Title: 5HT2CR Balance in Brain Connectivity in Cocaine Dependence

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Study Identification

1. * **Select the Principal Investigator:**
   Frederick Moeller

2. * **Study Title:**
   5-HT2AR: 5HT2CR Balance in Brain Connectivity in Cocaine Dependence

3. * **Is this a student or trainee project in which activities will be carried out by that individual under your supervision (for example, dissertation or degree-required projects):**
   - ○ Yes
   - ● **No**

4. * **Please select the primary department or center that this study is being conducted under:**
   Institute for Drug and Alcohol Studies

5. **If this is associated with other VCU IRB protocols or a resubmission of a withdrawn/closed protocol, select the VCU IRB numbers assigned to those studies:**

ID	Title	PI
HM20000294	Pre-Requisite Evaluation and Screening for CARI Research Eligibility and ENrollment (PRE-SCREEN)	Lori Keyser-Marcus

6. **Select all individuals who are permitted to edit the IRB protocol and should be copied on communications (study staff will be entered later). These individuals will be referred to as protocol editors:**

Last Name	First Name	E-Mail	Phone	Mobile
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]		
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7. * **Select one of the following that applies to the project (selection will branch to new pages):**
   Note: VCU IRB offers guidance for many types of studies, including secondary data analysis studies, internet research, registries, EFIC, HUD, and Emergency Use protocols.
   See *https://research.vcu.edu/human_research/guidance.htm*
   - ● **Research Project or Clinical Investigation [*most exempt, expedited, and full board research studies]**
   - ○ Exception from Informed Consent (EFIC) for Planned Emergency Research
   - ○ Humanitarian Use of Device for Treatment or Diagnosis
   - ○ Humanitarian Use of Device for Clinical Investigation
   - ○ Emergency Use of Investigational Drug, Biologic or Device
   - ○ Treatment Use (Expanded Access to Investigational Product for Treatment Use)
   - ○ Center or Institute Administrative Grant Review
   - ○ Request for Not Human Subject Research Determination (i.e. request a letter confirming that IRB review is not required)

HM15289 - Frederick Moeller
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Federal Regulations

1. * **Is this a FDA regulated study?**

   FDA regulated research includes all clinical investigations involving a test article and a human subject(s) that has been submitted for approval to the FDA or may be submitted in the future.
   Check Yes if
   - **the study involves an IND/IDE, abbreviated IDE, IND/IDE exemption, HUD, expanded access, or is otherwise subject to 21 CFR 56,**
   - **the study involves a test article being administered or dispensed to subjects NOT according to a clinicians' medical judgment but rather, per the study protocol, OR**
   - **the study does not involve a test article but intends to provide safety or efficacy data to the FDA.**

   ◉ **Yes** ○ No

2. * **Indicate the FDA regulated product(s) this study involves:**
   - ☑ **Drug**
   - ☐ Medical Device
   - ☐ Biologic
   - ☐ Dietary Supplement
   - ☐ Food/Food Additive
   - ☐ Color Additive
   - ☐ Electronic Products for Human Use (radiation producing)
   - ☐ Other

3. * **Is this study supported by the Department of Defense (DoD):**
   - ○ Yes
   - ◉ **No**

4. * **Check if any of the following funding sources apply to this research (including Direct and/or Indirect funding):**
   - ☐ Department of Education
   - ☐ Department of Justice
   - ☐ Environmental Protection Agency
   - ☑ **None of the above**

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Background, Rationale and Goals

1. * **Describe the study's background and what is currently known from the scientific literature, including citations, or upload a citation list in document upload. Use lay language whenever possible.**

A. Significance

Cocaine dependence continues as a significant health problem within the United States. The 5-HT neurotransmitter system has emerged as an important, therapeutically-overlooked target in the quest to understand vulnerability to addiction and relapse and to maximize treatment for this complex disorder. The central research theme of this grant revolves around our findings to suggest that impulsive action and cue reactivity are mechanistically-linked to disrupted 5-HT signaling through the 5-HT2AR and 5-HT2CR localized to prefrontal-striatal-thalamic circuitry; we postulate that restoration of the 5-HT2AR:5-HT2CR homeostasis will repair corticostriatal deficits and ameliorate relapse. The overall hypothesis that will be examined in this project is that homeostatic interactions between 5-HT2AR and 5-HT2CR contribute similarly to impulsive action and cue reactivity in overlapping brain prefrontal-striatal-thalamic circuits in cocaine-dependent human subjects. Specifically, this project will parallel preclinical studies showing that reduced function of the 5-HT2CR enhances the behavioral response to a 5-HT2AR antagonist. Given the importance of impulsivity and cue reactivity in the risk for initiation of drug use and its persistence as well relapse to addiction, the outcomes of these studies will contribute to a greater appreciation of the serotonergic neurobiology underlying these constructs as a means to conceptually advance new approaches to treatment and direct the next generation of pharmacotherapy discovery and development for addiction.

