way.

Table of Contents

List of Figures

List of Tables

List of Abbreviations

BIS: Barratt Impulsiveness Scale

BOLD: blood-oxgen-level-dependent

CAARS: Conners' Adult ADHD Rating Scales

CUD: cocaine use disorder

DLPFC: dorsolateral prefrontal cortex

EV: expected value

GM: gray matter

MPH: methylphenidate

OFC: orbitofrontal cortex

PFC: prefrontal cortex

VBM: voxel-based morphometry

VMPFC: ventromedial prefrontal cortex

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Publications

Peer-Reviewed Journal Articles:

1. Horga G, Parellada E, Lomeña P, Fernández-Egea E, Mané A, Font M, Falcón C, **Konova AB**, Pavia J, Ros D, Bernardo M (2011). Differential brain glucose metabolic patterns in antipsychotic-naïve first episode schizophrenia with and without auditory verbal hallucinations, *Journal of Psychiatry & Neuroscience*, 36(1): 100085.

2. Alia-Klein N, Parvaz MA, Woicik PA, **Konova AB**, Maloney T, Shumay E, Wang R, Telang F, Biegon A, Wang G-J, Fowler JS, Tomasi D, Volkow ND, Goldstein RZ (2011). Gene × disease interaction on orbitofrontal gray matter in cocaine addiction, *Archives of General Psychiatry*, 68(3):283-94.

3. *Parvaz MA, ***Konova AB**, Tomasi D, Volkow ND, Goldstein RZ (2012). Structural integrity of the prefrontal cortex modulates electrocortical sensitivity to reward, *Journal of Cognitive Neuroscience*, 24(7), 1560-70. ***=*shared first-authorship***

4. **Konova AB**, Moeller SJ, Tomasi D, Parvaz MA, Alia-Klein N, Volkow ND, Goldstein RZ (2012). Structural and behavioral correlates of abnormal encoding of money value in the sensorimotor striatum in cocaine addiction, *European Journal of Neuroscience*, 36(7), 2979-88.

5. Moeller SJ, Beebe-Wang N, Woicik PA, **Konova AB**, Maloney T, Goldstein RZ (2013). Choice to view cocaine images predicts concurrent and prospective drug use in cocaine addiction, *Drug & Alcohol Dependence*, 130(1-3), 178-85.

6. **Konova AB**, Moeller SJ, Tomasi D, Volkow ND, Goldstein RZ (2013). Effects of methylphenidate on resting-state functional connectivity of the mesocorticolimbic dopamine pathways in cocaine addiction, *JAMA Psychiatry*, 70(8), 857-68.

7. Moeller SJ, Parvaz MA, Shumay E, Beebe-Wang N, **Konova AB**, Alia-Klein N, Volkow ND, Goldstein RZ (2013). Gene × abstinence effects on drug cue reactivity in addiction: Multimodal evidence, *Journal of Neuroscience*, 33(24), 10027-36.

8. **Konova AB**, Moeller SJ, Goldstein RZ (2013). Common and distinct neural targets of treatment: Changing brain function in substance addiction, *Neuroscience & Biobehavioral Reviews*, 37(10), 2806-17.

9. Moeller SJ, **Konova AB**, Parvaz MA, Tomasi D, Lane RD, Fort C, Goldstein RZ (2013). Functional, structural, and emotional correlates of impaired insight in cocaine addiction, *JAMA Psychiatry*, 71(1), 61-70.

10. Moeller SJ, Parvaz MA, Shumay E, Wu S, Beebe-Wang N, **Konova AB**, Mysyrlis M, Alia-Klein N, Volkow ND, Goldstein RZ (2014). Monoamine polygenic liability in health and cocaine addiction: imaging genetics study of aversive processing and associations with depression symptomatology, *Drug & Alcohol Dependence*, 140, 17-24.

11. Parvaz MA, Maloney T, Moeller SJ, Malaker P, **Konova AB**, Alia-Klein N, Goldstein RZ (2014). Multimodal evidence of regional midcingulate gray matter volume underlying conflict monitoring, *Neuroimage: Clinical*, 5, 10-18.

12. Moeller SJ, Froböse MI, **Konova AB**, Misyrlis M, Parvaz MA, Goldstein RZ, Alia-Klein N (in press). Common and distinct neural correlates of inhibitory dysregulation: Stroop fMRI study of cocaine addiction and intermittent explosive disorder, *Journal of Psychiatric Research*.

Articles Submitted or in Preparation:

1. **Konova AB**, Moeller SJ, Woicik PA, Horga G, Goldstein RZ. Individual differences in risk preference in cocaine addiction, association with drug-related choice.

2. **Konova AB**, Moeller SJ, Parvaz MA, Froböse MI, Alia-Klein N, Goldstein RZ. The effects of cocaine addiction and sex converge in the posterior cingulate during monetary reward processing.

3. Parvaz MA, **Konova AB**, Dunning JP, Hajcak Proudfit G, Malaker P, Moeller SJ, Maloney T, Woicik PA, Alia-Klein N, Goldstein RZ. Electrocortical evidence of positive and negative reward prediction errors in health and their disruption in cocaine addiction.

4. **Konova AB**, Parvaz MA, Bernstein V, Moeller SJ, Goldstein RZ. Extinguishing cocaine cue associations in humans: role of the VMPFC.

5. **Konova AB**, Moeller SJ, Tomasi D, Goldstein RZ. Effects of chronic and acute stimulants on brain functional connectivity hubs.

Book Chapters, Commentaries:

1. Ungar AK, **Konova AB**, Patel A, Goldstein RZ, Hurd Y (2013). "Substance Use and Addictive Disorders" in Wayne K. Goodman, Asher B. Simon, & Antonia New (Eds.) Mount Sinai Experts Guide.

2. **Konova AB**, Goldstein RZ. "Role of Value Circuits in Addiction and Addiction Treatment" in Stephen J. Wilson (Ed.) Wiley-Blackwell Handbook on the Neuroscience of Addiction. *In preparation*.

3. Moeller SJ, **Konova AB**, Goldstein RZ (August, 2014). Multiple ambiguities in the measurement of drug craving, Invited Commentary on "Intensity Matters: Cue-Induced Craving and Neuroimaging," *Addiction*.

INTRODUCTION

Addiction is characterized by continued drug-seeking and drug use despite reduced pleasure derived from the drug and often in the face of catastrophic social, emotional, and legal consequences. The recurrent nature of the disease poses a large economic burden to society and significant personal distress to the individual and their family [1]. Limited treatment options are available, and many are only effective in a subset of individuals. Thus, a critical step toward improving treatments for addiction is to clarify the neurobiological mechanisms of addiction that contribute to more severe patterns of drug use and ultimately relapse.

Decades of work have anatomically outlined the mesocortical dopamine "reward" pathway of the brain. Regions comprising this circuit include midbrain (ventral tegmental area and substantia nigra) and basal ganglia structures including the ventral (nucleus accumbens) and dorsal striatum. Also within this pathway, the prefrontal cortex (PFC) is a major cortical projection region interfacing reward processing with higher order cognitive and emotional functions [2]. In this context, the orbitofrontal cortex (OFC) has been proposed to play an important role in the evaluation of appetitive stimuli [3, 4], while the anterior cingulate cortex (ACC) and dorsolateral PFC (DLPFC) have both been proposed to integrate cognitive and motivational information related to value, pleasure, and cost during reward-guided action selection [3, 5, 6].

Preclinical work suggests that an underlying neurobiological mechanism of addiction may involve adaptations within these brain circuits [7]. More specifically, although different drugs of abuse have different mechanisms of action, they all increase dopamine release in the brain's reward circuit to exert their reinforcing effects [8, 9]. Chronic drug use modifies dopamine signaling in these regions, facilitating the transition from recreational to habitual use that characterizes addiction [10]. These changes result in a state of impaired motivational drive and difficulty with inhibiting conditioned responses to drug-related cues, undermining more goal-directed behavior [7]. Following protracted use, exposure to drug-related cues activates the ventral striatum (among other regions like the cingulate cortices and amygdala) across substance addictions [11, 12] in ways that may facilitate relapse to drug use [13, 14]. In addition to craving, the negative emotional state of withdrawal during periods of abstinence may also involve the reward circuit [15]. However, brain regions (and their corresponding functions) outside the

reward system also appear affected by chronic drug use. In particular, drug addicted individuals exhibit alterations in the ACC, OFC, and DLPFC, where abnormalities are linked to impaired emotion regulation and inhibitory control [16]. Thus, the ability of addicted individuals to achieve abstinence is diminished both by pathologically strengthened drug-seeking behavior and impairments in the capacity to regulate such behavior [10, 17]. Studying the neural and behavioral processes subserved by this "reward" and "control" circuitry can aid in our mechanistic understanding of the neurobiological underpinnings of addictive behavior.

The set of research studies described here aim to accomplish this using multimodal neuroimaging and behavioral assessments and the highly generalizable reinforcer money. In all studies, clinical variables are also assessed to determine how the study observations relate to the critical real-world behaviors. The study population of interest is individuals with chronic, severe cocaine use disorders (CUD) (i.e., individuals with ~15-17 years of cocaine use that has led to serious social or personal losses).

More specifically, the aim of *Study 1* is to determine, more precisely than previously done, the effects of alterations in gray matter (GM) volume of the PFC and striatum on the functioning of these regions in terms of graded value representation and functional connectivity during this representation. This will be accomplished by first characterizing and mapping the functional changes in these regions associated with increasing value on a sustained attention task, second by quantifying how GM relates to these functional changes, and lastly by directly testing the strength of the functional connectivity, or crosstalk between these regions. The hypothesis is that CUD would exhibit reduced GM volume in the PFC, and this reduction would manifest as abnormal functioning of the PFC and connectivity with regions comprising the same circuits.

To assess how abnormal value representation may translate to biased or sub-optimal *behavior* in terms of decision making, *Study 2* aims to examine value computations related to risk (uncertainty) and how these computations influence decisions about risk and reward. This will be accomplished by developing a novel task that parametrically varies expected value and risk in a choice situation. The hypothesis is that risk-seeking individuals relative to risk-averse individuals and individuals with CUD relative to controls would endorse more impulsive traits on standard assessments of impulsivity, and within CUD, more drug-seeking on a laboratory measure previously associated with real-world drug use behavior.

While *Studies 1 & 2* examine how alterations in brain function and structure relate to behavior, it is not fully known whether these frontostriatal circuits impacted by addiction are at all *modifiable*. Therefore, *Study 3* examines whether functional connectivity of the mesocorticolimbic circuit during resting-state (i.e., during a task-independent state) can be modified by a stimulant drug with a similar mechanism of action to cocaine but with lower abuse potential [i.e., methylphenidate (MPH)] in individuals with CUD. It is hypothesized that given the previously observed normalizing effects of MPH on task-related activation and behavior in this population, MPH would differentially alter connectivity of pathways associated with addiction severity, strengthening connectivity with the medial PFC while attenuating connectivity with regions underlying compulsive drug-seeking such as the striatum.

CHAPTER 1

Structural and Behavioral Correlates of Abnormal Encoding of Money Value in the Sensorimotor Striatum in Cocaine Addiction (*Study 1* [18])

Background & Rationale

The prefrontal cortex, and specifically its ventromedial aspect (VMPFC), participates in evaluating the motivational value of rewards [3], particularly when one is faced with different rewarding options [19-22]. In this context of reward processing, the VMPFC has been linked to goal-directed behavior [23] and its adaptive adjustment [5]. While studies have also supported a role in goal-directed behavior for the ventral striatum and caudate nucleus [24-27], the sensorimotor striatum (post-commissural putamen) appears to have a unique, potentially implicit, role in reward processing, as it is engaged as stimulus–response–reward contingencies are learned [28, 29]. In the context of cocaine addiction, the functions of the VMPFC have been linked to self-control [30] and craving [31], the ventral striatum to impulsivity [32] and treatment course [33], and the sensorimotor striatum to the habitual aspects of drug-seeking [10, 34, 35].

Preclinical work suggests that cocaine affects the morphology of dopamine neurons and their target projection structures (like the VMPFC and striatum) to directly contribute to addiction (e.g., [36-38]). Studies in humans with poly-substance or cocaine dependence also report changes in GM volume, as most notably observed in the VMPFC [39-42] and striatum [43, 44], and link these frontostriatal GM changes to more compulsive patterns of cocaine use [45]. In a previous study, it was also found that individuals with CUD showed reduced GM in portions of the PFC and the amount of GM in some of these regions, including aspects of the VMPFC, was correlated with the magnitude of a reliable EEG marker of sensitivity to reward [46]. However, a direct link between brain structure and functioning of these same regions in human cocaine addiction has not been investigated.

The present study sought to extend this previous work by directly examining both functioning and GM volume of the VMPFC and striatum, and their relevance to behavior, in individuals with chronic CUD and closely matched healthy controls. Money, a highly generalizable reinforcer, was used to target these regions and evaluate their putative dysfunction in addiction. Previous studies examining response to money in cocaine [33] or alcohol

dependence with comorbid cocaine use [32] found relatively increased activation in the ventral striatum and putamen during the anticipation and receipt of monetary gain, which in the former case predicted poorer treatment outcome. Abnormalities in the VMPFC during notification of success versus failure to win money have also been observed [32]. Therefore, it was hypothesized that CUD would show abnormal frontostriatal GM volume, connectivity, and response to money, and that these variables would be predictive of less adaptive behavior on the task and more drug use among the CUD.

Methods

Subjects

Forty-two right-handed native English speakers were recruited using advertisements in local newspapers and by word-of mouth. Subjects were 21 healthy controls and 21 individuals with CUD. Subjects were otherwise healthy and not taking any medications, as ascertained during a full physical and neurological examination by a neurologist and a diagnostic interview by a clinical psychologist. This latter interview included the Structured Clinical Interview for DSM-IV Axis I Disorders (research version [47, 48]) and the Addiction Severity Index [49]. Exclusion criteria were: (1) history of head trauma with loss of consciousness (>30 min) or other neurological disorders of central origin; (2) abnormal vital signs at time of screening and history of major medical conditions, such as cardiovascular, endocrinological, oncological or autoimmune diseases; (3) history of a major psychiatric disorder (other than substance abuse or dependence in the CUD group); note also that subjects in either study group were not excluded for secondary alcohol or nicotine use disorders; (4) more than minimal levels of self-reported state depression (Beck depression inventory score>14); (5) history of probable pathological gambling as assessed with the South Oaks Gambling Questionnaire [50] (cutoff score>5); (6) except for cocaine, positive urine screens (Biopsych^{TM}) for psychoactive drugs or their metabolites (phencyclidine, benzodiazepines, amphetamines, cannabis, opiates, barbiturates, and inhalants) on any study day; (7) pregnancy as tested with a urine test in all females; and (8) contraindications to the MRI environment (e.g., metal in the body or claustrophobia). All subjects provided written informed consent for their involvement in all study procedures as approved by the local Institutional Review Board at Stony Brook University.

Individuals with CUD and healthy controls included in the analyses were matched on all demographic variables except for cigarette smoking history (**Table 1.1**). Nineteen of the 21 CUD used crack/cocaine (mostly smoked route) in the past 14 days and all CUD met DSM-IV criteria for current cocaine dependence (n = 15) or abuse (n = 6; five of these subjects met criteria for cocaine dependence in remission); 15 CUD tested positive for cocaine in urine. Current comorbid disorders met by the CUD group were for alcohol and ecstasy abuse and alcohol and marijuana dependence (total of n = 3 CUD).

Table 1.1. Demographic and drug use variables for healthy controls and individuals with cocaine use disorders (CUD) included in *Study 1*.

	Study 1		
	Test	**Control (N=21)**	**CUD (N=21)**
Gender: Male / Female	$\chi^2 = 0.2$	18 / 3	17 / 4
Race: African-American / Other	$\chi^2 = 2.9$	12 / 9	16 / 5
Age (years)	$t = 2.0$	38.9 ± 6.2	43.1 ± 7.4
Education (years)	$t = 0.9$	14.1 ± 1.7	13.6 ± 1.8
Verbal IQ: WRAT-3 Reading	$t = 1.8$	101.5 ± 11.4	94.9 ± 12.8
Non-Verbal IQ: WASI - Matrix Reasoning Scale	$t = 0.7$	10.8 ± 2.5	10.2 ± 3.4
Socioeconomic Status: Hollingshead Index	$t = 0.1$	34.6 ± 11.7	35.0 ± 13.3
Age of onset of cocaine use (years)	--	--	22.8 ± 6.2
Cocaine use (lifetime, years)	--	--	17.0 ± 6.3
Days/week of cocaine use during the past 30 days	--	--	2.9 ± 2.3
Days/week of cocaine use during the past 12 months	--	--	2.9 ± 2.3
Depression: Beck Depression Inventory II	$Z = 1.9$	2.7 ± 3.6	5.0 ± 4.7
Cocaine urine status, No. positive / negative	--	--	15 / 6
Severity of Dependence Scale	--	--	5.5 ± 3.8
Withdrawal symptoms: 18-item CSSA	--	--	12.7 ± 8.7
Cocaine Craving: 5-item Questionnaire	--	--	15.2 ± 10.4
Duration of current abstinence (days)	--	--	100.6 ± 397.7[1]

Note. Values are frequencies or means ± standard deviation (SD);
[1] When two extreme outliers (days abstinent = 1825 and 210 days, respectively) are excluded, group mean = 4.1 ± 1.0;
Race: Other (Caucasian / Hispanic / Asian); WRAT-3 = Wide Range Achievement Test (3rd edition); WASI = Wechsler Abbreviated Scale of Intelligence; CSSA = Cocaine Selective Severity Assessment Scale.

Task Design

Subjects completed a monetary reward paradigm that has been used previously [51-53]. In brief, the task required successful (fast and accurate) button pressing for the color of drug and neutral

words to earn money. There were 4 counterbalanced money conditions (0¢, 1¢, 25¢, or 50¢), presented twice for a total of 8 runs. Each run contained 40 trials (split into two blocks of 20 trials interleaved with three 20 s fixation periods). Each block began with a 3 s window informing subjects of the amount of money they could earn for every trial in that block. In total, there were 80 trials for each money condition. The trial structure consisted of fixation (500 ms), the presentation of a word cue (2000 ms), response (500 ms), and a feedback slide indicating the amount gained for a correct response (500 ms); in the case of an error, an "X" rather than money was displayed (**Figure 1.1**).

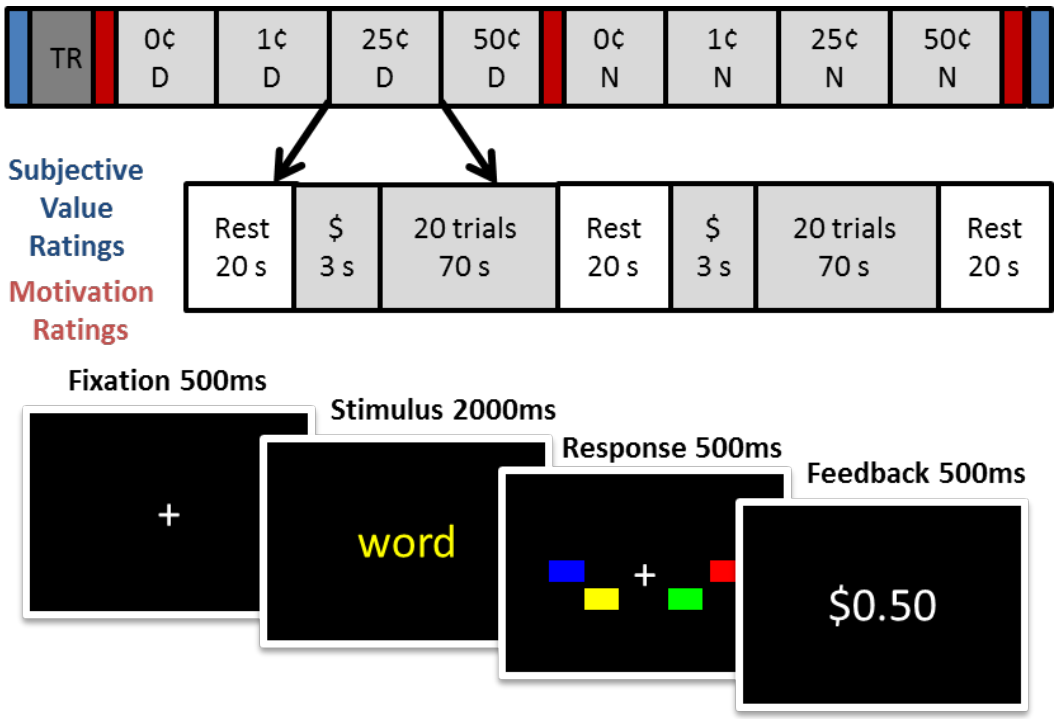

Figure 1.1. Experimental paradigm. Overall design and experimental runs are depicted at the top; each run was comprised of two 20 trial blocks separated by rest periods. Example trial is shown in the lower panel. Subjective value and motivation ratings were administered between runs as indicated. TR: training.

During the response window, subjects were instructed to provide fast and accurate responses by pressing 1 of 4 buttons (blue, yellow, green, and red) matching the color of the word they had just read. The total amount of money earned on the task (up to $75) was entirely contingent on performance (mean $65.69 ± 7.21, with no difference between the groups in this amount, $p>0.46$). There were no significant word × group or money × word × group interaction

effects on behavior (p>0.15) or neural activity in the current sample. Therefore, the analyses described below focused on the effects of money value collapsed across word type. To monitor task engagement, subjects were asked to provide money wanting ratings ("how much do you want money right now" from 0 to 10) at 4 time points during the experiment (before training, before the task, in the middle of the task, and immediately following the task). To assure that the four amounts included in the task did not differ in their subjective value between the groups, subjects also provided subjective value ratings ("how valuable" an amount is to them from 0 to 10) immediately before and after the task but before receiving remuneration.

Image Acquisition

Scanning was performed on a 4T whole-body Varian/Siemens MRI scanner. Blood-oxygen-level-dependent (BOLD) responses were measured as a function of time using a T_2*-weighted single-shot gradient-echo EPI sequence (TE/TR = 20/1600 ms, 4 mm slice thickness, 1 mm gap, 33 coronal slices, 20 cm field of view, 64 × 64 matrix size, 90^o-flip angle, 200 kHz bandwidth with ramp sampling, 128 time points, and 4 dummy scans, discarded to avoid non-equilibrium effects in the fMRI signal). Padding was used to minimize motion, and earplugs and headphones were used to minimize the influence of scanner noise on brain activation [54, 55].

Anatomical images were collected using a T_1-weighted 3D-MDEFT sequence [56] (TE/TR = 7/15ms, 0.94 × 0.94 × 0.94 mm spatial resolution, 144 axial slices, 256 readout and 192 × 96 phase-encoding steps, 16 min scan time). A modified T_2-weigthed Hyperecho image (TE/TR = 42/10000 ms, echo train length = 16, 256 × 256 matrix size, 30 coronal slices, 0.86 × 0.86 mm in-plane resolution, 5 mm slice thickness, no gap, 2 min scan time) was also acquired and reviewed by a neurologist to rule out gross structural brain abnormalities.

Image Processing and Analysis

Functional Data. Subsequent analyses were performed with SPM8 running on Matlab version 7.7 (Mathworks Inc., Natick, MA). A six-parameter rigid body transformation (3 rotations, 3 translations) was used for image realignment and to correct for head motion; 2 mm displacement and 2° rotation in any of the axes in any of the task runs were used as criteria for acceptable motion. Spatial normalization to a standard EPI template (Montreal Neurological Institute) was

performed using a 12-parameter affine transformation, resulting in a final voxel size of 3 × 3 × 3 mm. An 8 mm^3 full-width at half maximum Gaussian kernel was used to smooth the data.

For the task-based analysis, a general linear model and a box-car design convolved with a canonical hemodynamic response function and high-pass filter (cut-off frequency: 1/520 sec) were used to calculate individual BOLD-fMRI beta maps. Contrast maps reflecting % signal change from the fixation baseline were calculated for the 0¢, 1¢, 25¢, and 50¢ money conditions for each subject. These functional contrast maps were then entered into a second-level 4 (Money: 0¢, 1¢, 25¢, 50¢) × 2 (Group: CUD, control) mixed analysis of variance in SPM8.

The strength of functional connectivity between the VMPFC and striatum was also assessed. In this analysis, the time series for each money condition was concatenated by discarding all rest periods and 11 s from the start of each money block to account for the initial delay in the hemodynamic response as previously described [57]. A multi-linear regression approach that used the time-varying realignment parameters (3 translations and 3 rotations) was applied to minimize motion-related fluctuations in the MRI signal. The global signal was additionally normalized across time points by subtracting the mean signal and band-pass filtered (0.01-0.10 Hz). Cubic volumes (9 mm) centered in the right putamen/globus pallidus (coordinates corresponding to the peak statistical value of the group × money interaction effect on task activations, **Table 1.2**) and VMPFC (coordinates from the group effect, **Table 1.2**) were used as the seeds for connectivity analysis. Connectivity maps reflecting correlations between BOLD signals in the seed and those in all other voxels in the brain were calculated separately for each subject and money condition. The Fisher's *Z* transform was used to convert the step distributed Pearson linear correlation factors into normally distributed correlation coefficients. These normalized connectivity maps were then entered into a second-level 4 (Money: 0¢, 1¢, 25¢, 50¢) × 2 (Group: CUD, control) mixed ANOVA in SPM8.

Structural Data. Voxel-based morphometry (VBM) analysis was conducted with the VBM toolbox (VBM 8) (Gaser, C, University of Jena, Department of Psychiatry, Germany; http://dbm.neuro.uni-jena.de/vbm/), which combines spatial normalization, tissue segmentation, and bias correction into a unified model. The MDEFT scans were first spatially normalized to standard proportional stereotaxic space and segmented into GM, white matter, and cerebrospinal fluid tissue classes according to *a priori* tissue probability maps [58, 59]. The MDEFT sequence is particularly effective for such tissue differentiation, producing the most precise

characterization of GM tissue compared with other sequences [60]. A hidden Markov random field [61] was applied to maximize the accuracy of the segmentation. Jacobian modulation was used to compensate for the effect of spatial normalization and to restore the original absolute GM volume in the GM segments. Total brain volume was computed as the sum of the extracted total gray and white matter volumes for each subject. A one-way between-subjects ANOVA (CUD vs. controls) was performed after smoothing the normalized and modulated GM volume segments with a 10 mm^3 full-width at half maximum Gaussian kernel. Consistent with the VBM literature in addiction [39-42, 62], age and total brain volume were used as covariates of no interest.

Statistical Analyses

Mixed ANOVAs with money (50¢, 25¢, 1¢ and 0¢) as the within subject factor and group (controls, CUD) as the between subject factor were conducted for the task-related measures (accuracy, reaction time, and ratings).

For the imaging data (task-related activation, connectivity, and GM volume), voxels were considered significant if they exceeded a voxel-level threshold of $p<0.005$ uncorrected and $p<0.05$ family-wise error (FWE) corrected (within the two *a priori* regions of interest) and a minimum cluster size of 5 contiguous voxels. The striatum was isolated as an anatomical region of interest, created separately for the left and right side to correspond to the putamen, caudate, and pallidum in PickAtlas [63]. The VMPFC was isolated with an 18-mm radius sphere centered on coordinates reported in Ersche *et al.* (x=-2, y=32, z=-18; [45]), where individuals with CUD who had more compulsive patterns of cocaine use also had more GM loss compared with controls. Regions meeting the cluster-level $p<0.05$ FWE corrected threshold outside of the *a priori* regions of interest are also reported but are not the focus of the present study.

For follow-up analyses with task behavior across the entire sample and cocaine use variables in CUD, in SPSS 11.5 (SPSS Inc., Chicago, IL), the average percent signal change, connectivity strength, and GM volume in significant coordinates were extracted using the entire cluster around the peak with the EasyROI toolbox (http://www.sbirc.ed.ac.uk/cyril/cp_download.html). Bonferroni correction was used to correct for multiple comparisons in the analyses with cocaine use variables, which included lifetime years of use, current abstinence, frequency of cocaine use in the past 12 months, withdrawal symptoms, and cocaine craving ($0.05/5 = p<0.01$; **Table 1.1**). Cook's distance test was used to

assess the effect of potential outliers in all analyses (cutoff value $d < 1$). The Fisher's Z-transformation was used to determine differences in correlation coefficients between the groups.

Results

Subjective Ratings and Task Behavior

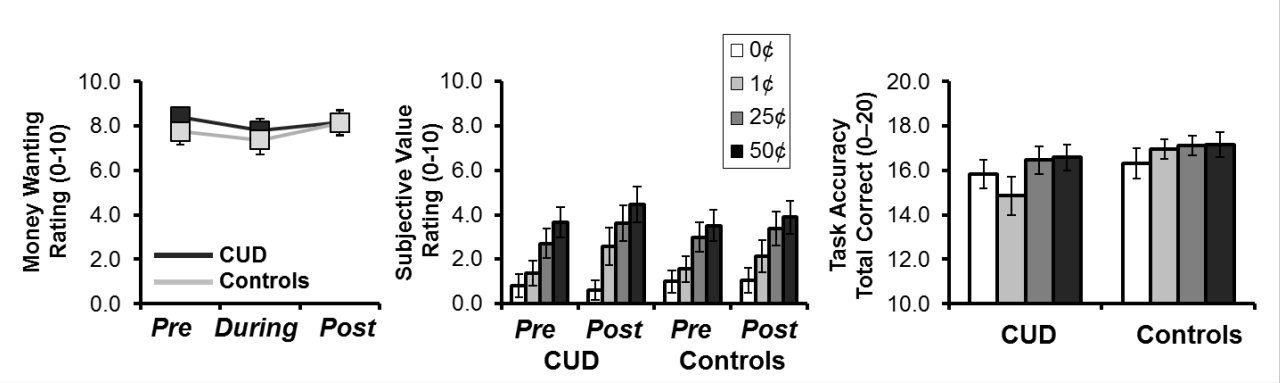

Figure 1.2. Subjective ratings and task behavior. Mean wanting ratings for the three time points and subjective value and task accuracy for the four monetary reward conditions (linear effect: 50¢>25¢>1¢>0¢). Bars are means ± SEM.

Motivation to obtain money remained high throughout the task and did not differ between the groups (F<2.03, p>0.14). Similarly, both groups provided higher subjective value ratings for the higher money amounts than the lower ones [main effect of money: 50¢ (mean ± standard error of the mean, 3.89 ± 0.49) > 25¢ (3.18 ± 0.48) > 1¢ (1.92 ± 0.45) > 0¢ (0.87 ± 0.30), $F_{(3,120)}$=65.78, linear effect, p<0.001] and across subjects and money amounts, these ratings increased following the task (main effect of time: after (2.72 ± 0.45) > before (2.21 ± 0.39), $F_{(1,40)}$=4.02, p=0.05; all other effects: F<2.35, p>0.09).

These self-reported ratings were reflected in subjects' behavior on the task. Task accuracy improved with increasing potential gain such that accuracy was higher for the high than the low money conditions [main effect of money: 50¢ = 25¢ > 1¢ = 0¢, $F_{(3,120)}$=3.82, p=0.01, linear effect, p=0.003; **Figure 1.2**]. There were no significant group or money × group interaction effects on accuracy (F<2.43, p>0.069). Reaction times for correct (or all) trials did not differ as a function of money amount or group (F<1.11, p>0.35).

Table 1.2. VMPFC and striatum region of interest analyses on task activations and functional connectivity.

	BA	Side	Voxels	peak *Z*	*p*-corrected	*x*	*y*	*z*
Task Activation								
Money (Linear Contrast: 50¢ > 25¢ > 1¢ > 0¢): All Subjects								
Striatum: Caudate		L	22	+3.9	0.010	–18	–10	22
VMPFC: Pre/ Subgenual ACC	25,11	L	43	–3.7	0.016	–6 0	32 26	–2 –2
Controls > CUD								
VMPFC: Subgenual ACC/ Medial OFC	25,10,11	L	18	3.9	0.005	**–9**	**44**	**–11**
CUD > Controls								
None								
Money (Linear Contrast: 50¢ > 25¢ > 1¢ > 0¢) × Group Interaction								
Striatum: Putamen/ Globus Pallidus		R	68	3.4	0.044	**27**	**2**	**–2**
Money (Linear Contrast: 50¢ > 25¢ > 1¢ > 0¢): CUD								
Striatum: Putamen/ Globus Pallidus		R	85	+3.8	0.015	24	5	–2
Striatum: Putamen/ Globus Pallidus		L	25	+3.2	0.083	–33	2	1
Money (Linear Contrast: 50¢ > 25¢ > 1¢ > 0¢): Controls								
None								
Functional Connectivity (seed: VMPFC)								
Controls > CUD								
Striatum: Putamen/ Globus Pallidus		R	5	3.8	0.035	**30**	**3**	**6**

Note. Statistical threshold: $p<0.005$ uncorrected and $p<0.05$ family-wise error (FWE) corrected at voxel-level, $k>5$ voxels;
Striatum was defined anatomically with PickAtlas to correspond to the caudate, putamen, and pallidum;
Ventromedial prefrontal cortex (VMPFC) was defined as an 18-mm radius sphere centered on x=–2, y=32, z=–18 (from Ersche *et al*., 2011);
ACC: anterior cingulate cortex; OFC: orbitofrontal cortex; R: right; L: left;
+/− Z values indicate direction of significant contrast;
Coordinates in bold font are depicted in the figures.

Group Differences in Neural Activity Associated with Money Value

Following the observed linear progression in self-reported subjective value ratings and behavior, region of interest analyses were performed to determine (1) if the VMPFC and striatum similarly tracked money value and (2) if their pattern or magnitude of activation differed between the groups. The 4 (money: 0¢, 1¢, 25¢, 50¢) × 2 (group: control, CUD) mixed ANOVA revealed a significant money main linear effect (50¢ > 25¢ > 1¢ > 0¢) and a significant group main effect (Controls > CUD) in the VMPFC (**Figure 1.4A**, **Table 1.2**). That is, across the entire sample, the caudate and VMPFC tracked money value. Irrespective of the money amount, CUD additionally deactivated the VMPFC to a greater extent than controls. In addition to these main effects, a

significant money (linear effect) × group interaction was observed in the right putamen extending to the external segment of the globus pallidus (**Figure 1.3**, **Table 1.2**), which was explained by increased activations in this region to money in CUD but not controls. Follow-up *t*-contrasts indicated that this interaction was driven by the maximal differential, 50¢>0¢ (CUD>controls); in addition, significant effects in the right putamen were observed within CUD for 50¢>0¢, 25¢>0¢, and any money > 0¢ (all $p<0.05$ FWE-corrected). Similar pattern of effects was observed within CUD for the left putamen but did not reach significance.

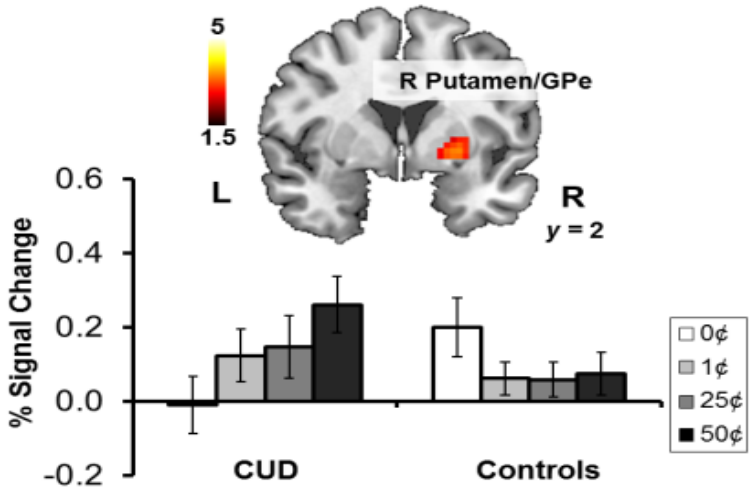

Figure 1.3. Money × group interaction on sensorimotor striatum response to money value. Only individuals with CUD but not healthy controls exhibited increased linear activation in this region to money. Bars are means±SEM. Color bar represents *t* values.

Whole-brain significant regional activations are summarized in **Table 1.3**. Across subjects, the linear contrast for money revealed increased activation in several brain regions that have been reported in previous studies to track value [64], including the right cerebellum and left inferior frontal gyrus (a cluster encompassing the left anterior insula). In addition, parametric deactivations with increasing money value were observed in the left pre/subgenual ACC and bilateral middle/posterior cingulate, consistent with these regions' roles within the default mode network [65, 66]. There were no other significant group or interaction effects that survived whole-brain cluster-level correction for multiple comparisons.

Table 1.3. Whole-brain results from the Money × Group analysis of variance on task activations and functional connectivity.

	BA	Side	Voxels	peak *Z*	*p*-corrected	*x*	*y*	*z*
Task Activation								
Money (Linear Contrast: 50¢ > 25¢ > 1¢ > 0¢): All Subjects								
						6	–64	–17
Cerebellum: Vermis		R	220	+3.9	0.046	21	–46	–50
						12	–46	–17
						–45	5	13
Inf. Frontal G./Insula	44,45,6	L	204	+3.7	0.060	–33	11	22
						–30	17	28
						–3	29	10
VMPFC: Pre/Subgenual ACC	24,25,11	L	459	–4.3	0.001	–18	35	–5
						9	–25	37
Mid./Posterior Cingulate G.	23	R, L	211	–3.6	0.053	–3	–16	31
						–15	–19	52
Controls > CUD								
None								
CUD > Controls								
None								
Money (Linear Contrast: 50¢ > 25¢ > 1¢ > 0¢) × Group Interaction								
None								
Functional Connectivity (seed: VMPFC)								
Money (Linear Contrast: 50¢ > 25¢ > 1¢ > 0¢): All Subjects								
						–51	–60	0
Mid. Temporal G./Mid.Occipital	37,39	L	441	+4.0	0.002	–42	–72	6
						–39	–75	30
Controls > CUD								
None								
CUD > Controls								
						–18	–48	–51
Cerebellum	30	L	118	4.0	0.043	–21	–42	–36
						–21	–39	–24
Money (Linear Contrast: 50¢ > 25¢ > 1¢ > 0¢)× Group Interaction								
						–45	–36	45
Supramarginal G./Postcenral G.	2,3	L	149	3.5	0.013	–27	–33	51
						–60	–30	48

Note. Statistical threshold: $p<0.005$ uncorrected and $p<0.05$ family-wise error (FWE) corrected at cluster-level, $k>5$ voxels;
Inf.: inferior; Mid.: middle; VMPFC: ventromedial prefrontal cortex; ACC: anterior cingulate cortex; R: right; L: left;
+/− Z values indicate direction of significant contrast.

Group Differences in Functional Connectivity

For the VMPFC seed, the 4 (money: 0¢, 1¢, 25¢, 50¢) × 2 (group: control, CUD) mixed analysis of variance revealed a significant group main effect (Controls > CUD) in the right putamen

(**Figure 1.4B**, **Table 1.2**). A similar result was observed in complementary analyses where the right putamen was used as seed but did not reach significance. There were no interactions with money value, suggesting a more global deficit in CUD. Whole-brain significant results are summarized in **Table 1.3**, which additionally revealed group differences in connectivity with the cerebellum (CUD > Controls) among others.

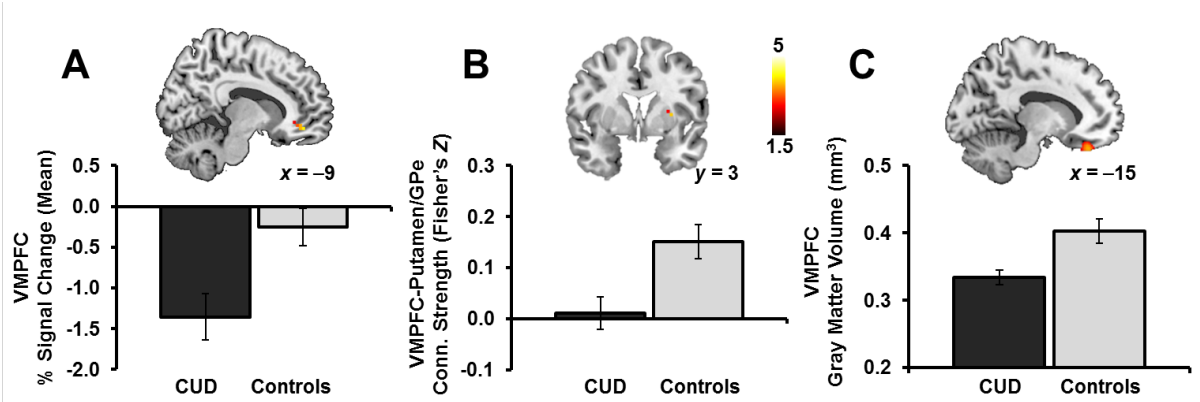

Figure 1.4. Group differences in (**A**) activation, (**B**) connectivity with the putamen, and (**C**) GM volume of the VMPFC. Bars are means ± SEM. Color bar represents *t* values.

Group Differences in Gray Matter Volume

An ANCOVA, statistically controlling for the effects of age and total brain volume, was performed to identify any differences between the groups in GM volume within the regions of interest. Compared with controls, CUD had reduced GM volume of the medial OFC extending to the gyrus rectus (**Figure 1.4C**, **Table 1.4**). No group differences were observed for the striatum. Outside of the regions of interest, GM reductions in CUD did not survive whole-brain cluster-level correction for multiple comparisons. Similarly, there were no significant regions of increased GM volume in CUD compared with controls.

Region of Interest Correlations with Neural Activity and Gray Matter Volume

Because CUD had reduced GM volume, greater overall task-related deactivations in the VMPFC (average of the four money values), greater activations to money (50¢>0¢) in the putamen, and reduced connectivity between the VMPFC and putamen, the relationship between these measures was inspected in follow-up analyses in SPSS. However, these relationships were not significant across the entire sample or within either subject groups separately (all $r<|0.20|$, $p>0.19$).