B. Background

Impulsive action and cue reactivity are linked in cocaine dependence. There is a growing appreciation of impulsivity and cue reactivity as interlocked contributors to relapse vulnerability, a cardinal facet of addiction.22;57 Impulsivity is defined clinically as rapid unplanned reactions to stimuli without regard to the consequences,34 and this multidimensional clinical construct is recognized to play a key role in the initiation and maintenance of addictions (for review22). Highly impulsive cocaine-dependent subjects are more prone to leaving treatment.37 Cue reactivity is also thought to have a significant effect on treatment success.47 Recent clinical and preclinical studies from our group support a relationship between behavioral laboratory measures of impulsivity and cue reactivity and cocaine dependence. In clinical studies, cocaine users had significantly higher impulsivity (measured by questionnaire and a behavioral laboratory measure) as well as increased cue reactivity (measured by an attentional bias for cocaine related words on the Stroop task). 27 These data suggest that impulsivity and cue reactivity are related processes and that there may be an associated underlying neurobiology.

Indeed, parallel studies in animals revealed that cocaine increases impulsive responses in an analogous rat model of impulsivity, and animals who exhibit high impulsivity develop cocaine self-administration more rapidly1 and show higher cue reactivity to cocaine- associated stimuli. Together, these data indicate that impulsivity and cue reactivity are related processes that may be mediated by a common underlying neurobiology.

5-HT2AR:5-HT2CR balance is implicated in impulsivity and cue reactivity. Clinical studies have consistently found an association between measures of 5-HT function and impulsive behaviors, including impulsive aggression.34 However, with the accessibility to more selective pharmacologic tools, preclinical studies have gone one step further to identify pivotal roles for specific 5-HT receptors in impulsive behaviors. Of relevance to the present proposal, the majority of preclinical studies report an inverse relationship between 5-HT2AR and 5-HT2CR function related to impulsivity in that 5-HT2AR antagonists and 5-HT2CR agonists reduce impulsive responding. These studies further support an associated neurobiology underlying impulsivity and cue reactivity, possibly due to an enhanced 5-HT2AR function and/or reduced 5-HT2CR tone.

Few studies have examined the relationship between 5-HT receptor function and cue reactivity in humans. Preliminary studies from our group demonstrate that African American cocaine-dependent subjects carrying the C allele (Ser23 variant) of the Cys23Ser 5-HT2CR SNP displayed significantly higher attentional bias scores on the cocaine Stroop task. The Cys23Ser SNP appears to result in altered 5-HT2CR function, perhaps through modified desensitization/resensitization properties,43 suggesting that enhanced cue reactivity is related to expression of a less-functional Ser23 5-HT2CR protein. These data are consistent with preliminary studies which demonstrate that selective elimination of the 5-HT2CR in nucleus accumbens (NAc) resulted in (1) concomitant increases in impulsive action and cue reactivity and (2) an enhanced potency of a 5-HT2AR antagonist to suppress impulsivity. These data support the utility of the Ser23 variant expression as a model of reduced 5-HT2CR function to explore the implications of 5-HT2AR:5-HT2CR homeostasis in impulsivity and cue reactivity in cocaine-dependent subjects.

The structural neurobiology of impulsivity and cue reactivity overlaps in prefrontal-striatal-thalamic circuits. The neuroanatomy of impulsivity and cue reactivity has been studied in humans using a combined approach of functional neuroimaging during the conduct of an appropriate behavioral laboratory measure. Review of recent studies indicates that several brain regions within prefrontal-striatal-thalamic circuitry display increased activation during an impulsivity task as well as upon exposure to drug-associated cues.4;6
Interestingly, these same brain regions have been shown to be sites of 5-HT2AR and 5-HT2CR in human brain.17;24;33;44 Thus, an overarching hypothesis of this project is that nodes within prefrontal-striatal-thalamic circuitry are likely sites of action through which the 5-HT2AR:5-HT2CR imbalance regulates expression of impulsivity and cue reactivity.

The overall goal of this project is to evaluate the interaction between 5-HT2AR and 5-HT2CR in the functional circuitry underlying impulsivity and cue reactivity associated with cocaine addiction. Specifically, this project will evaluate the role of the 5-HT2CR:5-HT2AR balance in impulsive action and cue reactivity in cocaine-dependent subjects as compared to non-drug using controls. Subjects will be selected based on prescreening for the functionally-relevant 5-HT2CR Cys23Ser SNP. We are currently employing fMRI- based DCM to examine the neurocircuitry of addictions29 given its value in informing the causal influences of one brain region over another underlying behaviors.55 In the present project, we will employ DCM to uncover the effective connectivity within nodes of the neurocircuitry involved in impulsivity and cue reactivity