Table 1.4. VMPFC and striatum region of interest analyses on gray matter volume.

	BA	Side	Voxels	peak *Z*	*p*-corrected	*x*	*y*	*z*
Controls > CUD								
VMPFC: Medial OFC	11	L	347	3.5	0.029	**–15** –3	**36** 39	**–25** –28
CUD > Controls								
None								

Note. Statistical threshold: $p<0.005$ uncorrected and $p<0.05$ family-wise error (FWE) corrected at voxel-level, $k>5$ voxels;
Striatum was defined anatomically with PickAtlas to correspond to the caudate, putamen, and pallidum;
Ventromedial prefrontal cortex (VMPFC) was defined as an 18-mm radius sphere centered on x=–2, y=32, z=–18 (from Ersche *et al*., 2011);
OFC: orbitofrontal cortex; L: left;
Coordinates in bold font are depicted in the figures.

Region of Interest Correlations with Behavior

To establish the specific relationship of money-related brain activations to behavior, correlations were performed with task accuracy and drug use. Behavioral sensitivity to money (differential task-related accuracy, 50¢>0¢) was negatively correlated with activation in the putamen to money (50¢>0¢) when considering the entire sample (r=-0.33, p=0.03), but this effect appeared to be driven by the CUD. Therefore, this this correlation was tested separately in each group. Two outliers (one control, one CUD) were removed (Cook's d>1 when considering the groups separately). In CUD, accuracy was negatively correlated with putamen BOLD (50¢>0¢) such that higher activity was associated with lower differential accuracy 50¢>0¢ (r=-0.50, p=0.024; **Figure 1.5A**). In controls, this relationship was not significant (r=-0.019, p=0.94). This difference in correlations between the groups did not reach significance (Z=-1.55, p=0.060). VMPFC BOLD (average of the four money values) was not correlated with average accuracy on the task across the entire sample or within each group separately (r<-0.42, p>0.063).

Cocaine use days/week in the past year correlated positively with activation in the putamen 50¢>0¢ (after removing one outlier, Cook's d>1; r=0.62, p=0.006; **Figure 1.5B**). There were no other significant correlations with drug use (p>0.11). For the VMPFC (cluster from the group effect), there was a negative correlation with cocaine craving (p=0.01; all other effects did not survive correction for multiple comparisons, p>0.03), such that subjects who reported more craving deactivated this region to a greater extent overall.

VMPFC GM volume and connectivity strength were not associated with task accuracy in either group (p>0.58) or with drug use in CUD (p>0.20).

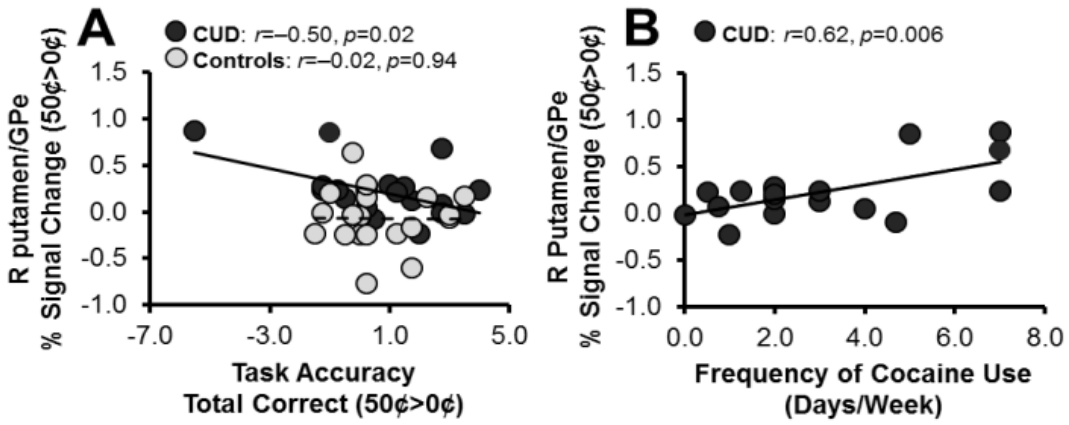

Figure 1.5. Correlations between sensorimotor striatum activation and (**A**) behavioral adjustment to money (50¢>0¢) across subjects and (**B**) cocaine use in the past 12 months in CUD.

Discussion

The present study evaluated the hypothesis that functioning of the VMPFC and striatum under varying reward contingencies would be altered in cocaine addiction. It was further hypothesized that such altered VMPFC-striatum neural activity would be related to alterations in the GM volume and connectivity of these regions and would have negative consequences for behavior in individuals with CUD. Consistent with the first hypothesis, CUD showed abnormal response to money value in the right putamen, a region extending to the external segment of the globus pallidus, and greater overall deactivations in the VMPFC across the money conditions. Consistent with the second hypothesis, CUD also had reduced GM volume in the VMPFC and reduced functional connectivity between the VMPFC and the putamen. Abnormal responses to money in the putamen and VMPFC were related to task behavior and cocaine use, such that individuals with more severe use and craving, and less behavioral adjustment to money, had the highest activations in the putamen and deactivations in the VMPFC. Thus, these findings, which are consistent with preclinical models of addiction (e.g., [36-38]) and extend prior work that has separately examined VMPFC and striatum function [32, 33] or GM volume [39-45] in human cocaine addiction, provide concrete evidence for frontostriatal abnormalities in the neural mechanisms of valuation in addiction and link these functional abnormalities with deficits in brain structure.

Consistent with previous studies [64], across the entire sample, the VMPFC, associative striatum (dorsal caudate), and posterior cingulate varied with money value, but in CUD there was

also an ectopic response in the sensorimotor striatum (right putamen/globus pallidus). The post-commissural putamen (or dorsolateral striatum in rodents) is centrally implicated in habits [29], stimulus-response associations that render behavior insensitive to outcomes [67-69]. With the progression of cocaine addiction [70], this striatal region is suggested to underlie the habitual aspects of drug use like cue-induced drug-seeking and craving in both rodents [34, 71] and humans [35]. This increased sensitivity to money in the putamen is in line with previous studies that have revealed hypersensitivity to money in individuals addicted to cocaine [33] and marijuana [72]. While studies have also reported increased [32] or decreased [73, 74] response to money in the ventral striatum in alcohol dependence, likely due to the low level of uncertainty associated with the task, activity in this region was not observed in either group. Importantly, increased activity in the putamen was associated with reduced adjustments in task accuracy with higher money value and with more frequent cocaine use in CUD. Thus, these differential associations with behavior on the task and drug use outside the lab point to altered neural valuation mechanisms in CUD that may render these individuals less sensitive to potentially positive (e.g., earning more money on the task) or potentially negative (e.g., the physical and emotional impact of their use) behavioral outcomes.

In contrast to differential responses in the striatum, parametric deactivations in the VMPFC were observed with increasing money value in both CUD and controls, in line with this region's role in processing motivational value during goal-directed behavior, including that for money and drugs of abuse [3]. Although the pattern of activation in the VMPFC is consistent with that observed in default mode network regions, where deactivations vary as a function of task engagement or task features [65, 66], the directionality of these results is at odds with previous studies showing positive activations in the VMPFC to reward value. This apparent inconsistency may reflect differences in the tasks used to elicit responses (e.g., blocked designs like the current one capture sustained activation while event-related designs capture transient activation). Indeed, because blocked designs may produce initial positive responses in the hemodynamic signal that are followed by sustained negative responses, as has been observed in regions of the default mode and particularly in midline structures [75], the estimate for the block can be negative when the model assumes homogeneity in the signal.

Although there was no significant difference between the groups as a function of money value, echoing prior findings in CUD and controls [52], across the four money conditions, CUD,

and especially those with higher self-reported craving, deactivated the VMPFC to a greater extent than controls. In addition, the VMPFC and putamen were weakly connected in CUD. Thus, enhanced VMPFC deactivation in the cocaine users might represent a compensatory mechanism necessary to maintain comparable levels of task performance, particularly in those individuals with higher activations in the putamen and more severe craving. Also consistent with previous studies [39-42, 45], GM volume of the VMPFC was reduced in CUD. Although the current data cannot answer questions related to causality, the functional disturbances in the VMPFC (and striatum) in CUD could also signal inefficiency of cortical processing due to GM loss in this region. Interestingly, repeated psychostimulant exposure [10, 38, 76-79] or lesions of the VMPFC [80, 81] in experimental animals have been shown to shift control of behavior in response to reinforcers and drug-seeking to the putamen, suggesting that these two regions compete [67].

Because this study was concerned with identifying *which* regions represented money value, a blocked design was used. Blocked designs are more sensitive compared with event-related designs in detecting such regional activations because they offer maximal variance in terms of BOLD amplitude changes between conditions (i.e., value in this case) [82]. The cost is in the ability to separate anticipatory from outcome related activity. However, frontostriatal abnormalities in addicted individuals during both anticipation of monetary gain [72-74] and at gain outcome [32, 33, 72] suggest that such a separation is not likely to substantially modify interpretations. Indeed, meta-analyses report vastly overlapping neuroanatomical correlates of anticipation of reward and reward outcome [64]. This is particularly relevant in the case of money where reward delivery is always delayed and therefore somewhat anticipatory even in event-related studies (e.g., note "real" vs. hypothetical money has similar neural and behavioral correlates [83]). A second design consideration is the use of 100% probabilities in reward delivery (a consideration addressed in *Study 2* further below) – that is, by not introducing uncertainty, the current design may have precluded detection of subtler dopamine dependent responses in the ventral striatum and other dopamine rich regions.

In summary, CUD had abnormal value signals in the sensorimotor striatum (right putamen extending to the external globus pallidus), potentially explained by reduced GM volume and connectivity of the VMPFC. As value signals represent acquired associations, these results could indicate disadvantageous associative learning in CUD. Indeed, activity in this region was

differentially associated with maladaptive task- and drug use-related behaviors. Future studies are needed that in inspect resistance to extinction procedures in CUD to more fully establish the role of habit systems in addiction in humans. Elucidating the relationship between brain structure and function may not only facilitate better comparison with findings reported in the animal literature, but may also help move beyond reporting of GM differences in addiction in humans and attempt to understand the relationship of these differences to behavior and to the underlying function of connected networks of brain regions.

CHAPTER 2

Behavioral Correlates of Decision Making Involving Economic Risk and Reward (*Study 2*)

Background & Rationale

Study 1 investigated whether individuals with CUD exhibit abnormalities in value processing, potentially stemming from the effects of cocaine on frontostriatal brain structure, function, and connectivity. However, this study cannot speak to whether abnormalities extend to value when outcomes are uncertain or to how these abnormalities translate to actual *decisions* in CUD. Therefore, the focus of *Study 2* was to understand these two keys questions better using behavioral economics.

Economic theories posit that decision makers evaluate the utility (i.e., subjective value) of a given option with respect to its expected value (EV; defined as objective reward magnitude × probability of reward) and risk [84]. Risk is a form of uncertainty, analogous to the variance or standard deviation of known probability distributions of reward magnitudes. For example, an equal chance of winning $4 or $20 is said to be "riskier" than an equal chance of winning $10 or $14 in that despite the two options having equal EV ($12), the spread of potential outcomes is larger in the first option. Utility is influenced by subjective preference for risk, such that the utility of risky options is low for risk-averse individuals and high for risk-seeking individuals.

Applying this framework to the study of drug addiction, and in particular individual differences in risk preference, has the potential to elucidate the often risky behavior that characterizes this psychopathology and account for unexplained variance in clinical outcome. However, risky decision-making has been studied in substance users primarily with tasks that manipulate naturalistic risk (e.g., the Iowa Gambling Task and Balloon Analogue Risk Task), while economic risk remains largely unexplored. Although naturalistic risk tasks show relatively good ecological validity, a core limitation of these tasks is that they conflate risk with delay, learning, ambiguity, or loss and gain sensitivity, and therefore these tasks cannot isolate the specific influence of risk on decision-making [85]. In contrast, tasks based on economic theory can be decomposed into specific constructs (i.e., risk) with distinct neural and behavioral correlates; the application of economic models to behavior on these tasks can further foster a mechanistic understanding of how changes in risk produce changes in behavior.

The goal of the present study was two-fold. The first goal was to examine risk preferences in chronic cocaine users and healthy controls on a novel task that parametrically varied economic risk in a choice situation. This task was adapted from O'Neill and Schultz [86] who showed distinct neuronal coding of risk in monkey OFC, a region of central importance to addiction [16]. To determine whether economic risk preferences and real-world impulsive behaviors were correlated across the entire sample, we inspected associations between the risk parameter and psychometric tests of impulsivity. A second goal was to inspect the association between subjects' economic risk preferences, as captured by this laboratory measure, and their drug-related behaviors. For this purpose, a subset of CUD subjects completed two behavioral tasks, the risky decision making task and a probabilistic picture viewing task. The risky decision making task data were analyzed with an expected utility theory model to estimate individual subjects' level of risk-seeking. Correlations were then assessed between this subject level-derived risk parameter and choices for viewing cocaine-related relative to pleasant images on the picture viewing task (a previously validated measure of drug-seeking that is predictive of recent and prospective drug use in this population [87-89]). The hypothesis was that risk-seeking preferences would be positively correlated with both drug-related (in CUD) and non drug-related, but impulsive, behaviors (both groups).

Methods

Subjects

Subjects were 32 healthy controls and 34 individuals with CUD. All subjects were recruited, screened, and consented as described in *Study 1* with a few differences. First, most subjects completed the study at the Icahn School of Medicine at Mount Sinai according to procedures laid out by the local Institutional Review Board. Second, because subjects only completed behavioral testing, we did not impose the MRI-related requirements (e.g., metal in body, neurological examination). Lastly, a subsample of CUD was recruited as part of an initial treatment center study (see further below). CUD and healthy controls included in the analyses were matched on race and general intellectual functioning; however the groups differed in age, sex, and education (**Table 2.1**). From these three potential confounds, only education appeared to be related to any of the dependent variables (risk-seeking parameter, impulsivity; $p<0.03$) and therefore education was included as a covariate in all analyses comparing CUD and controls. Fourteen of the 34

CUD used crack/cocaine (mostly smoked route) in the past 14 days and all CUD met DSM-IV criteria for cocaine dependence (n=33) or abuse (n=1); 12 CUD tested positive for cocaine in urine.

Table 2.1. Demographic and drug use variables for healthy controls and individuals with cocaine use disorders (CUD) included in *Study 2*.

	Study 2*		
	Test	**Control (N=32)**	**CUD (N=34)**
Gender: Male / Female [a]	$\chi^2 = 5.2$	22 / 10	31 / 3
Race: African-American / Other	$\chi^2 = 0.1$	22 / 10	23 / 11
Age (years) [a]	$t = 2.9$	40.1 ± 9.6	46.6 ± 8.9
Education (years) [a]	$t = 3.3$	14.2 ± 2.0	12.5 ± 2.1
Verbal IQ: WRAT-3 Reading	--	--	--
Non-Verbal IQ: WASI - Matrix Reasoning Scale	$t = 1.6$	10.7 ± 2.6	9.5 ± 2.9
Socioeconomic Status: Hollingshead Index	--	--	--
Age of onset of cocaine use (years)	--	--	--
Cocaine use (lifetime, years)	--	--	--
Days/week of cocaine use during the past 30 days	--	--	--
Days/week of cocaine use during the past 12 months	--	--	--
Depression: Beck Depression Inventory II	--	--	--
Cocaine urine status, No. positive / negative	--	--	12 / 22
Severity of Dependence Scale	--	--	--
Withdrawal symptoms: 18-item CSSA	--	--	--
Cocaine Craving: 5-item Questionnaire	--	--	11.5 ± 11.7
Duration of current abstinence (days)	--	--	331.0 ± 739.1[1]

Note. Values are frequencies or means ± standard deviation (SD);
*A subsample of n=16 CUD also completed the drug choice task as part of a treatment center pilot study;
[a] $p<0.05$, CUD vs. Control;
[1] When five extreme outliers (days abstinent > 1000 days) are excluded, group mean = 73.4 ± 121.0;
Race: Other (Caucasian / Hispanic / Asian); WRAT-3 = Wide Range Achievement Test (3rd edition); WASI = Wechsler Abbreviated Scale of Intelligence; CSSA = Cocaine Selective Severity Assessment Scale.

The subsample of CUD subjects who also completed the picture viewing choice task were 16 cocaine dependent males (age: *M*=42.00, *SD*=10.31, education: *M*=11.93, *SD*=2.02, and non-verbal IQ: *M*=9.63, *SD*=2.70) who provided written informed consent to participate in the study in accordance with Stony Brook University's Institutional Review Board. Twelve were in a residential treatment facility; the other 4 were non-treatment seeking and were recruited through advertisements in local newspapers and by word-of-mouth. All subjects met DSM-IV criteria for cocaine dependence, reporting an average of 4.19 (*SD*=3.39; range: 0-13) previous entries into rehabilitation or detoxification programs, 18.44 years of cocaine use (*SD*=8.99), and 2.64 days/week of cocaine use (*SD*=2.13) in the previous month (or the month before entering treatment for subjects in treatment). Average scores on the Severity of Dependence scale [90] were 9.0 (*SD*=4.01). Except for current abstinence from cocaine, which ranged from 2-510 days (*M*=102.25, *SD*=121.69; *p*=0.001), cocaine use histories did not differ by treatment-seeking status (*p*>0.17).

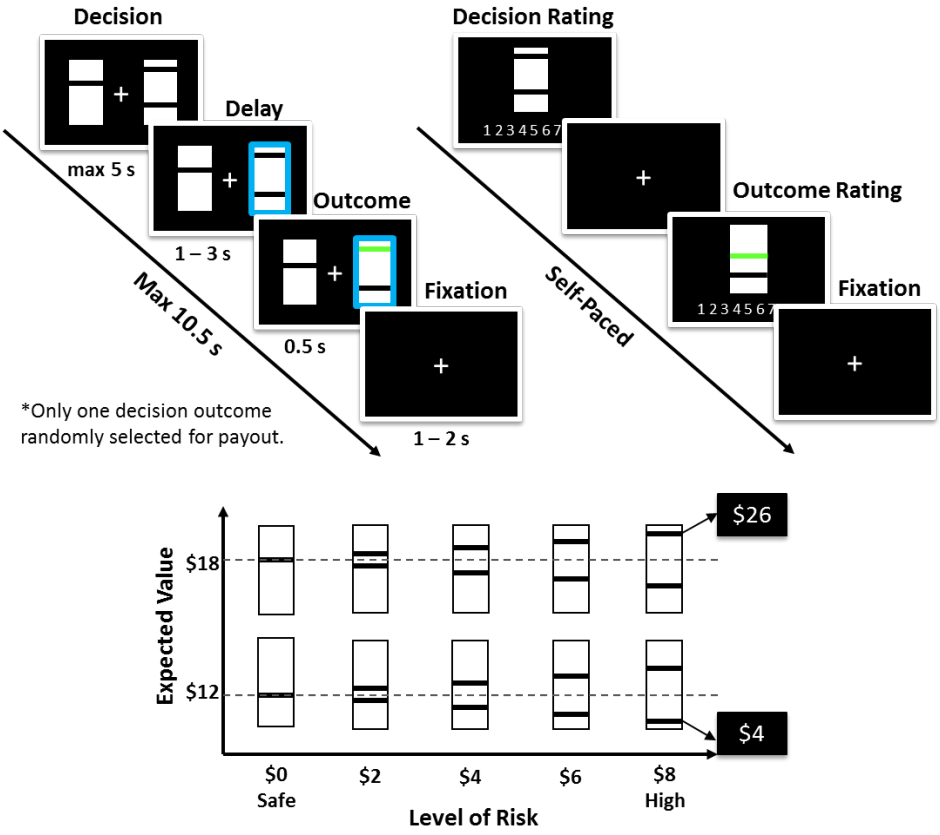

Figure 2.1. Timeline of a trial on the risky decision making task (**top left**), post task pleasantness ratings (**top right**), and all decision stimuli (**bottom**).

Risky Decision Making Task

On each trial, subjects chose between two options with equal EV but that differed in the amount of associated risk (defined here as the standard deviation of two possible outcomes; **Figure 2.1**). Two levels of EV ($12 and $18) and five levels of risk [safe ($0), $2, $4, $6, and $8] were used. Risky options offered a 50% chance to gain either a larger or smaller monetary reward, represented by the distance between two bars; safe options offered a 100% chance of an intermediate amount equal to the EV, represented by a single bar. Following choice of a risky option, one of the two bars turned green (determined randomly on each trial), indicating the outcome of that choice. Following choice of a safe option, the single bar turned green. Each level of risk appeared 8 times against each of the remaining levels of risk, for a total of 80 trials. Trial order was randomized and position of the stimuli (left or right side of the screen) was equated. A brief practice session familiarized subjects with the task. Following standard procedures from behavioral economics, to ensure that each decision was perceived as independent and important, subjects were told that their payout (in real money) would be determined by one randomly-selected decision outcome. Response times were collected on all trials. Pleasantness ratings for the task stimuli (decision and outcome) were collected following the task.

Probabilistic Picture Viewing Task

A subsample of CUD also completed a task designed to simulate drug-seeking that has been described in detail previously [87-89]. Briefly, this measure captures the extent to which subjects' choose to view cocaine images relative to pleasant, unpleasant, or neutral images. Choices are made between images that are hidden under flipped-over cards, and thus location of the image categories is identified through experience with the task. During each trial, subjects chose one of four "decks" of cards; an image from that deck was then shown for 2000 ms of passive viewing. Deck identity (pleasant, unpleasant, neutral, or cocaine) was determined probabilistically. Each deck contained 26 (out of a total of 30) images from one image category (e.g., cocaine) and 4 interspersed images from the remaining categories. At the conclusion of each run (which occurred when the same deck was selected a total of 8 times), the location of the decks shifted such that each deck was now identified by a different image category. Subjects completed four runs of the task. The total number of images selected per image category across the four runs was summed; as in prior studies [87-89], a difference score was computed

subtracting pleasant choice from cocaine choice ('cocaine>pleasant choice') to index drug-seeking.

Impulsivity Measures

Subjects completed questionnaires previously used to reliably assess trait impulsivity in addiction. Most (n=42) subjects completed the Barratt Impulsiveness Scale (BIS-11) [91] and the Conners' Adult ADHD Rating Scales (CAARS) [92]; the n=16 CUD who participated in the treatment center study completed the Substance Use Risk Profile Scale (SURPS) [93]. The BIS-11 is the most widely cited instrument for the assessment of impulsiveness and consists of 30-items describing common impulsive or non-impulsive (for reverse scored items) behaviors and preferences. The CAARS provides a self-assessment of the severity of ADHD symptoms on five subscales: inattention/memory, hyperactivity/restlessness, impulsivity/emotional lability, problems with self-concept, and ADHD Index, while the SURPS considers four personality dimensions which are thought to play a role in the risk for substance abuse (hopelessness, anxiety sensitivity, impulsivity, and sensation seeking). BIS-11 total scores, scores on the impulsivity subscale of the CAARS, and scores on the impulsivity subscale of the SURPS were *Z* normalized so that data could be combined from the two samples. Because *Z*-scores on the BIS-11 and CAARS were highly correlated (r=0.68, p<0.001), the two were averaged prior to combining them with *Z*-scores on the SURPS for the remaining CUD. A final trait impulsivity measure was then obtained and used in all subsequent analyses (described below).

Statistical Analyses

Taking into account choices on a trial-by-trial basis, the risk aversion parameter alpha (α) was estimated for each subject. Expected utility theory predicts that behavior is guided by the magnitude of anticipated reward, x, and the probability, p, of receiving that reward, such that individuals choose options that yield the highest expected utility (*EU*), as determined by:

$$EU = \mathrm{u}(x) \times p$$

Risk aversion is a subjective factor that can influence the expected utility of a given option. The level of risk aversion, denoted by α, is estimated as the curvature of the expected utility function.

$$\mathrm{u}(x) = x^{\alpha}$$

An α=1 indicates risk-neutrality such that the perceived utility of a given option is equal to its expected value. Risk-averse individuals have concave utility functions with α<1, while risk-seeking individuals have convex utility functions with α>1. Thus, given the *EU* for the left and the right options that appeared simultaneously on the screen, it was assumed that subjects chose between the two options in an unbiased manner, following:

$$P_{Li} = \frac{EU_{Li}^{\frac{1}{\mu}}}{EU_{Li}^{\frac{1}{\mu}} + EU_{Ri}^{\frac{1}{\mu}}}$$
$$P_{Ri} = 1 - P_{Li}$$

where P_{Li} is the probability of choosing the option presented on the left on a given trial, *i*, P_{Ri} is the probability of choosing the option on the right, EU_{Li} is the expected utility of the option on the left, and EU_{Ri} is the expected utility of the option on the right [94]. The parameter μ specifies noise, or random deviations from the deterministic choice specified by expected utility theory. Values of μ closer to 0 indicate that subjects behave exactly as predicted (always choosing the option with higher utility). Using maximum likelihood estimation in Matlab, these functions were simultaneously fit to the choice behavior data for all trials for each subject, with α as the free parameter. To maximize the reliability of parameter estimation for α, μ was set to be a constant (0.1) because there is some collinearity in the estimates of α and μ when the two are estimated together as free parameters. A similar approach has been used in the context of reinforcement learning (e.g., [95]). Nevertheless, results were mostly unchanged when μ was also free to vary.

Model-free analyses with percent choice and post-task pleasantness ratings were also used to cross-validate risk preferences. Here, mixed ANOVAs were performed with risk preference based on α (risk-seeking, risk-averse) and diagnosis (CUD, controls) as between-subjects factors and EV and level of risk as within-subjects factors, controlling for education.

The relationship between α and *Z*-transformed scores on the impulsivity questionnaires was then tested, as were correlations between α and the laboratory measure of simulated drug-seeking ('cocaine>pleasant choice').

Results

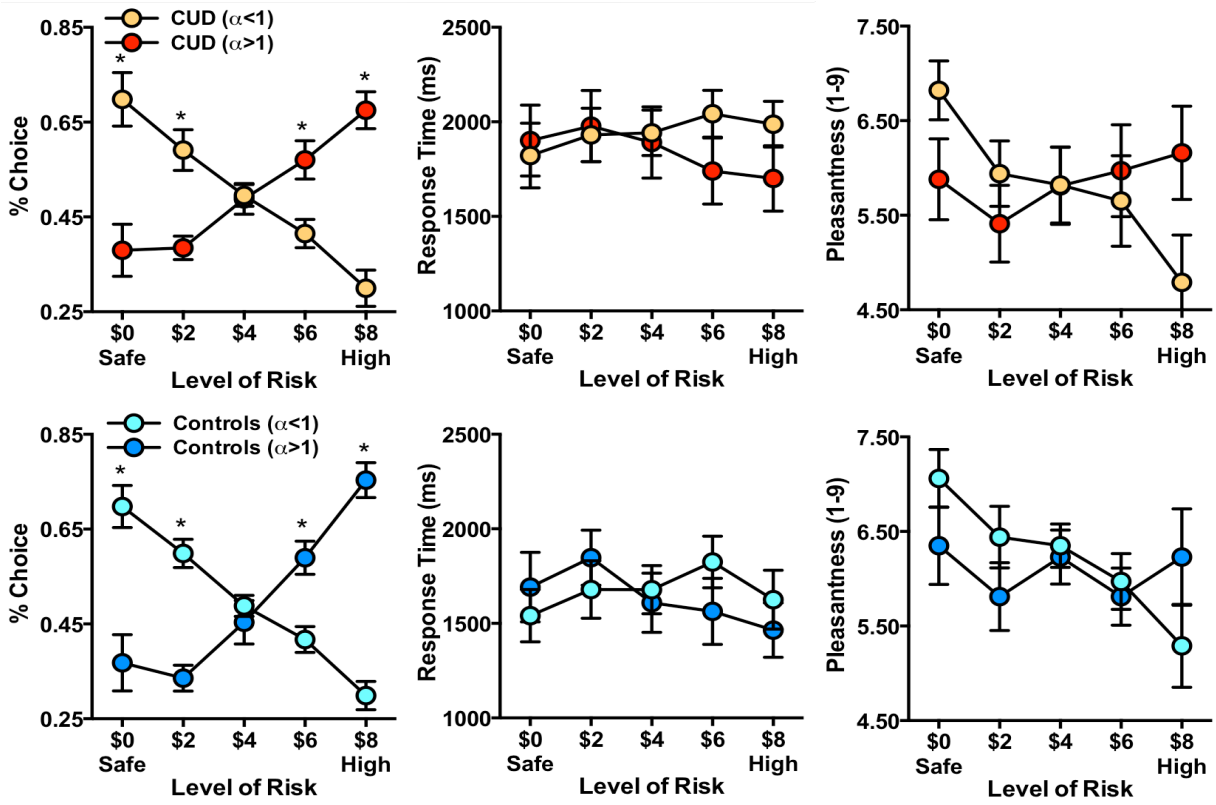

Figure 2.2. Percent choice (**left**), response times (**middle**), and pleasantness ratings for the decision stimuli (**right**) as a function of level of risk, diagnosis, and risk preferences. Plots are means ± SEM. Asterisks indicate group differences (risk-averse vs. risk-seeking).

The model-based analysis identified a range of risk preferences among all subjects, who could be classified as risk-averse (n=36; α<1, *M*=0.56, *SD*=0.18) or risk-seeking (n=30; α>1, *M*=1.83, *SD*=1.63). Risk preferences were confirmed at the group level with model-free analyses. As expected, α was positively correlated with the percentage of choices where the riskier of the two options was chosen (r_S=0.79, p<0.001). However, the number of risk-seekers and the degree of risk-seeking did not differ between CUD and controls (p>0.45; **Figure 2.4**).

When treating α as a categorical measure in a 2 (EV: \$12, \$18) × 5 (risk: \$0, \$2, \$4, \$6, \$8) × 2 (diagnosis: CUD, controls) × 2 (risk status: risk-seeking, risk-averse) mixed ANOVA for percent choice, controlling for education, a significant level of risk × risk status interaction [$F_{(4,240)}$=45.35, p<0.001], and follow-up linear contrasts performed separately in each group to clarify the nature of this interaction, indicated that choice for the risky options decreased linearly

with increasing level of risk in risk-averse (p<0.001) but not in risk-seeking individuals who showed the opposite effect (increased choice with increasing level of risk, p<0.001); the groups also differed in choice for all risk options except for the intermediate level of risk (p<0.001; **Figure 2.2**). There were no other significant main or interaction effects for percent choice (p>0.19).

The same analysis for response times revealed a significant main effect of level of risk [$F_{(4,212)}$=2.89, p=0.023], which was qualified by a significant level of risk × risk status interaction [$F_{(4,212)}$=3.07, p=0.018, all other effects, p>0.09], such that response times decreased linearly with increasing level of risk in risk-seeking (p=0.03) but not in risk-averse individuals (p=0.27).

Individual Differences in Risk Preference: Subjective Ratings

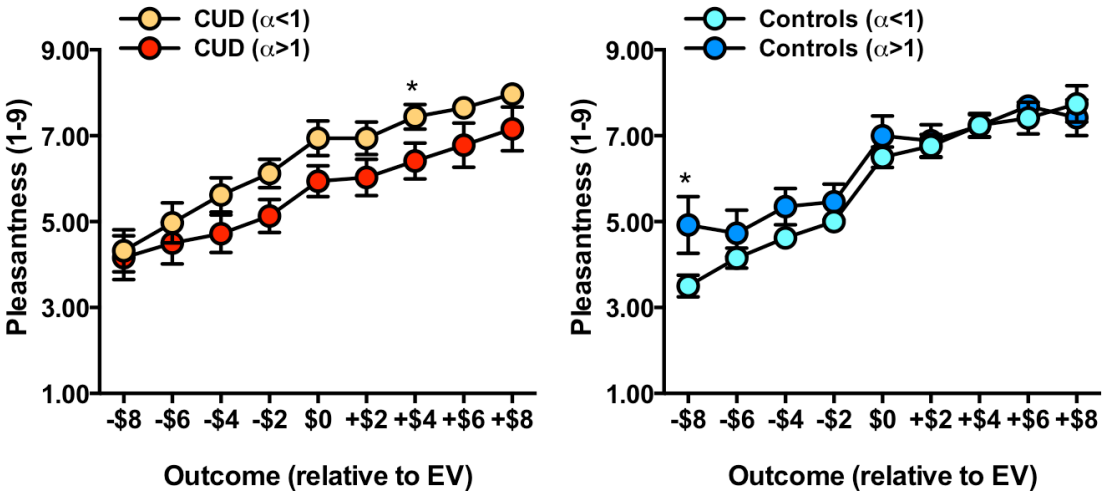

Figure 2.3. Pleasantness ratings for the outcome stimuli as a function of level of relative reward magnitude, diagnosis, and risk preferences. Plots are means ± SEM. Asterisks indicate group differences (risk-averse vs. risk-seeking).

The 2×5×2×2 ANOVA, controlling for education, for *decision* stimulus ratings revealed only a significant level of risk × risk status interaction [$F_{(4,228)}$=6.09, p<0.001]. Again, this interaction was explained by linearly decreasing ratings of pleasantness for the increasingly risky options in risk-averse (p<0.001) but not in risk-seeking (p=0.19) individuals, who rated the high risk option as more pleasant, and the safe option as less pleasant, than risk-averse individuals (p<0.02, **Figure 2.2**). No other effects reached significance (p>0.28).

Finally, to ensure that all subjects understood the task contingencies and were sensitive to the reward magnitudes used in the task, subjects' ratings for the *outcome* stimuli were also analyzed. Here, two mixed ANOVAs for the "win" (where the top bar turned green) and "loss" (where the bottom bar turned green) outcome stimuli were performed separately, with risk preference based on α (risk-seeking, risk-averse) and diagnosis (CUD, controls) as between-subjects factors and EV ($12, $18) and relative reward magnitude (±$0, $2, $4, $6, $8; i.e., distance of the green bar with respect to the EV) as within-subjects factors. "Safe" outcomes (i.e., ±$0) were included in both ANOVAs. For both the relative "win" and "loss" outcome stimuli, there was a significant main effect of reward magnitude (F>9.54, p<0.001), such that, across subjects, pleasantness ratings increased linearly with increasing relative gain (p<0.002). Significant reward magnitude × risk status and diagnosis × risk status interactions were additionally observed for the "loss" outcome stimuli [F>4.00, $p\leq$0.05; **Figure 2.3**]. These interactions were explained by lower ratings of pleasantness in risk-seeking CUD relative to risk-averse CUD, with the opposite pattern observed in controls (risk-seeking>risk-averse). No other effects reached significance (p>0.08).

Together, these data indicate that higher α was associated with more, and faster, risky choices and more pleasantness for the risky *decision* stimuli across the diagnostic groups, suggesting that this parameter was a robust estimate of subjects' risk preference. However, α was differentially associated with pleasantness for the relative "loss" *outcome* stimuli in CUD relative to controls, suggesting that tolerance to loss may differentially drive risky decisions in these two groups.

Relationship to Impulsivity

As expected, a 2 (diagnosis: CUD, controls) × 2 (risk status: risk-seeking, risk-averse) ANOVA, controlling for education, on the combined, Z-transformed, measure of trait impulsivity revealed a trend main effect of group [$F_{(1,54)}$=4.46, p=0.066], such that CUD were more impulsive than controls, but no differences between risk-averse and risk-seeking individuals and no interactions (p>0.37). Nevertheless, α and impulsivity were positively correlated, such that more risk-seeking individuals were also more impulsive (r_S=0.34, p=0.009; **Figure 2.4**), and this relationship did not differ between CUD and controls (CUD: r_S=0.33, p=0.07; Controls: r_S=0.35, p=0.07).

Relationship to Drug-Seeking

Within the n=16 CUD who also completed the drug-choice task, α was positively correlated with cocaine>pleasant choice (i.e., more risk-seeking individuals were also more drug-seeking; r_S=0.54, p=0.032; **Figure 2.4**). Controlling for treatment-seeking status or current cocaine abstinence with partial correlations did not attenuate this effect (p<0.02).

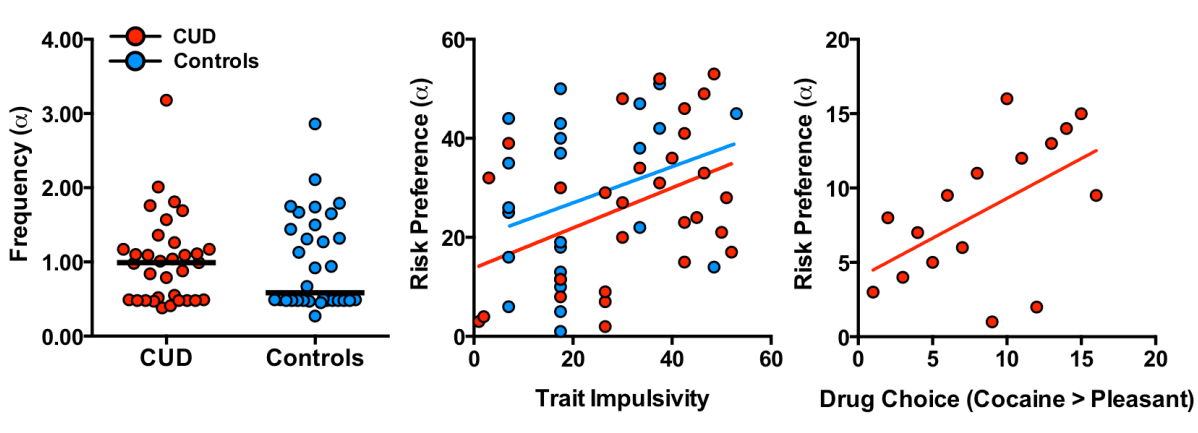

Figure 2.4. Distribution of α for each group, CUD and controls (**left**; note one CUD who always chose the riskier option with α=10 is not shown), relationship between α and trait impulsivity across groups (**middle**), and relationship between α and cocaine>pleasant choice in CUD (**right**). For the latter two, both the abscissa and ordinate are ranked (r_S=Spearman correlation).

Discussion

These data show that cocaine users' decisions for monetary rewards are influenced by risk, holding other factors constant such as expected value, and that the extent of this influence at the group level does not significantly differ from that observed in healthy controls. Consistent with the idea that most people are risk-averse when gambling for monetary gains [96-98], 60% of healthy controls and 50% of CUD subjects were risk-averse. Individual differences in risk preference were only partly explained by differences in reward sensitivity (all subjects rated relative gains and losses as pleasant/unpleasant while risk-seeking CUD and risk-averse controls tended to rate losses as more unpleasant). Instead, choice behavior closely paralleled subjective pleasantness of risk. These findings thus extend previous work that has assessed risky decision-making in cocaine addiction using tasks that could not isolate the specific influence of risk to decision-making involving economic risk.

The present study also found that risk preferences were associated with trait impulsivity and drug-related behavior, such that more risk-seeking individuals across both groups were also

more impulsive and more risk-seeking CUD were also more drug-seeking. These data suggest that risk preferences should be investigated at the individual rather than group level, as afforded by economic models, and that variability in risk preferences may be an important determinant of real-world impulsive drug and non drug-related behaviors. In particular, as higher drug-seeking (indexed by more cocaine>pleasant choices) is predictive of recent and prospective drug use in cocaine users [87-89], these data suggest that risk-seeking preference, through its relationship with drug-related choice, could represent a vulnerability marker for relapse (and possibly treatment [99-101]) in cocaine addiction.

An ongoing fMRI study in CUD and healthy controls is aimed at isolating the neural mechanisms of risk and utility. Based on [86], studies in humans with similar definitions of risk [96-98], and the literature more broadly in decision making involving economic risk [102], a neural correlate of risk is likely to be observed in the OFC, insula, striatum, and thalamus in all subjects. Making decisions about risky options is also likely to involve regions that participate in value-based decision-making more generally, including those that assign subjective value (utility) to the options under consideration and that then compare these values to make a choice [103-105]. In particular, studies using different species and techniques consistently link computation of subjective values with activity in the VMPFC and posterior cingulate cortex [106]. Involvement of the DLPFC is also expected, which similarly to the VMPFC frequently tracks subjective value [20, 107-110] but additionally participates in self-control control during decision making [19, 111]. Finally, involvement of the dorsomedial PFC is expected given that this region is implicated in the *comparison* of subjective values to determine the optimal course of action [112, 113]. Overall, when making decisions about risky options, it is hypothesized that increased activation will be observed in these regions (VMPFC, DLPFC, dorsomedial PFC), as indicative of higher utility assigned to the higher risk options, in risk seeking versus risk averse subjects and in CUD versus controls.

Future studies could also investigate risk processing in the context of other rewards (e.g., primary or drug rewards) and motivational states (e.g., craving), and in relation to drug use and relapse assessed prospectively. Subjective craving in particular is an important determinant of relapse [13]. It is speculated that craving could bias processing of risk information in ways that increase risk-seeking behaviors. Indeed, risk preferences are not as stable as once thought and may be susceptible to motivational states (e.g., food-deprivation), as has been recently observed

for money [114] and primary rewards like food and water [115], and conceivably extending to drugs. In sum, with this novel task economic risk was parametrically modulated to examine its impact on decision-making, expanding the arsenal of tools available to study basic neuropsychological functions in drug addiction and possibly other disorders of self-control.

CHAPTER 3

Effects of Methylphenidate on Resting-State Functional Connectivity of the Mesocorticolimbic Dopamine Pathways in Cocaine Addiction (*Study 3* [116])

Background & Rationale

Resting-state functional connectivity is a noninvasive and replicable method for assessing neural circuitry function in neuropsychiatric disorders [117]. This method captures the synchronicity of low-frequency, spontaneous fluctuations in BOLD signals that reflect fluctuations in neuronal activity [118] between brain regions in the absence of external stimulation [119]. These synchronous fluctuations are confined to GM and can be observed for monosynaptic or polysynaptic anatomic connections [118, 120]. Importantly, resting-state connectivity is linked to task-related functioning of discrete brain regions comprising the same circuits [121] and to corresponding behavior [121, 122]. Thus, resting-state connectivity can have utility for advancing neural systems-level understanding of the functional and behavioral abnormalities that characterize neuropsychiatric disorders like addiction, with the potential to also serve as a target for therapeutic interventions.

Perturbations in resting-state connectivity within and between functional brain networks that subserve attentional, emotional, and inhibitory control processes have been observed in individuals addicted to nicotine [123, 124], opioids [125-127], and cocaine [128, 129]. Specifically, individuals with CUD exhibit reduced connectivity of the dorsal frontoparietal attention network [129]; in addition, and especially pertinent to the current study, cocaine users also exhibit reduced connectivity of the mesocorticolimbic dopamine pathways [128], of relevance to the findings of *Studies 1 & 2* described above. However, thus far it has not been shown whether this abnormal connectivity could be modified in individuals with chronic, severe CUD.

Methylphenidate (MPH) is a psychostimulant widely used to treat attention deficit hyperactivity disorder. Like cocaine, MPH competitively blocks dopamine and norepinephrine transporters, thereby increasing extracellular concentration of these neuromodulatory neurotransmitters [130]. However, unlike cocaine, the rate of clearance of orally administered MPH from the brain is substantially slower (90 min half-life as compared with 20 min for

cocaine), contributing to its lower abuse potential [131] and possible viability as a therapeutic agent in treating cocaine addiction [132]. MPH improves task-related regional brain activation in the dopamine innervated VMPFC and dorsal ACC [53] and corresponding stop signal reaction times in CUD [133]. Oral MPH is also shown to attenuate changes in glucose metabolism in the OFC and inferior frontal gyrus, hippocampus, and ventral striatum (nucleus accumbens) when cocaine users are exposed to drug-related cues [134].

This study used a placebo-controlled, before-after, crossover experimental design to examine the effects of short-term MPH administration on resting-state connectivity in active cocaine users. Previously, the only study that assessed drug-induced changes in resting-state connectivity in CUD included a small sample size, used intravenous cocaine, and focused on the sensorimotor cortices [135]. The present study in contrast examined connectivity using a seed correlation approach, based on a more recent study reporting that cocaine addiction was associated with reduced connectivity of the mesocorticolimbic pathways, including pathways through the VMPFC and nucleus accumbens [128]. Given the normalizing effects of MPH on task-related activation and behavior in CUD [53, 133], the hypothesis was that MPH would strengthen connectivity of the medial frontal cortex with regions involved in emotion regulation (e.g., amygdala and hippocampus [136-138]) and inhibitory control (e.g., dorsal and lateral PFC). In addition, because MPH attenuated brain metabolism following exposure to cocaine cues [134], it was also expected that MPH would reduce connectivity between regions underlying craving (e.g., OFC, ventral and dorsal striatum, and amygdala [11, 12, 35]). Finally, to examine if MPH modified connectivity in pathways directly associated with addictive behavior, correlations between connectivity strength and severity of cocaine addiction were inspected.

Methods

Subjects

Eighteen right-handed, non-treatment seeking native English speakers were recruited, screened, and consented as described in *Study 1*. All subjects were currently using cocaine and identified cocaine as their primary drug of choice, meeting criteria for current cocaine dependence (n=17) or abuse (n=1). Current comorbidities included heroin dependence (n=1), marijuana abuse (n=1), alcohol abuse (n=1), and nicotine dependence (n=14). Additional exclusion criteria for this study

were history of glaucoma and past prescription use of MPH. Nine subjects tested positive for cocaine on MPH day and eight tested positive for cocaine on placebo day.

Cocaine withdrawal symptoms were assessed prior to medication administration at each study day with the Cocaine Selective Severity Assessment Scale [139]; subjects also completed the Cocaine Craving Questionnaire [140] and the Severity of Dependence Scale which captures perceived control over drug taking and difficulty with stopping drug use over the past year. For each subject, the severity of addiction was quantified as a composite score (average *Z* value) of the severity of withdrawal, craving, and dependence as assessed on placebo day and the frequency of use of cocaine in the past 30 days as assessed during the clinical interview. The severity of withdrawal and dependence did not significantly differ between the study days ($p>0.11$); however subjects reported more recent use of cocaine and more severe craving on MPH day than on placebo day (**Table 3.1**).

Table 3.1. Demographic and drug use variables for individuals with cocaine use disorders (CUD) included in *Study 3*.

	Study 3	
	CUD (N=18)	
Gender: Male / Female	16 / 2	
Race: African-American / Other	15 / 3	
Age (years)	45.6 ± 7.3	
Education (years)	12.9 ± 1.8	
Verbal IQ: WRAT-3 Reading	91.8 ± 9.2	
Non-Verbal IQ: WASI - Matrix Reasoning Scale	9.3 ± 3.1	
Socioeconomic Status: Hollingshead Index	35.8 ± 8.4	
Age of onset of cocaine use (years)	26.9 ± 6.3	
Cocaine use (lifetime, years)	15.3 ± 7.5	
Days/week of cocaine use during the past 30 days †	2.7 ± 2.1	
Days/week of cocaine use during the past 12 months	2.7 ± 2.1	
	MPH	**Placebo**
Depression: Beck Depression Inventory II	6.9 ± 5.5	6.1 ± 4.8
Cocaine urine status, No. positive / negative	9 / 9	8 / 10
Severity of Dependence Scale †	7.4 ± 2.5	7.3 ± 2.6
Withdrawal symptoms: 18-item CSSA †	15.9 ± 10.6	12.2 ± 7.8
Cocaine Craving: 5-item Questionnaire [b]†	22.0 ± 13.4	17.4 ± 12.7
Duration of current abstinence (days) [b]	5.4 ± 6.5	7.8 ± 9.5

Note. Values are frequencies or means ± standard deviation (SD);
[b] $p<0.05$, MPH vs. Placebo;
† Variables used to compute the "Addiction Severity" composite score;
Race: Other (Caucasian / Hispanic / Asian); WRAT-3 = Wide Range Achievement Test (3rd edition); WASI = Wechsler Abbreviated Scale of Intelligence; CSSA = Cocaine Selective Severity Assessment Scale; MPH = methylphenidate.

Study Sessions

At each of the two study sessions (conducted 8.9 ± 4.0 days apart), subjects were randomized to receive a single oral dose of MPH (20 mg) or placebo (lactose). This dose has been previously shown to affect task-related brain activation and behavior in CUD [53, 134]. The study was initially performed such that only subjects were blinded to the administered challenge (n=13). Once it became clear that risks were minimal, the study transitioned to double-blind administration (n=5), where personnel were also blinded to the medication condition.

The MPH and placebo sessions consisted of identical procedures (**Figure 3.1A**). Resting scans were acquired twice, shortly after medication administration (before onset of drug effects) and approximately 120 minutes later, within the window of peak MPH effects [141]. Plasma concentrations of MPH collected via venous blood draws at 0 min, 45 min, and 120 min using capillary GC-MS [142] confirmed peak levels. To inspect whether MPH affected cardiovascular reactivity and mood state, subjects' heart rate, blood pressure, desire for MPH, and feelings of being alert, anxious, high, or restless were assessed throughout the study sessions.

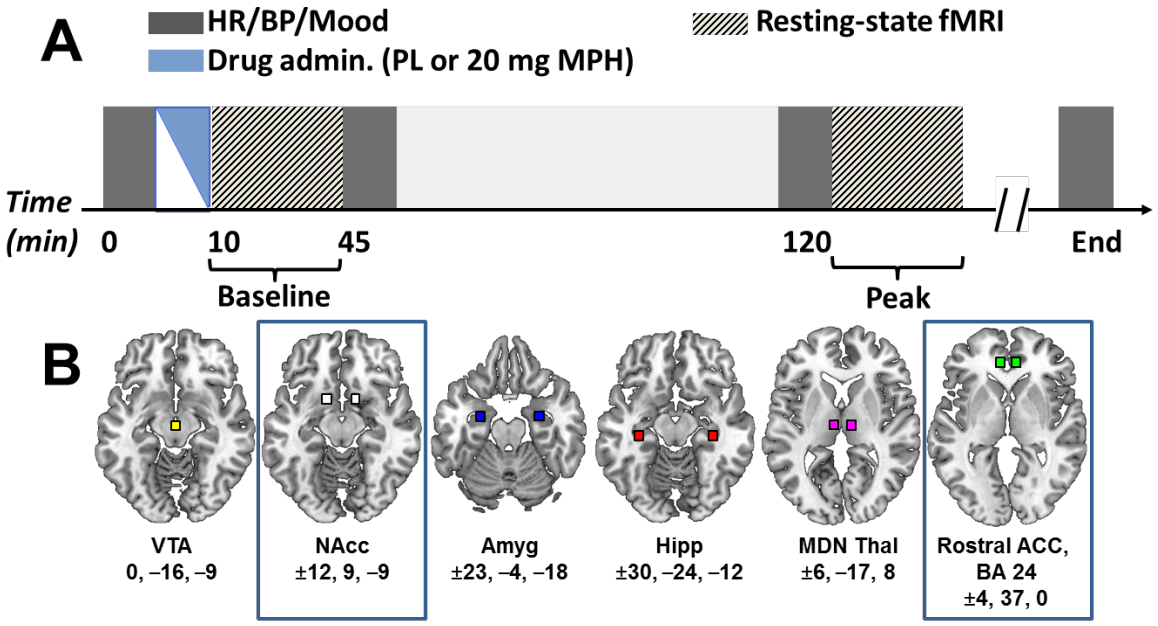

Figure 3.1. (**A**) Timeline of the study protocol. (**B**) Center coordinates and locations of the mesocorticolimbic seed regions. The listed x, y, z coordinates follow Montreal Neurological Institute (MNI) convention.

Image Acquisition

Functional imaging was performed using the same sequence and parameters as described in *Study 1*. Subjects were instructed to keep their eyes open, lie as still as possible, and remain awake during the resting scans. Each resting scan was approximately 8 min in duration. This length is comparable to previous studies of this type [123, 124] and in the recommended range for optimal assessment of seed-based connectivity [143].

Image Processing and Construction of the Functional Connectivity Maps

Image processing and analyses were performed in SPM8 (Wellcome Trust Centre for Neuroimaging, London UK). The data were first realigned, slice time corrected, and spatially normalized to a standard Montreal Neurological Institute frame, resulting in a final voxel size of 3×3×3 mm. Other preprocessing steps were carried out in IDL (ITT Visual Information Solutions, Boulder, CO) and included motion correction using the six time-varying realignment parameters (3 translations and 3 rotations), global signal normalization, and band-pass filtering (0.01-0.10 Hz). Because a recent study showed that movement at a finer time scale can increase the variability of functional connectivity measures [144], the mean absolute displacement of the brain from every time frame to the next was additionally computed. Displacement was in the minimal range for all four resting scans (0.14-0.21 mm) but higher overall on placebo day than on MPH day ($F_{(1,17)}$=5.56, p=0.03; for all other effects, p>0.68).

Functional seed regions were defined by centering bilateral 9-mm cubes (27 voxels) at the coordinates shown in **Figure 3.1B**. The size of the seed regions was chosen based on previous studies [57, 145, 146] and was kept constant across regions. These seeds were identical to those used in Gu *et al*. [128]; although the current discussion will focus on two of these seeds [the VMPFC (rostral ACC) and ventral striatum], **Table 3.2** and **Figure 3.2** provide a complete summary of findings for all seeds. Control seeds were also placed in the primary motor (coordinates in MNI space: x=±44, y=–10, z=40), auditory (x=±44, y=–36, z=13), and visual cortices (x=±10, y=–91, z=1). Whole-brain cross-correlation maps were calculated separately for each seed and for each subject for each of the four scans [MPH peak effects, placebo "peak" effects (i.e., after the parallel time has elapsed, reflecting an 'active baseline'), MPH baseline (i.e., before the expected onset of medication effects), and placebo baseline], reflecting correlations over time between average BOLD signal fluctuations in the respective seed region

(averaged time series across all voxels in the seed) and those in all other voxels of the brain. These cross-correlation coefficient maps were converted to *Z*-score maps and smoothed with an 8-mm full-width at half-maximum Gaussian kernel prior to group-level analyses in SPM8.

Functional Connectivity Analysis

A 2 (medication: MPH, placebo) × 2 (time: baseline, peak drug effects at 120 min) repeated measures analysis of covariance in SPM8 was used to analyze differences in the strength of each seed's connectivity as a function of MPH administration. To control for differences between the MPH and placebo days in abstinence, craving, the potential influence of the medication administration paradigm, and micromotion, days since last cocaine use, Craving Questionnaire scores, a dummy regressor indicating whether subjects received single- or double-blind medication administration, and mean absolute head displacement were included as covariates.

The primary analysis involved a comparison of MPH peak effects vs. placebo "peak" effects. Significant whole-brain changes in connectivity were identified using a cluster-level $p<0.05$ FWE–corrected threshold with an *a priori* a minimum height ($p<0.005$ uncorrected) and cluster extent (20 adjacent voxels) threshold. Significant regions from the MPH vs. placebo peak contrast were extracted as 3 mm radius spheres, chosen based on the image smoothness (i.e., the volume of the resolution elements or "resels" [147]), using the EasyROI toolbox (http://www.sbirc.ed.ac.uk/cyril/cp_download.html). The extracted average signal in these regions was used for visual representation of the data, comparison with healthy controls, and multiple regression analysis with addiction severity, described below. Anatomical specificity was determined with the Anatomy toolbox [148].

Secondary analyses compared MPH peak effects vs. same day baseline and MPH same day baseline vs. placebo same day baseline, both used to rule out ancillary factors particular to each study session (e.g., pre-medication administration cocaine craving and days since last cocaine use; **Table 3.1**). Results from these secondary analyses were masked by the MPH peak effects vs. placebo "peak" effects contrast ($p<0.05$ uncorrected) and are reported at $p<0.005$ uncorrected with a minimum cluster extent of 20 adjacent voxels.

Finally, to determine if MPH modified connectivity in CUD to a level that no longer significantly differs from healthy individuals, connectivity strength during placebo and, separately, during MPH was compared with that of an independent sample of control subjects for

whom resting-state data were acquired under baseline/placebo conditions. These were 16 right-handed healthy individuals (mean age 38±7 years, all male) that were matched to CUD on all socio-demographic and neuropsychological measures except for age (p=0.008).

Association of Connectivity Strength with Severity of Cocaine Addiction

To determine if MPH modified connectivity between regions that, under placebo, were directly associated with the severity of cocaine addiction, the composite addiction severity score (**Table 3.1**) was used as the dependent variable in a multiple regression analysis in SPSS, restricting the predictors to include connectivity measures in regions that both changed after MPH and differed significantly from healthy controls (either in the present study or as reported by Gu *et al*. [128]) (six total predictors).

Results

Effects of Methylphenidate on Cardiovascular Reactivity and Subjective Mood

Except for diastolic blood pressure (which was higher after receiving MPH than after placebo), changes in cardiovascular reactivity and mood did not significantly differ between the MPH and placebo study sessions (for all, p>0.05). Consistent with prior studies using 20 mg of oral MPH [53, 134], self-reports of cocaine wanting also did not increase after MPH (p=0.15).

Effects of Methylphenidate on Connectivity Strength

Primary Analyses (MPH peak effects vs. placebo "peak" effects): MPH modified two corticolimbic connections that were previously reported to be disrupted in CUD [128]: compared with placebo, MPH increased connectivity of (1) the right and left hippocampus with the left postcentral gyrus (BAs 4, 6) (peak coordinate in MNI space: x=–60, y=–3, z=33, Z=4.39, FWE–corrected p=0.008; and x=–63, y=3, z=30, Z=4.05, FWE–corrected p=0.033, respectively) and (2) the left rostral ACC with the right parahippocampal gyrus (x=15, y=–36, z=–9, Z=3.57, FWE–corrected p=0.019).

Whole-brain analyses revealed additional effects of MPH (**Table 3.2, Figure 3.2**). Most notably, compared with placebo, MPH *increased* connectivity of (1) the right rostral ACC with the left dorsal cingulate (**Figure 3.3**) and (2) the right nucleus accumbens with the medial OFC (**Figure 3.4A**). MPH also *reduced* connectivity of the right nucleus accumbens with the left

putamen/globus pallidus (**Figure 3.4B**). No changes in connectivity strength were observed at the corrected level for the bilateral amygdala, left thalamus, or left nucleus accumbens seeds.

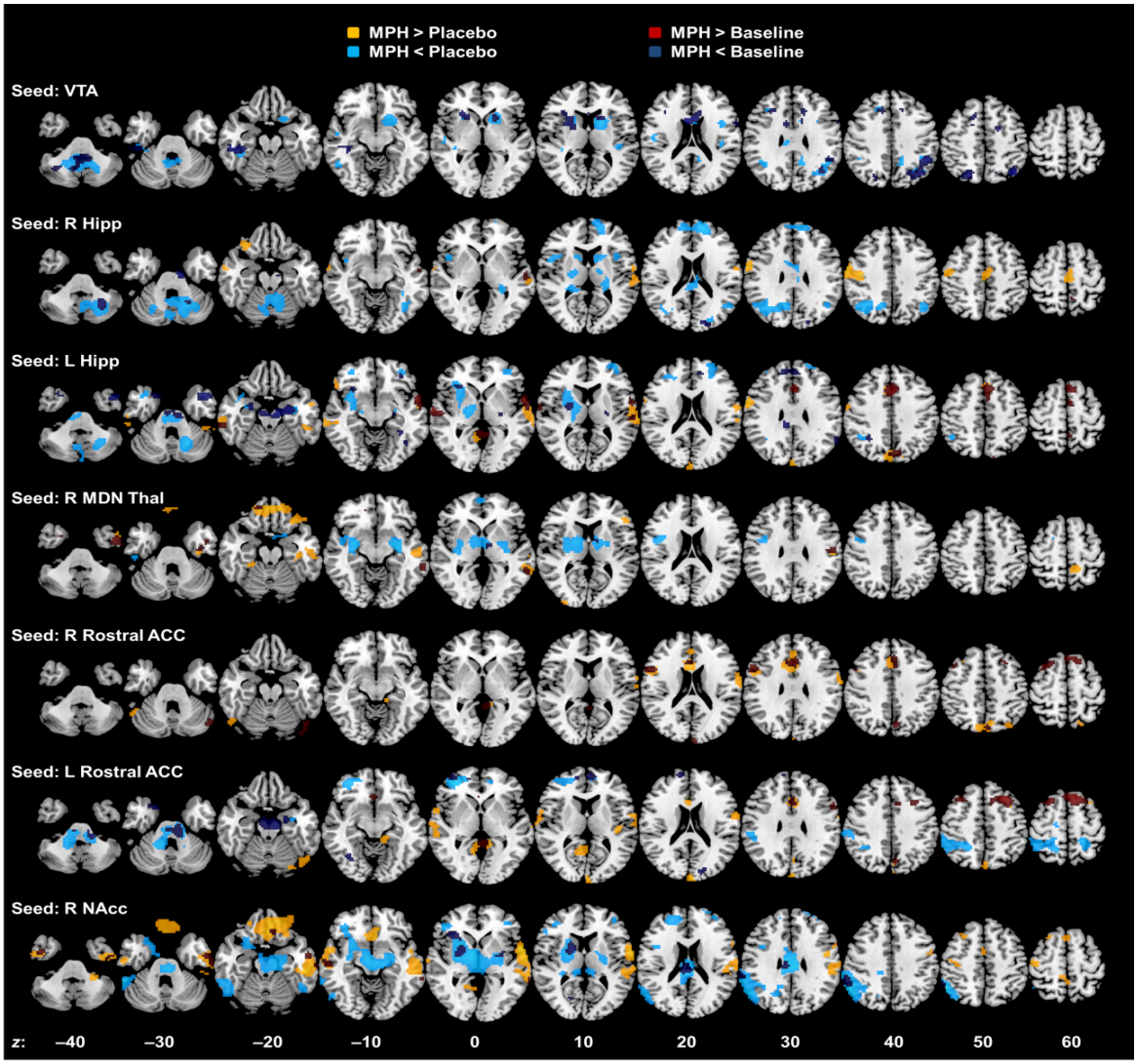

Figure 3.2. Whole-brain changes in connectivity strength with MPH in CUD. Color maps show increased (orange) or decreased (cyan) connectivity strength with MPH versus placebo in a *t*-score window from ±1.5 to 7. Increases or decreases from same day baseline (MPH>baseline and MPH<baseline) are shown in red and dark blue. Regions correspond to those reported in **Table 3.2**.

Table 3.2. Whole-brain changes in resting-state functional connectivity with methylphenidate[a]

	BA	Side	Cluster Size, mm^3	peak Z	*p*-corrected	*x*	*y*	*z*
Seed: VTA								
Caudate/Putamen*		R	385	–4.3	0.033	15 18	15 6	6 15
Cerebellum*		L R	540	–3.7	0.008	–6 –6	–45 –48	–45 –33
Seed: R Hippocampus								
Cerebellum*		R	943	–4.3	<0.001	30 15	–60 –66	–36 –27
Sup. Frontal G.	10	R L	397	–3.9	0.042	15 9	57 60	18 27
Mid. Occipital/Angular G./Precuneus*	40,7,23	L	436	–3.5	0.030	–39 –9	–66 –60	39 30
Seed: L Hippocampus								
Sup. Temp G./Postcentral G.*	43,22	R	417	+3.6	0.032	60 63	–6 –21	–3 6
Insula/Thalamus/Putamen*		L	702	–4.0	0.003	–33 –15	27 –9	–3 6
Seed: R MDN Thalamus								
Med. OFC/G. Rectus*	11	L R	408	+4.6	0.040	–18 0	48 48	–15 –21
Putamen/Thalamus*		L R	1148	–4.1	<0.001	–30 30	–6 –9	–9 –6
Seed: R Rostral ACC (BA 24)								
Dorsal ACC*	32,24	L	335	+4.0	0.058	–3 0	18 39	24 27
Seed: L Rostral ACC (BA 24)								
Cerebellum*		R L	593	–4.3	0.007	12 –12	–24 –45	–30 –33
Inf. Parietal/Supramarginal G.[c]*	40,2	L	501	–3.7	0.016	–33 –51	–45 –51	69 54
Seed: R NAcc								
Sup. Temporal G./Postcentral G./Rolandic Oper.[c]*	20,22,38	R	1292	+4.7	<0.001	57 63	3 –18	0 –27
Med. OFC/G. Rectus*	11	R	823	+4.5	0.001	6 9	30 45	–15 –24
Inf. Parietal/Angular G.*	40,39	L	841	–5.2	<0.001	–54 –54	–51 –60	48 33
Putamen/Globus pallidus/Thalamus[b,c]*		L	2671	–5.0	<0.001	–27 –6	–3 –6	0 –3

Note. Statistical Threshold: cluster-level $p<0.05$ family-wise error (FWE) corrected with a voxel-level $p<0.005$ uncorrected height threshold and k=20 voxels (T=2.65);
+Z score indicates increased connectivity strength with methylphenidate (MPH; MPH > placebo peak effects);
–Z score indicates decreased connectivity strength with methylphenidate (MPH < placebo peak effects);
No significant effects of MPH were observed for the bilateral amygdala, left thalamus, or left nucleus accumbens seeds at the set significance threshold;
*****Region also showing effects for the MPH peak effects vs. same day baseline contrast (voxel-level $p<0.005$ uncorrected and k=20 voxels within a MPH vs. placebo peak effects $p<0.05$ uncorrected inclusive mask);
[a] Analysis of covariance (covariates: medication administration paradigm, baseline craving, days since last cocaine use, and micromotion);
[b] Region associated with the "Addiction Severity" composite score;
[c] Region significantly different from healthy controls during placebo "peak" effects;
Coordinates follow Montreal Neurological Institute (MNI) convention;
Abbreviations: ACC: anterior cingulate cortex; MDN: mediodorsal nucleus; SMA: supplementary motor area; NAcc: nucleus accumbens; OFC: orbitofrontal cortex; Med.: medial; Mid.: middle; Sup.: superior; Inf.: inferior; R: right; L: left; BA: Brodmann Area.

Secondary analyses: Supporting the idea that these changes in connectivity were due to the pharmacological effects of MPH (and not differences between the study days or the expectation to receive MPH), baseline connectivity did not significantly differ between the two study days for any of the seeds (as inspected with the MPH baseline vs. placebo baseline contrast, masked by the MPH peak > placebo "peak" or MPH peak < placebo "peak" contrasts reported above). The MPH peak effect vs. same day baseline contrast was similarly examined and, in contrast, revealed significant results in most brain regions identified by the MPH peak vs. placebo "peak" contrast (regions identified in both analyses are starred in **Table 3.2**).

Notably, MPH generally did not modify connectivity with the control seeds [with the exception of an increase in connectivity between the primary motor cortex and the cerebellum, a well-established motor pathway that also depends on dopamine].

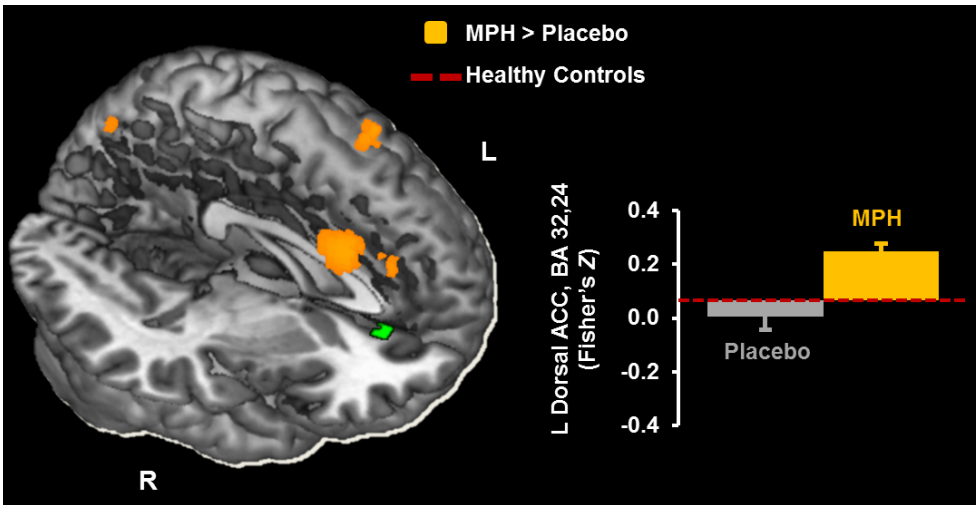

Figure 3.3. Increased right rostral ACC (BA 24) (seed shown in green) with left dorsal cingulate connectivity with MPH in CUD. Color map shows increased connectivity with MPH versus placebo (orange) in a *t*-score window from ±3.0 to 7. Bar plot shows the Fisher's *Z* values for placebo "peak" effects (gray) and MPH peak effects (orange) plotted from values of healthy controls. Bars are means ± SEM.

Comparison to Health

Within these connections modulated by MPH, relative to healthy controls who were studied during placebo/baseline, CUD showed reduced connectivity of (1) the bilateral hippocampus with the left postcentral gyrus (corroborating findings by Gu *et al.* [128]) and (2) the right nucleus accumbens with the right superior temporal gyrus, extending to the postcentral gyrus and

rolandic operculum and increased connectivity of (3) the left rostral ACC with the left inferior parietal cortex and (4) the right nucleus accumbens with the left putamen/globus pallidus. Importantly, after MPH, group differences in all of these connections were no longer significant, suggesting that MPH normalized connectivity strength between these regions.

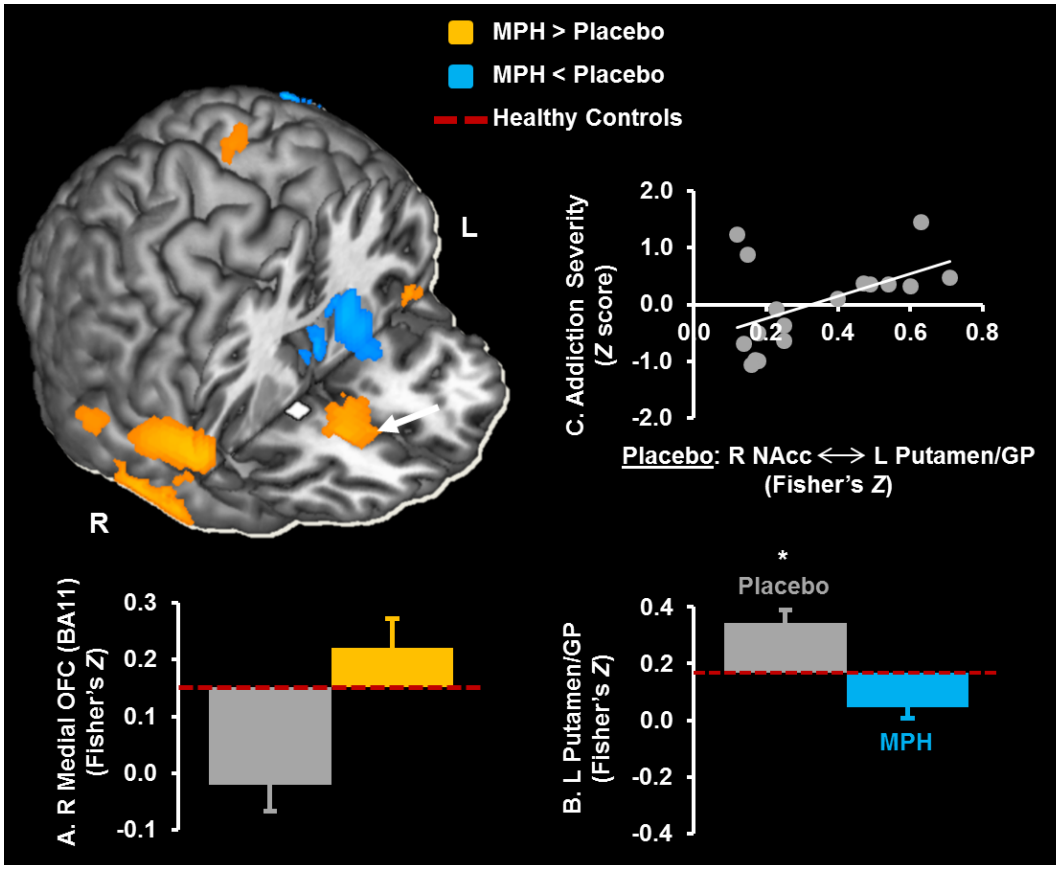

Figure 3.4. Changes in connectivity of the right nucleus accumbens (seed shown in white) with the (**A**) right medial OFC and (**B**) left putamen/globus pallidus with MPH. Color maps show increased (orange) or decreased (cyan) connectivity strength with MPH versus placebo in a *t*-score window from ±3.0 to 7. Bar plots show the Fisher's Z values for placebo "peak" effects (gray) and MPH peak effects (orange and cyan) plotted from values of healthy controls. Bars are means ± SEM. (**C**) Connectivity strength between the right nucleus accumbens and left putamen/globus pallidus during placebo uniquely positively correlated with addiction severity. *p<0.05

Relationship to Severity of Cocaine Addiction

To determine if connectivity modified by MPH was directly associated with cocaine addiction severity, a multiple regression analysis was conducted in SPSS with addiction severity as the dependent variable. The predictors in this analysis included the six connectivity pathways that

significantly differed from healthy controls during placebo in the present study or as reported by Gu *et al.* [128], and that were normalized in strength with MPH. These six predictors accounted for 24% of the variance in addiction severity (adjusted R^2=0.24, p=0.18). However, only connectivity between the right nucleus accumbens and left putamen/globus pallidus accounted for significant unique variance (β=0.61, p=0.035, for all other p>0.16) (**Figure 3.4C**). That is, MPH reduced connectivity strength between these regions (described above), and lower connectivity strength during placebo was associated with less severe addiction.

Discussion

Using short-term oral administration of MPH, the present study showed that mesocorticolimbic connectivity is susceptible to dopaminergic manipulation in CUD. Taking into account differences in baseline connectivity from healthy individuals and correlations between these measures and severity of addiction, the direction of change in connectivity strength with MPH is consistent with a beneficial response to the drug, extending its previously reported efficacy in normalizing task-related brain activation and behavior in this population [53, 133]. Moreover, study design considerations suggested that connectivity with the seed regions was stable such that the observed changes in connectivity were due to the effects of MPH and not ancillary factors particular to each study session.

MPH strengthened connectivity of the bilateral hippocampus with the postcentral gyrus and of the rostral ACC with the parahippocampal gyrus–corticolimbic connections suggested to underlie successful emotion regulation [136-138] that were reported to be disrupted in cocaine addiction [128]. In particular, the postcentral gyrus is involved in craving suppression [149] and both the postcentral gyrus and hippocampus fail to normally activate when cocaine users are exposed to stress, abnormalities that could underlie stress-related vulnerability to cocaine relapse [150]. Strengthened connectivity in emotion processing and memory formation pathways with MPH may contribute to enhanced retention of emotional associative learning (as has been shown in rodents [151, 152]) and better control over emotional disturbances and emotional memories (e.g., when combined with exposure therapy), particularly those associated with withdrawal symptoms and conditioned responses that frequently lead to relapse in addiction [153].

In addition to strengthened corticolimbic connectivity, MPH strengthened connectivity of the rostral ACC with the dorsal cingulate. These cingulate regions have differential anatomic

connections with emotion and cognitive control networks [154], and our lab previously found reduced correlations between these regions during processing of salient cues in cocaine users [52]. Therefore, strengthened frontal connectivity with MPH may point to the mechanism that contributes to the MPH-induced improvements in behavioral and neural measures of self-control on both neutral [133] and salient [53] tasks of executive function in CUD. This finding is also important in view of tractography studies in CUD, where higher fractional anisotropy in regions of the frontal cortex, and the rostral corpus callosum linking these regions, predicts longer abstinence [155].

Most notably, MPH reduced connectivity of the ventral tegmental area, hippocampus, thalamus, and nucleus accumbens with the dorsal striatum. In particular, connectivity within striatal circuits, possibly instantiated via the spiraling dopamine connections through the midbrain that link the nucleus accumbens with the dorsolateral striatum or via other nodes of the cortico-thalamic-striatal loops [156], is strongly implicated in drug-seeking [157]. Because the progression of cocaine addiction involves a shift in striatal circuits from ventral to dorsal [10, 35, 70, 158], the strength of connectivity between these regions may be marking individual differences in disease severity. Indeed, higher connectivity of the nucleus accumbens with the putamen/globus pallidus uniquely correlated with more severe addiction. The finding that short-term MPH can modify this connection may be clinically relevant given that blocking striato-midbrain-striatal serial connectivity selectively decreased drug-seeking in rats trained to habitually self-administer cocaine [157]. Future longer-term intervention studies should test whether systematic, prolonged weakening of this connection helps restore control over drug-seeking behavior in humans. Other effects of MPH may also contribute to increased control over craving and drug-seeking, including MPH-strengthened connectivity of the nucleus accumbens with a region encompassing the superior temporal and postcentral gyri and the rolandic operculum. Indeed, cognitive control of craving is associated with inverse coupling between these cortical regions and the nucleus accumbens in addicted individuals using different strategies to resist craving [31, 159]. Similarly, increased nucleus accumbens–medial OFC connectivity may have general benefits for value processing encompassing drug *and* non-drug rewards following findings from *Studies 1 & 2*.

Several caveats should be considered. First, like most stimulants, MPH produced cardiovascular changes that differed from placebo. However, because BOLD fluctuations

correlating with heart rate and respiration are global [160, 161], these changes are not likely to significantly influence the results. At the neurochemical level, a second concern is that the effects of MPH are not specific to dopamine, as MPH also blocks the norepinephrine transporter [162]. Nevertheless, even if effects are due to norepinephrine transporter blockade, the underlying mechanism could still be dopaminergic, since dopamine also has high affinity for norepinephrine transporters—particularly in regions where norepinephrine transporters are more abundant than dopamine transporters such as the frontal cortex [163]. Lastly, it is not known whether MPH-induced modulation of connectivity is a viable target for treatment approaches in CUD. Future studies would need to examine the effects of MPH using dose-dependent and/or prolonged administration (i.e., occurring over days or weeks). In addition, as MPH as a stand-alone may be insufficient to achieve a positive clinical outcome in cocaine addiction [164, 165], except for in instances of co-morbidity with attention deficit hyperactivity disorder [166], the therapeutic effects of MPH should be explored in conjunction with behavioral interventions which are shown to target regions of the PFC, and particularly those involved in self-control and action selection, more strongly than pharmacological interventions across addictions [167].

In summary, the current study provides evidence that functional connectivity is susceptible to modification by pharmacological agents targeting dopamine in individuals with chronic, severe CUD. MPH primarily strengthened connections between regions underlying emotion regulation and cognitive control and reduced connections between regions underlying habits, including compulsive drug-seeking and craving. While the precise mechanism of these effects remains to be determined, the data suggest that MPH may transiently, and independently of task demands, modify striatal and cortical synchronous activity with connected brain regions. These changes could serve to facilitate goal-directed behavior or make cortical processing underlying behavior more efficient [168-171], or less difficult to override [172]. A better understanding of the potentially therapeutic effects of MPH on neural circuitry function in CUD (e.g., with future studies evaluating the clinical efficacy of MPH) may promote the development of improved treatment options for stimulant addictions.

GENERAL CONCLUSIONS

Using multimodal neuroimaging and targeted behavioral and clinical assessments, the set of research studies described in this thesis are aimed to advance our understanding of the neural circuits underlying value processing and self-control that may be altered by chronic cocaine use.

In previous work, it was found that the amount of GM volume in regions of the PFC that send projections to the neural generator of a reliable EEG marker of response to reward was directly related to this marker's response to money in healthy controls, and that individuals with CUD showed reductions in both GM of the PFC and this functional marker [46]. *Study 1* extended this structure-function investigation in several ways. First, another measure of neural activity was used, namely fMRI, which provides better spatial resolution than EEG. Second, additional levels of reward value were used to more directly test specificity of the functional effects to value. Lastly, in addition to brain structure, brain functional connectivity between regions of interest in the PFC (namely the VMPFC) and striatum was examined. The results from *Study 1* suggest that abnormal representation of value in the sensorimotor striatum (the part of the striatum implicated in habits) in CUD, which had negative consequences for both behavior in the study (led to less behavioral adjustments with higher potential gains) and outside the lab (more frequent cocaine use), may stem from reduced GM volume, function, and connectivity of the VMPFC with the striatum in CUD.

Study 2 delved deeper into the behavioral implications of abnormal value representation in CUD as they relate to decision making involving risk (uncertainty) and reward. A behavioral study in CUD and healthy individuals showed that risk-seeking preferences, that is the tendency to select riskier options relative to lower risk options when making decisions involving real money, could be quantified using an economic framework but did not differ between the diagnostic groups. Nevertheless, much variability in risk preferences was observed, and this variability appeared to have implications for real-world behaviors. Specifically, risk-seeking preferences correlated with impulsive traits across both groups (as assessed with standardized questionnaires). In addition, within a subgroup of CUD, risk-seeking preferences correlated with more severe drug-seeking (this time assessed using an implicit behavioral measure in the laboratory), suggesting that value computations related to economic risk may also be directly relevant for drug-related behaviors. Thus, these collective data suggest that future studies may

benefit from accounting for individual differences in risk preference in addiction, particularly when examining the neural correlates of deciding about risk.

A key question following *Studies 1 & 2* remains as to whether these neural circuits underlying value processing and self-control can be at all modified by treatment in addiction. In an initial step toward answering this question, *Study 3* tested whether a single dose of MPH can modify functional connectivity among regions of the mesocorticolimbic dopamine pathways, including the VMPFC and striatum in CUD. MPH primarily *strengthened* connections between regions underlying emotion regulation and self-control (e.g., between the VMPFC and dorsomedial PFC, as well as between the VMPFC and striatum and hippocampus) while it *reduced* connections between regions underlying habits, including compulsive drug-seeking and craving (e.g., between the ventral and dorsal striatum). Thus, while the precise mechanism of the effects of MPH on connectivity remains to be determined, the data suggest that MPH may transiently, and independently of task demands, modify striatal and cortical synchronous activity with connected brain regions. Specifically, some of these effects may be therapeutically pertinent as connectivity of the ventral with dorsal striatum uniquely marked individual differences on a composite measure of addiction severity.

While these studies used noninvasive measures of neural integrity, results remain to be validated with postmortem or lesion studies to determine the precise histopathological characteristics that influence abnormalities in GM volume, function, and connectivity observed in the current samples of CUD. The extant postmortem literature has nonetheless provided some insights. For example, studies have shown that genes related to myelin in the ventral striatum (nucleus accumbens) are dysregulated in cocaine users compared with matched healthy controls and even heroin users [173, 174], as further supported by an increased presence of markers of axonal damage in this region and across the brain in individuals with protracted cocaine use [175]. Other studies also show that dynorphin, a neuropeptide that interacts with the brain dopamine system, is markedly upregulated in the ventral striatum and putamen [174], potentially contributing to alterations in dopamine signaling in these regions. As such, dopamine transporter levels and dopamine uptake are found to be abnormally increased in the ventral striatum [176] and dopamine cell numbers abnormally decreased in the midbrain [177] of cocaine users. Thus, it is likely that in much of the same regions MRI measures capture underlying abnormalities related to neuronal integrity (structure and function) in this population.

A second consideration pertains to the specificity of the observed effects to cocaine and not other psychosocial factors or comorbid drug use. Specifically, although the influence of common potential confounds (e.g., cigarette smoking, age, education, etc.) was statistically inspected and controlled for where appropriate in the analyses, their potential impact on results remains to be separately investigated. In particular, because only a few (~20%) controls and most (~75%) CUD reported a history of cigarette smoking across all three studies, control for differences in smoking status between the groups was not possible [178]. Given that it is not practical to exclude cigarette smoking CUD, where concomitant use of nicotine and comorbid nicotine dependence are much higher than in the general population (70-80% for nicotine use and 50% for nicotine dependence as compared to 22% and 13% in controls, respectively [179-183]), results remain to be tested against a group of cigarette smoking controls.

A third important consideration pertains to the issue of causality (i.e., abnormalities stemming from drug use) versus pre-disposing factors in driving these differences from health. Since dopamine influences cerebral morphology during development and throughout adulthood, and drug-induced depletion of dopamine occurs after withdrawal from chronic intoxication [184], it is expected that chronic exposure to substances that trigger supraphysiological dopamine responses might cause persistent cellular changes resulting in changes in brain morphology. Previous studies in individuals addicted to various substances have shown changes in GM volume or cortical thickness in the VMPFC and striatum, among other regions, compared to healthy individuals [39-42, 185-194]. Some of these changes were observed irrespective of the length of time since last drug use [62, 195, 196] and in children with family history of substance use disorders [197], suggesting these differences in addicted individuals may track stable traits, potentially predisposing individuals to drug use and addiction during development. However, younger populations of drug users do not tend to show these same abnormalities [198, 199] (with some notable exceptions, e.g., [200, 201]) and changes in GM volume, function, and connectivity have been shown to directly correlate with more lifetime use (e.g., of alcohol [202, 203], nicotine [194], heroin [190], and cocaine [39, 128]), suggesting that chronic drug exposure accounts at least for a portion of these changes.

In summary, together, the studies described in this thesis aim to strengthen our understanding of the impact of chronic cocaine use on value and risk assessment, and the brain circuits supporting these functions. This knowledge may serve as an empirical foundation for the

development of interventions targeting frontostriatal circuit dysfunction in cocaine addiction. Indeed, functional neuroimaging has informed much of what is known about neural abnormalities associated with human drug addiction. More recently, this tool has also allowed researchers to investigate whether and how these abnormalities can be targeted and potentially normalized by therapeutic interventions. In a recent meta-analysis of the literature in addiction that used pharmacological and cognitive-based therapeutic interventions yoked to neuroimaging measures [167], it was found that, although some distinct neural patterns were observed in studies of pharmacological and cognitive-based strategies, both types of interventions produced changes in the ventral striatum and portions of the PFC. These results emerged across studies using single-dose (as in *Study 3*) or repeated administration interventions, across different types of addiction, and across different task contexts. In contrast, activation in portions of the medial PFC, and more posterior brain regions implicated in attention, was more likely to be observed in studies of cognitive-based interventions than pharmacological interventions. Together, these findings suggest a potential mechanism by which the tandem use of pharmacological and cognitive-based strategies may produce synergistic (due to their common targets) or complementary (due to their distinct targets) therapeutic effects on the some of the brain regions highlighted in the current thesis. To more directly modulate brain activity in *specific* brain regions, more recently researchers have turned to the use of real-time fMRI neurofeedback. Although still in its infancy, the existing literature supports the feasibility of using real-time fMRI-based neurofeedback to modulate activation in the VMPFC [204-206]. Studies in healthy individuals also support the use of this technique to volitionally increase activation in the dopaminergic midbrain [207] and positive arousal via increases in ventral striatum activation [208]. Importantly, in both of these latter studies, while not specifically a goal of the neurofeedback training, neurofeedback relative to the control or no feedback conditions increased the functional coupling of the midbrain with the ventral and dorsal striatum [207] and of the ventral striatum with the medial PFC [208], suggesting that there might be secondary, circuit-level, reconfiguration associated with the intervention. Thus these different approaches (pharmacological, cognitive, and learning-based) support the feasibility of targeting VMPFC and striatum function, connectivity, and possibly even GM volume, underlying value and risk processing in cocaine addiction. Given the relationship between these regions and drug and non-drug use *behaviors*, such changes are sure to improve clinical outcome in this population.

REFERENCES

1. Volkow, N.D., R.D. Baler, and R.Z. Goldstein, *Addiction: pulling at the neural threads of social behaviors.* Neuron, 2011. **69**(4): p. 599-602.

2. Haber, S.N. and B. Knutson, *The reward circuit: linking primate anatomy and human imaging.* Neuropsychopharmacology, 2010. **35**(1): p. 4-26.

3. Grabenhorst, F. and E.T. Rolls, *Value, pleasure and choice in the ventral prefrontal cortex.* Trends Cogn Sci, 2011. **15**(2): p. 56-67.

4. Rolls, E.T., *The functions of the orbitofrontal cortex.* Brain Cogn, 2004. **55**(1): p. 11-29.

5. Hikosaka, K. and M. Watanabe, *Delay activity of orbital and lateral prefrontal neurons of the monkey varying with different rewards.* Cereb Cortex, 2000. **10**(3): p. 263-71.

6. Hornak, J., et al., *Reward-related reversal learning after surgical excisions in orbito-frontal or dorsolateral prefrontal cortex in humans.* J Cogn Neurosci, 2004. **16**(3): p. 463-78.

7. Kalivas, P.W. and N.D. Volkow, *The neural basis of addiction: a pathology of motivation and choice.* Am J Psychiatry, 2005. **162**(8): p. 1403-13.

8. Chen, B.T., F.W. Hopf, and A. Bonci, *Synaptic plasticity in the mesolimbic system: therapeutic implications for substance abuse.* Ann N Y Acad Sci, 2010. **1187**: p. 129-39.

9. Sulzer, D., *How addictive drugs disrupt presynaptic dopamine neurotransmission.* Neuron, 2011. **69**(4): p. 628-49.

10. Everitt, B.J. and T.W. Robbins, *Neural systems of reinforcement for drug addiction: from actions to habits to compulsion.* Nat Neurosci, 2005. **8**(11): p. 1481-9.

11. Kuhn, S. and J. Gallinat, *Common biology of craving across legal and illegal drugs - a quantitative meta-analysis of cue-reactivity brain response.* Eur J Neurosci, 2011. **33**(7): p. 1318-26.

12. Chase, H.W., et al., *The neural basis of drug stimulus processing and craving: an activation likelihood estimation meta-analysis.* Biol Psychiatry, 2011. **70**(8): p. 785-93.

13. Kosten, T.R., et al., *Cue-induced brain activity changes and relapse in cocaine-dependent patients.* Neuropsychopharmacology, 2006. **31**(3): p. 644-50.

14. Grusser, S.M., et al., *Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics.* Psychopharmacology (Berl), 2004. **175**(3): p. 296-302.

15. Treadway, M.T. and D.H. Zald, *Reconsidering anhedonia in depression: lessons from translational neuroscience.* Neurosci Biobehav Rev, 2011. **35**(3): p. 537-55.

16. Goldstein, R.Z. and N.D. Volkow, *Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications.* Nat Rev Neurosci, 2011. **12**(11): p. 652-69.

17. Kalivas, P.W., *The glutamate homeostasis hypothesis of addiction.* Nat Rev Neurosci, 2009. **10**(8): p. 561-72.

18. Konova, A.B., et al., *Structural and behavioral correlates of abnormal encoding of money value in the sensorimotor striatum in cocaine addiction.* Eur J Neurosci, 2012. **36**(7): p. 2979-88.

19. Hare, T.A., C.F. Camerer, and A. Rangel, *Self-control in decision-making involves modulation of the vmPFC valuation system.* Science, 2009. **324**(5927): p. 646-8.

20. Kable, J.W. and P.W. Glimcher, *The neural correlates of subjective value during intertemporal choice.* Nat Neurosci, 2007. **10**(12): p. 1625-33.

21. McClure, S.M., et al., *Separate neural systems value immediate and delayed monetary rewards.* Science, 2004. **306**(5695): p. 503-7.

22. Smith, D.V., et al., *Distinct value signals in anterior and posterior ventromedial prefrontal cortex.* J Neurosci, 2010. **30**(7): p. 2490-5.

23. Hare, T.A., et al., *Dissociating the role of the orbitofrontal cortex and the striatum in the computation of goal values and prediction errors.* J Neurosci, 2008. **28**(22): p. 5623-30.

24. O'Doherty, J., et al., *Dissociable roles of ventral and dorsal striatum in instrumental conditioning.* Science, 2004. **304**(5669): p. 452-4.

25. Tricomi, E.M., M.R. Delgado, and J.A. Fiez, *Modulation of caudate activity by action contingency.* Neuron, 2004. **41**(2): p. 281-92.

26. Valentin, V.V., A. Dickinson, and J.P. O'Doherty, *Determining the neural substrates of goal-directed learning in the human brain.* J Neurosci, 2007. **27**(15): p. 4019-26.

27. Wrase, J., et al., *Different neural systems adjust motor behavior in response to reward and punishment.* Neuroimage, 2007. **36**(4): p. 1253-62.

28. Graybiel, A.M., *The basal ganglia: learning new tricks and loving it.* Curr Opin Neurobiol, 2005. **15**(6): p. 638-44.

29. Tricomi, E., B.W. Balleine, and J.P. O'Doherty, *A specific role for posterior dorsolateral striatum in human habit learning.* Eur J Neurosci, 2009. **29**(11): p. 2225-32.

30. Baler, R.D. and N.D. Volkow, *Drug addiction: the neurobiology of disrupted self-control.* Trends Mol Med, 2006. **12**(12): p. 559-66.

31. Volkow, N.D., et al., *Cognitive control of drug craving inhibits brain reward regions in cocaine abusers.* Neuroimage, 2010. **49**(3): p. 2536-43.

32. Bjork, J.M., A.R. Smith, and D.W. Hommer, *Striatal sensitivity to reward deliveries and omissions in substance dependent patients.* Neuroimage, 2008. **42**(4): p. 1609-21.

33. Jia, Z., et al., *An Initial Study of Neural Responses to Monetary Incentives as Related to Treatment Outcome in Cocaine Dependence.* Biol Psychiatry, 2011.

34. Pierce, R.C. and L.J. Vanderschuren, *Kicking the habit: the neural basis of ingrained behaviors in cocaine addiction.* Neurosci Biobehav Rev, 2010. **35**(2): p. 212-9.

35. Volkow, N.D., et al., *Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction.* J Neurosci, 2006. **26**(24): p. 6583-8.

36. Gerdeman, G.L., et al., *It could be habit forming: drugs of abuse and striatal synaptic plasticity.* Trends Neurosci, 2003. **26**(4): p. 184-92.

37. Kauer, J.A. and R.C. Malenka, *Synaptic plasticity and addiction.* Nat Rev Neurosci, 2007. **8**(11): p. 844-58.

38. Robinson, T.E. and B. Kolb, *Structural plasticity associated with exposure to drugs of abuse.* Neuropharmacology, 2004. **47 Suppl 1**: p. 33-46.

39. Alia-Klein, N., et al., *Gene x disease interaction on orbitofrontal gray matter in cocaine addiction.* Arch Gen Psychiatry, 2011. **68**(3): p. 283-94.

40. Franklin, T.R., et al., *Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients.* Biol Psychiatry, 2002. **51**(2): p. 134-42.

41. Matochik, J.A., et al., *Frontal cortical tissue composition in abstinent cocaine abusers: a magnetic resonance imaging study.* Neuroimage, 2003. **19**(3): p. 1095-102.

42. Tanabe, J., et al., *Medial orbitofrontal cortex gray matter is reduced in abstinent substance-dependent individuals.* Biol Psychiatry, 2009. **65**(2): p. 160-4.

43. Berman, S., et al., *Abuse of amphetamines and structural abnormalities in the brain.* Ann N Y Acad Sci, 2008. **1141**: p. 195-220.

44. Chang, L., et al., *Structural and metabolic brain changes in the striatum associated with methamphetamine abuse.* Addiction, 2007. **102 Suppl 1**: p. 16-32.

45. Ersche, K.D., et al., *Abnormal structure of frontostriatal brain systems is associated with aspects of impulsivity and compulsivity in cocaine dependence.* Brain, 2011. **134**(Pt 7): p. 2013-24.

46. Parvaz, M.A., et al., *Structural integrity of the prefrontal cortex modulates electrocortical sensitivity to reward.* J Cogn Neurosci, 2012. **24**(7): p. 1560-70.

47. First, M.B., et al., *Williams J. Structured Clinical Interview for DSM-IV Axis I disorders - Patient Edition (SCID-I/P, Version 2.0)*. 1996, Biometrics Research Department, New York State Psychiatric Institute: New York.

48. Ventura, J., et al., *Training and quality assurance with the Structured Clinical Interview for DSM-IV (SCID-I/P).* Psychiatry Res, 1998. **79**(2): p. 163-73.

49. McLellan, A.T., et al., *The Fifth Edition of the Addiction Severity Index.* J Subst Abuse Treat, 1992. **9**(3): p. 199-213.

50. Lesieur, H.R. and S.B. Blume, *The South Oaks Gambling Screen (SOGS): a new instrument for the identification of pathological gamblers.* Am J Psychiatry, 1987. **144**(9): p. 1184-8.

51. Goldstein, R.Z., et al., *Role of the anterior cingulate and medial orbitofrontal cortex in processing drug cues in cocaine addiction.* Neuroscience, 2007. **144**(4): p. 1153-9.

52. Goldstein, R.Z., et al., *Anterior cingulate cortex hypoactivations to an emotionally salient task in cocaine addiction.* Proc Natl Acad Sci U S A, 2009. **106**(23): p. 9453-8.

53. Goldstein, R.Z., et al., *Oral methylphenidate normalizes cingulate activity in cocaine addiction during a salient cognitive task.* Proc Natl Acad Sci U S A, 2010. **107**(38): p. 16667-72.

54. Tomasi, D., et al., *fMRI-acoustic noise alters brain activation during working memory tasks.* Neuroimage, 2005. **27**(2): p. 377-86.

55. Tomasi, D.G. and T. Ernst, *Echo planar imaging at 4 Tesla with minimum acoustic noise.* J Magn Reson Imaging, 2003. **18**(1): p. 128-30.

56. Lee, J.H., et al., *High contrast and fast three-dimensional magnetic resonance imaging at high fields.* Magn Reson Med, 1995. **34**(3): p. 308-12.

57. Tomasi, D., et al., *Disrupted functional connectivity with dopaminergic midbrain in cocaine abusers.* PLoS One, 2010. **5**(5): p. e10815.

58. Ashburner, J. and K.J. Friston, *Voxel-based morphometry--the methods.* Neuroimage, 2000. **11**(6 Pt 1): p. 805-21.

59. Ashburner, J. and K.J. Friston, *Unified segmentation.* Neuroimage, 2005. **26**(3): p. 839-51.

60. Tardif, C.L., D.L. Collins, and G.B. Pike, *Sensitivity of voxel-based morphometry analysis to choice of imaging protocol at 3 T.* Neuroimage, 2009. **44**(3): p. 827-38.

61. Cuadra, M.B., et al., *Comparison and validation of tissue modelization and statistical classification methods in T1-weighted MR brain images.* IEEE Trans Med Imaging, 2005. **24**(12): p. 1548-65.

62. Makris, N., et al., *Decreased volume of the brain reward system in alcoholism.* Biol Psychiatry, 2008. **64**(3): p. 192-202.

63. Maldjian, J.A., et al., *An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets.* Neuroimage, 2003. **19**(3): p. 1233-9.

64. Liu, X., et al., *Common and distinct networks underlying reward valence and processing stages: a meta-analysis of functional neuroimaging studies.* Neurosci Biobehav Rev, 2011. **35**(5): p. 1219-36.

65. Gusnard, D.A., et al., *Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function.* Proc Natl Acad Sci U S A, 2001. **98**(7): p. 4259-64.

66. Buckner, R.L., J.R. Andrews-Hanna, and D.L. Schacter, *The brain's default network: anatomy, function, and relevance to disease.* Ann N Y Acad Sci, 2008. **1124**: p. 1-38.

67. Balleine, B.W. and J.P. O'Doherty, *Human and rodent homologies in action control: corticostriatal determinants of goal-directed and habitual action.* Neuropsychopharmacology, 2010. **35**(1): p. 48-69.

68. Yin, H.H. and B.J. Knowlton, *The role of the basal ganglia in habit formation.* Nat Rev Neurosci, 2006. **7**(6): p. 464-76.

69. Yin, H.H., B.J. Knowlton, and B.W. Balleine, *Inactivation of dorsolateral striatum enhances sensitivity to changes in the action-outcome contingency in instrumental conditioning.* Behav Brain Res, 2006. **166**(2): p. 189-96.

70. Porrino, L.J., et al., *The effects of cocaine: a shifting target over the course of addiction.* Prog Neuropsychopharmacol Biol Psychiatry, 2007. **31**(8): p. 1593-600.

71. Vanderschuren, L.J., P. Di Ciano, and B.J. Everitt, *Involvement of the dorsal striatum in cue-controlled cocaine seeking.* J Neurosci, 2005. **25**(38): p. 8665-70.

72. Nestor, L., R. Hester, and H. Garavan, *Increased ventral striatal BOLD activity during non-drug reward anticipation in cannabis users.* Neuroimage, 2010. **49**(1): p. 1133-43.

73. Beck, A., et al., *Ventral striatal activation during reward anticipation correlates with impulsivity in alcoholics.* Biol Psychiatry, 2009. **66**(8): p. 734-42.

74. Wrase, J., et al., *Dysfunction of reward processing correlates with alcohol craving in detoxified alcoholics.* Neuroimage, 2007. **35**(2): p. 787-94.

75. Meltzer, J.A., M. Negishi, and R.T. Constable, *Biphasic hemodynamic responses influence deactivation and may mask activation in block-design fMRI paradigms.* Hum Brain Mapp, 2008. **29**(4): p. 385-99.

76. Briand, L.A., et al., *Persistent alterations in cognitive function and prefrontal dopamine D2 receptors following extended, but not limited, access to self-administered cocaine.* Neuropsychopharmacology, 2008. **33**(12): p. 2969-80.

77. Nelson, A. and S. Killcross, *Amphetamine exposure enhances habit formation.* J Neurosci, 2006. **26**(14): p. 3805-12.

78. Wickens, J.R., et al., *Dopaminergic mechanisms in actions and habits.* J Neurosci, 2007. **27**(31): p. 8181-3.

79. Zapata, A., V.L. Minney, and T.S. Shippenberg, *Shift from goal-directed to habitual cocaine seeking after prolonged experience in rats.* J Neurosci, 2010. **30**(46): p. 15457-63.

80. Corbit, L.H. and B.W. Balleine, *The role of prelimbic cortex in instrumental conditioning.* Behav Brain Res, 2003. **146**(1-2): p. 145-57.

81. Yin, H.H., et al., *The role of the dorsomedial striatum in instrumental conditioning.* Eur J Neurosci, 2005. **22**(2): p. 513-23.

82. Huettel, S.A., Song, A.W., and McCarthy, G. , *Functional Magnetic Resonance Imaging.* Sinauer Associates, Inc., Sunderland, MA., 2008.

83. Bickel, W.K., et al., *Congruence of BOLD response across intertemporal choice conditions: fictive and real money gains and losses.* J Neurosci, 2009. **29**(27): p. 8839-46.

84. Schoemaker, P.J.H., *The expected utility model: Its variants, purposes, evidence and limitations.* Journal of Economic Literature, 1982: p. 529-563.

85. Schonberg, T., C.R. Fox, and R.A. Poldrack, *Mind the gap: bridging economic and naturalistic risk-taking with cognitive neuroscience.* Trends Cogn Sci, 2011. **15**(1): p. 11-9.

86. O'Neill, M. and W. Schultz, *Coding of reward risk by orbitofrontal neurons is mostly distinct from coding of reward value.* Neuron, 2010. **68**(4): p. 789-800.

87. Moeller, S.J., et al., *Choice to view cocaine images predicts concurrent and prospective drug use in cocaine addiction.* Drug Alcohol Depend, 2012.

88. Moeller, S.J., et al., *Enhanced choice for viewing cocaine pictures in cocaine addiction.* Biol Psychiatry, 2009. **66**(2): p. 169-76.

89. Moeller, S.J., et al., *Impaired insight in cocaine addiction: laboratory evidence and effects on cocaine-seeking behaviour.* Brain, 2010. **133**(Pt 5): p. 1484-93.

90. Gossop, M., et al., *Severity of dependence and route of administration of heroin, cocaine and amphetamines.* British Journal of Addiction, 1992. **87**(11): p. 1527-1536.

91. Patton, J.H., M.S. Stanford, and E.S. Barratt, *Factor structure of the Barratt impulsiveness scale.* J Clin Psychol, 1995. **51**(6): p. 768-74.

92. Conners, C.K., D. Erhardt, and E.P. Sparrow, *Conners' Adult ADHD Rating Scales (CAARS): Technical manual*. 1999, North Tonawanda, NY: Multi-Health.

93. Woicik, P.A., et al., *The substance use risk profile scale: A scale measuring traits linked to reinforcement-specific substance use profiles.* Addictive Behaviors, 2009. **34**(12): p. 1042-1055.

94. Dave, C., et al., *Eliciting risk preferences: When is simple better?* Journal of Risk and Uncertainty, 2010. **41**(3): p. 219-243.

95. Schonberg, T., et al., *Reinforcement learning signals in the human striatum distinguish learners from nonlearners during reward-based decision making.* J Neurosci, 2007. **27**(47): p. 12860-7.

96. Tobler, P.N., et al., *Risk-dependent reward value signal in human prefrontal cortex.* Proc Natl Acad Sci U S A, 2009. **106**(17): p. 7185-90.

97. Christopoulos, G.I., et al., *Neural correlates of value, risk, and risk aversion contributing to decision making under risk.* J Neurosci, 2009. **29**(40): p. 12574-83.

98. Tobler, P.N., et al., *Reward value coding distinct from risk attitude-related uncertainty coding in human reward systems.* J Neurophysiol, 2007. **97**(2): p. 1621-32.

99. Carroll, K.M., et al., *Cognitive function and treatment response in a randomized clinical trial of computer-based training in cognitive-behavioral therapy.* Subst Use Misuse, 2011. **46**(1): p. 23-34.

100. Verdejo-Garcia, A., et al., *Self-regulation and treatment retention in cocaine dependent individuals: a longitudinal study.* Drug Alcohol Depend, 2012. **122**(1-2): p. 142-8.

101. Schmitz, J.M., et al., *Baseline neurocognitive profiles differentiate abstainers and non-abstainers in a cocaine clinical trial.* J Addict Dis, 2009. **28**(3): p. 250-7.

102. Mohr, P.N., G. Biele, and H.R. Heekeren, *Neural processing of risk.* J Neurosci, 2010. **30**(19): p. 6613-9.

103. Rangel, A. and T. Hare, *Neural computations associated with goal-directed choice.* Curr Opin Neurobiol, 2010. **20**(2): p. 262-70.

104. Padoa-Schioppa, C., *Neurobiology of economic choice: a good-based model.* Annu Rev Neurosci, 2011. **34**: p. 333-59.

105. Rushworth, M.F., et al., *Frontal cortex and reward-guided learning and decision-making.* Neuron, 2011. **70**(6): p. 1054-69.

106. Bartra, O., J.T. McGuire, and J.W. Kable, *The valuation system: a coordinate-based meta-analysis of BOLD fMRI experiments examining neural correlates of subjective value.* Neuroimage, 2013. **76**: p. 412-27.

107. Plassmann, H., J. O'Doherty, and A. Rangel, *Orbitofrontal cortex encodes willingness to pay in everyday economic transactions.* J Neurosci, 2007. **27**(37): p. 9984-8.

108. Plassmann, H., J.P. O'Doherty, and A. Rangel, *Appetitive and aversive goal values are encoded in the medial orbitofrontal cortex at the time of decision making.* J Neurosci, 2010. **30**(32): p. 10799-808.

109. Litt, A., et al., *Dissociating valuation and saliency signals during decision-making.* Cereb Cortex, 2011. **21**(1): p. 95-102.

110. Sokol-Hessner, P., et al., *Decision value computation in DLPFC and VMPFC adjusts to the available decision time.* Eur J Neurosci, 2012. **35**(7): p. 1065-74.

111. Hare, T.A., J. Malmaud, and A. Rangel, *Focusing attention on the health aspects of foods changes value signals in vmPFC and improves dietary choice.* J Neurosci, 2011. **31**(30): p. 11077-87.

112. Hare, T.A., et al., *Transformation of stimulus value signals into motor commands during simple choice.* Proc Natl Acad Sci U S A, 2011. **108**(44): p. 18120-5.

113. Blair, K., et al., *Choosing the lesser of two evils, the better of two goods: specifying the roles of ventromedial prefrontal cortex and dorsal anterior cingulate in object choice.* J Neurosci, 2006. **26**(44): p. 11379-86.

114. Symmonds, M., et al., *Metabolic state alters economic decision making under risk in humans.* PLoS One, 2010. **5**(6): p. e11090.

115. Levy, D.J., A.C. Thavikulwat, and P.W. Glimcher, *State dependent valuation: the effect of deprivation on risk preferences.* PLoS One, 2013. **8**(1): p. e53978.

116. Konova, A.B., et al., *Effects of methylphenidate on resting-state functional connectivity of the mesocorticolimbic dopamine pathways in cocaine addiction.* JAMA Psychiatry, 2013. **70**(8): p. 857-68.

117. Rosazza, C. and L. Minati, *Resting-state brain networks: literature review and clinical applications.* Neurol Sci, 2011. **32**(5): p. 773-85.

118. Shmuel, A. and D.A. Leopold, *Neuronal correlates of spontaneous fluctuations in fMRI signals in monkey visual cortex: Implications for functional connectivity at rest.* Hum Brain Mapp, 2008. **29**(7): p. 751-61.

119. Fox, M.D. and M.E. Raichle, *Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging.* Nat Rev Neurosci, 2007. **8**(9): p. 700-11.

120. Damoiseaux, J.S. and M.D. Greicius, *Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity.* Brain Struct Funct, 2009. **213**(6): p. 525-33.

121. Hampson, M., et al., *Brain connectivity related to working memory performance.* J Neurosci, 2006. **26**(51): p. 13338-43.

122. Kelly, A.M., et al., *Competition between functional brain networks mediates behavioral variability.* Neuroimage, 2008. **39**(1): p. 527-37.

123. Cole, D.M., et al., *Nicotine replacement in abstinent smokers improves cognitive withdrawal symptoms with modulation of resting brain network dynamics.* Neuroimage, 2010. **52**(2): p. 590-9.

124. Hong, L.E., et al., *Association of nicotine addiction and nicotine's actions with separate cingulate cortex functional circuits.* Arch Gen Psychiatry, 2009. **66**(4): p. 431-41.

125. Ma, N., et al., *Addiction related alteration in resting-state brain connectivity.* Neuroimage, 2010. **49**(1): p. 738-44.

126. Upadhyay, J., et al., *Alterations in brain structure and functional connectivity in prescription opioid-dependent patients.* Brain, 2010. **133**(Pt 7): p. 2098-114.

127. Ma, N., et al., *Abnormal brain default-mode network functional connectivity in drug addicts.* PLoS One, 2011. **6**(1): p. e16560.

128. Gu, H., et al., *Mesocorticolimbic circuits are impaired in chronic cocaine users as demonstrated by resting-state functional connectivity.* Neuroimage, 2010. **53**(2): p. 593-601.

129. Kelly, C., et al., *Reduced interhemispheric resting state functional connectivity in cocaine addiction.* Biol Psychiatry, 2011. **69**(7): p. 684-92.

130. Kuczenski, R. and D.S. Segal, *Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine: comparison with amphetamine.* J Neurochem, 1997. **68**(5): p. 2032-7.

131. Volkow, N.D., et al., *Dopamine in drug abuse and addiction: results from imaging studies and treatment implications.* Mol Psychiatry, 2004. **9**(6): p. 557-69.

132. Levin, F.R., et al., *Treatment of cocaine dependent treatment seekers with adult ADHD: double-blind comparison of methylphenidate and placebo.* Drug Alcohol Depend, 2007. **87**(1): p. 20-9.

133. Li, C.S., et al., *Biological markers of the effects of intravenous methylphenidate on improving inhibitory control in cocaine-dependent patients.* Proc Natl Acad Sci U S A, 2010. **107**(32): p. 14455-9.

134. Volkow, N.D., et al., *Methylphenidate attenuates limbic brain inhibition after cocaine-cues exposure in cocaine abusers.* PLoS One, 2010. **5**(7): p. e11509.

135. Li, S.J., et al., *Cocaine administration decreases functional connectivity in human primary visual and motor cortex as detected by functional MRI.* Magn Reson Med, 2000. **43**(1): p. 45-51.

136. Diekhof, E.K., et al., *Fear is only as deep as the mind allows: a coordinate-based meta-analysis of neuroimaging studies on the regulation of negative affect.* Neuroimage, 2011. **58**(1): p. 275-85.

137. Mak, A.K., et al., *Neural correlates of regulation of positive and negative emotions: an fmri study.* Neurosci Lett, 2009. **457**(2): p. 101-6.

138. Kanske, P., et al., *How to regulate emotion? Neural networks for reappraisal and distraction.* Cereb Cortex, 2011. **21**(6): p. 1379-88.

139. Kampman, K.M., et al., *Reliability and validity of the Cocaine Selective Severity Assessment.* Addict Behav, 1998. **23**(4): p. 449-61.

140. Tiffany, S.T., et al., *The development of a cocaine craving questionnaire.* Drug Alcohol Depend, 1993. **34**(1): p. 19-28.

141. Volkow, N.D., et al., *Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral methylphenidate.* Am J Psychiatry, 1998. **155**(10): p. 1325-31.

142. Srinivas, N.R., et al., *Extensive and enantioselective presystemic metabolism of dl-threo-methylphenidate in humans.* Prog Neuropsychopharmacol Biol Psychiatry, 1991. **15**(2): p. 213-20.

143. Van Dijk, K.R., et al., *Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization.* J Neurophysiol, 2010. **103**(1): p. 297-321.

144. Van Dijk, K.R., M.R. Sabuncu, and R.L. Buckner, *The influence of head motion on intrinsic functional connectivity MRI.* Neuroimage, 2012. **59**(1): p. 431-8.

145. Tomasi, D. and N.D. Volkow, *Language network: segregation, laterality and connectivity.* Mol Psychiatry, 2012. **17**(8): p. 759.

146. Tomasi, D. and N.D. Volkow, *Abnormal functional connectivity in children with attention-deficit/hyperactivity disorder.* Biol Psychiatry, 2012. **71**(5): p. 443-50.

147. Worsley, K.J., et al., *A three-dimensional statistical analysis for CBF activation studies in human brain.* J Cereb Blood Flow Metab, 1992. **12**(6): p. 900-18.

148. Eickhoff, S.B., et al., *A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data.* Neuroimage, 2005. **25**(4): p. 1325-35.

149. Brody, A.L., et al., *Neural substrates of resisting craving during cigarette cue exposure.* Biol Psychiatry, 2007. **62**(6): p. 642-51.

150. Sinha, R., et al., *Neural activity associated with stress-induced cocaine craving: a functional magnetic resonance imaging study.* Psychopharmacology (Berl), 2005. **183**(2): p. 171-80.

151. Bethancourt, J.A., Z.Z. Camarena, and G.B. Britton, *Exposure to oral methylphenidate from adolescence through young adulthood produces transient effects on hippocampal-sensitive memory in rats.* Behav Brain Res, 2009. **202**(1): p. 50-7.

152. Abraham, A.D., C.L. Cunningham, and K.M. Lattal, *Methylphenidate enhances extinction of contextual fear.* Learn Mem, 2012. **19**(2): p. 67-72.

153. Koob, G.F. and M. Le Moal, *Addiction and the brain antireward system.* Annu Rev Psychol, 2008. **59**: p. 29-53.

154. Margulies, D.S., et al., *Mapping the functional connectivity of anterior cingulate cortex.* Neuroimage, 2007. **37**(2): p. 579-88.

155. Xu, J., et al., *White matter integrity is associated with treatment outcome measures in cocaine dependence.* Neuropsychopharmacology, 2010. **35**(7): p. 1541-9.

156. Haber, S.N., J.L. Fudge, and N.R. McFarland, *Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum.* J Neurosci, 2000. **20**(6): p. 2369-82.

157. Belin, D. and B.J. Everitt, *Cocaine seeking habits depend upon dopamine-dependent serial connectivity linking the ventral with the dorsal striatum.* Neuron, 2008. **57**(3): p. 432-41.

158. Everitt, B.J., et al., *Review. Neural mechanisms underlying the vulnerability to develop compulsive drug-seeking habits and addiction.* Philos Trans R Soc Lond B Biol Sci, 2008. **363**(1507): p. 3125-35.

159. Kober, H., et al., *Prefrontal-striatal pathway underlies cognitive regulation of craving.* Proc Natl Acad Sci U S A, 2010. **107**(33): p. 14811-6.

160. Birn, R.M., et al., *Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI.* Neuroimage, 2006. **31**(4): p. 1536-48.

161. Chang, C. and G.H. Glover, *Effects of model-based physiological noise correction on default mode network anti-correlations and correlations.* Neuroimage, 2009. **47**(4): p. 1448-59.

162. Hannestad, J., et al., *Clinically relevant doses of methylphenidate significantly occupy norepinephrine transporters in humans in vivo.* Biol Psychiatry, 2010. **68**(9): p. 854-60.

163. Moron, J.A., et al., *Dopamine uptake through the norepinephrine transporter in brain regions with low levels of the dopamine transporter: evidence from knock-out mouse lines.* J Neurosci, 2002. **22**(2): p. 389-95.

164. Gawin, F., C. Riordan, and H. Kleber, *Methylphenidate treatment of cocaine abusers without attention deficit disorder: a negative report.* Am J Drug Alcohol Abuse, 1985. **11**(3-4): p. 193-7.

165. Grabowski, J., et al., *Replacement medication for cocaine dependence: methylphenidate.* J Clin Psychopharmacol, 1997. **17**(6): p. 485-8.

166. Collins, S.L., et al., *Response to cocaine, alone and in combination with methylphenidate, in cocaine abusers with ADHD.* Drug Alcohol Depend, 2006. **82**(2): p. 158-67.

167. Konova, A.B., S.J. Moeller, and R.Z. Goldstein, *Common and distinct neural targets of treatment: changing brain function in substance addiction.* Neurosci Biobehav Rev, 2013. **37**(10 Pt 2): p. 2806-17.

168. Volkow, N.D., et al., *Methylphenidate decreased the amount of glucose needed by the brain to perform a cognitive task.* PLoS One, 2008. **3**(4): p. e2017.

169. Marquand, A.F., et al., *Pattern classification of working memory networks reveals differential effects of methylphenidate, atomoxetine, and placebo in healthy volunteers.* Neuropsychopharmacology, 2011. **36**(6): p. 1237-47.

170. Tomasi, D., et al., *Methylphenidate enhances brain activation and deactivation responses to visual attention and working memory tasks in healthy controls.* Neuroimage, 2011. **54**(4): p. 3101-10.

171. Mehta, M.A., et al., *Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain.* J Neurosci, 2000. **20**(6): p. RC65.

172. Epstein, J.N., et al., *ADHD- and medication-related brain activation effects in concordantly affected parent-child dyads with ADHD.* J Child Psychol Psychiatry, 2007. **48**(9): p. 899-913.

173. Albertson, D.N., et al., *Distinctive profiles of gene expression in the human nucleus accumbens associated with cocaine and heroin abuse.* Neuropsychopharmacology, 2006. **31**(10): p. 2304-12.

174. Frankel, P.S., et al., *Striatal and ventral pallidum dynorphin concentrations are markedly increased in human chronic cocaine users.* Neuropharmacology, 2008. **55**(1): p. 41-6.

175. Buttner, A., et al., *Widespread axonal damage in the brain of drug abusers as evidenced by accumulation of beta-amyloid precursor protein (beta-APP): an immunohistochemical investigation.* Addiction, 2006. **101**(9): p. 1339-1346.

176. Mash, D.C., et al., *Dopamine transport function is elevated in cocaine users.* Journal of Neurochemistry, 2002. **81**(2): p. 292-300.

177. Little, K.Y., et al., *Decreased brain dopamine cell numbers in human cocaine users.* Psychiatry Research, 2009. **168**(3): p. 173-180.

178. Miller, G.A. and J.P. Chapman, *Misunderstanding analysis of covariance.* J Abnorm Psychol, 2001. **110**(1): p. 40-8.

179. Weinberger, A.H. and M. Sofuoglu, *The impact of cigarette smoking on stimulant addiction.* Am J Drug Alcohol Abuse, 2009. **35**(1): p. 12-7.

180. Kalman, D., S.B. Morissette, and T.P. George, *Co-morbidity of smoking in patients with psychiatric and substance use disorders.* Am J Addict, 2005. **14**(2): p. 106-23.

181. Lasser, K., et al., *Smoking and mental illness: A population-based prevalence study.* JAMA, 2000. **284**(20): p. 2606-10.

182. Budney, A.J., et al., *Nicotine and caffeine use in cocaine-dependent individuals.* J Subst Abuse, 1993. **5**(2): p. 117-30.

183. Grant, B.F., et al., *Nicotine dependence and psychiatric disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions.* Arch Gen Psychiatry, 2004. **61**(11): p. 1107-15.

184. Fadda, F. and Z.L. Rossetti, *Chronic ethanol consumption: from neuroadaptation to neurodegeneration.* Prog Neurobiol, 1998. **56**(4): p. 385-431.

185. Schwartz, D.L., et al., *Global and local morphometric differences in recently abstinent methamphetamine-dependent individuals.* Neuroimage, 2010. **50**(4): p. 1392-401.

186. Taki, Y., et al., *Both global gray matter volume and regional gray matter volume negatively correlate with lifetime alcohol intake in non-alcohol-dependent Japanese men: a volumetric analysis and a voxel-based morphometry.* Alcohol Clin Exp Res, 2006. **30**(6): p. 1045-50.

187. Fein, G., et al., *Brain atrophy in long-term abstinent alcoholics who demonstrate impairment on a simulated gambling task.* Neuroimage, 2006. **32**(3): p. 1465-71.

188. Almeida, O.P., et al., *Smoking is associated with reduced cortical regional gray matter density in brain regions associated with incipient Alzheimer disease.* Am J Geriatr Psychiatry, 2008. **16**(1): p. 92-8.

189. Durazzo, T.C., et al., *Chronic cigarette smoking and heavy drinking in human immunodeficiency virus: consequences for neurocognition and brain morphology.* Alcohol, 2007. **41**(7): p. 489-501.

190. Yuan, Y., et al., *Gray matter density negatively correlates with duration of heroin use in young lifetime heroin-dependent individuals.* Brain Cogn, 2009. **71**(3): p. 223-8.

191. Liu, X., et al., *Smaller volume of prefrontal lobe in polysubstance abusers: a magnetic resonance imaging study.* Neuropsychopharmacology, 1998. **18**(4): p. 243-52.

192. Fein, G., V. Di Sclafani, and D.J. Meyerhoff, *Prefrontal cortical volume reduction associated with frontal cortex function deficit in 6-week abstinent crack-cocaine dependent men.* Drug Alcohol Depend, 2002. **68**(1): p. 87-93.

193. Sim, M.E., et al., *Cerebellar gray matter volume correlates with duration of cocaine use in cocaine-dependent subjects.* Neuropsychopharmacology, 2007. **32**(10): p. 2229-37.

194. Brody, A.L., et al., *Differences between smokers and nonsmokers in regional gray matter volumes and densities.* Biol Psychiatry, 2004. **55**(1): p. 77-84.

195. Wobrock, T., et al., *Effects of abstinence on brain morphology in alcoholism: a MRI study.* Eur Arch Psychiatry Clin Neurosci, 2009. **259**(3): p. 143-50.

196. Chanraud, S., et al., *Dual tasking and working memory in alcoholism: relation to frontocerebellar circuitry.* Neuropsychopharmacology, 2010. **35**(9): p. 1868-78.

197. Hill, S.Y., et al., *Disruption of orbitofrontal cortex laterality in offspring from multiplex alcohol dependence families.* Biol Psychiatry, 2009. **65**(2): p. 129-36.

198. Medina, K.L., et al., *Prefrontal cortex volumes in adolescents with alcohol use disorders: unique gender effects.* Alcohol Clin Exp Res, 2008. **32**(3): p. 386-94.

199. Medina, K.L., et al., *Prefrontal cortex morphometry in abstinent adolescent marijuana users: subtle gender effects.* Addict Biol, 2009. **14**(4): p. 457-68.

200. Orr, C., et al., *Altered resting-state connectivity in adolescent cannabis users.* Am J Drug Alcohol Abuse, 2013. **39**(6): p. 372-81.

201. Peters, J., et al., *Lower ventral striatal activation during reward anticipation in adolescent smokers.* Am J Psychiatry, 2011. **168**(5): p. 540-9.

202. Chanraud, S., et al., *Brain morphometry and cognitive performance in detoxified alcohol-dependents with preserved psychosocial functioning.* Neuropsychopharmacology, 2007. **32**(2): p. 429-38.

203. Fein, G., et al., *Cortical gray matter loss in treatment-naive alcohol dependent individuals.* Alcohol Clin Exp Res, 2002. **26**(4): p. 558-64.

204. Canterberry, M., et al., *Sustained reduction of nicotine craving with real-time neurofeedback: exploring the role of severity of dependence.* Nicotine Tob Res, 2013. **15**(12): p. 2120-4.

205. Hanlon, C.A., et al., *Reduction of cue-induced craving through realtime neurofeedback in nicotine users: the role of region of interest selection and multiple visits.* Psychiatry Res, 2013. **213**(1): p. 79-81.

206. Li, X., et al., *Volitional reduction of anterior cingulate cortex activity produces decreased cue craving in smoking cessation: a preliminary real-time fMRI study.* Addict Biol, 2013. **18**(4): p. 739-48.

207. Sulzer, J., et al., *Neurofeedback-mediated self-regulation of the dopaminergic midbrain.* Neuroimage, 2013. **83**: p. 817-25.

208. Greer, S.M., et al., *Control of nucleus accumbens activity with neurofeedback.* Neuroimage, 2014.