C. Preliminary Progress

1. Impulsivity and cue reactivity are interrelated constructs:
Recent studies support a relationship between behavioral laboratory measures of impulsive action and cue reactivity in both humans27 and animals. We measured impulsivity and cue reactivity in 37 cocaine dependent subjects and 32 non-drug using controls using the Barratt Impulsiveness Scale (BIS), a common clinical instrument for the evaluation of motor impulsivity, a continuous performance test [immediate memory task (IMT)], a behavioral measure of “impulsive action”, and the cocaine word Stroop task (cue reactivity). Results revealed that cocaine users had significantly higher impulsivity as measured both by the BIS and
IMT, and also had an attentional bias for cocaine-related words on the Stroop task. Within cocaine-dependent subjects, there was a significant correlation between attentional bias and commission errors on the IMT. This correlation between impulsivity and cue reactivity is not simply due to attentional processes as the number of correct detections (a measure of attention) on the IMT does not correlate with attentional bias on the cocaine Stroop. Parallel studies performed in animals demonstrated a positive correlation (r=0.25, p=0.05) between levels of impulsive action and cue reactivity; this correlation is also unrelated to attentional deficits as % accuracy was identical in high impulsivity (HI) and low impulsivity (LI) rats. These data suggest that impulsivity and cue reactivity are related processes and that there may be an associated underlying neurobiology.

2. Shared neural circuits are engaged in impulsivity and cue reactivity:
The neuroanatomy of impulsivity has been studied in humans employing fMRI during Go-NoGo tasks in which subjects must withhold a pre-potent response. The inability to withhold the response during a “NoGo” stimulus is considered a commission error, and is operationally defined as an impulsive response. Several recent studies using Go-NoGo paradigms in conjunction with fMRI have identified a pattern of activated brain regions during performance of the task, using the contrast of “NoGo” minus “Go. When summarized, these studies indicate a putative prefrontal-striatal-thalamic circuit associated with the ability to withhold an impulsive response.

Several brain regions are identified as displaying increased activation both during response inhibition and upon exposure to drug cues, including the inferior, middle, and superior frontal gyrus in the prefrontal cortex (PFC), and ventral striatal regions including the caudate (indicated by blue font in P1-Tables 1 and 2) when compared to brain circuits shown in imaging studies to be activated upon exposure of substance-dependent subjects to drug-related cues. Interestingly, these same prefrontal cortical and stratal brain regions are enriched in 5-HT2AR and 5-HT2CR in human brain. Thus, the overarching hypothesis of this project is that ventrolateral and dorsolateral prefrontal cortices and striatum are likely sites of action in which the 5-HT2AR:5-HT2CR imbalance underlies expression of impulsivity and cue reactivity.

3. 5-HT2CR SNP is associated with cue reactivity phenotype.
Based on previous preclinical studies from our research group and others , hypofunctionality of 5-HT2CR signal transduction may play a key
role in impulsive action and cue reactivity, and this hypothesis will be explored in Project 2 (of funding proposal). In this project, we tested the hypothesis that the Cys23Ser SNP (rs6318) of the 5-HT2CR gene (HTR2C) was associated with attentional bias in cocaine dependent subjects. Prior studies have associated this polymorphism with the treatment response to clozapine50 and antipsychotic induced weight gain, however, one study suggested that this SNP was not associated with alcohol dependence.20 Our present study demonstrated that cocaine-dependent subjects (n=50) showed a higher attentional bias score than non-drug using controls (n = 20; p = 0.01). Cocaine dependent subjects with one or two C alleles, which confers the Ser23 form of the receptor (males with CC genotype and females with CC or CG genotype) displayed higher attentional bias for the entire task (p = 0.03).
In the African American cocaine-dependent individuals, there was a significant difference between individuals with C and G alleles of the 5-HT2CR in average attentional bias for the Stroop task, and subjects with the C allele had higher attentional bias (p = 0.02) These results suggest that the 5-HT2CR Ser23 polymorphism is related to attentional bias (cue reactivity) in cocaine-dependent subjects.

4. The nonselective 5-HT2AR antagonist mirtazapine reduces attentional bias and brain activation in regions important for impulsivity and cue reactivity.
To test the hypothesis that a 5-HT2AR:5-HT2CR imbalance underlies impulsivity and cue reactivity inhumans, we will investigate the interaction of the 5-HT2CR Cys23Ser SNP and a 5-HT2AR antagonist on the functional circuitry affiliated with performance of the Go-NoGo (Specific Aim 1) and cocaine-word Stroop task (Specific Aim 2). There are no FDA-approved selective 5-HT2AR antagonists available, thus we will employ the non-selective 5-HT2AR antagonist mirtazapine. This pilot study assessed the biobehavioral effects of mirtazapine in cocaine-dependent subjects. Cocaine-dependent subjects (n=6) received a dose of mirtazapine (30 mg) or placebo in randomized order separated by at least 72 hours prior to performing an event-related Go-NoGo and an attentional bias task in the fMRI (See behavioral methods below). For the Go-NoGo task, there are two levels of difficulty (Easy and Hard). For the contrast "Hard NoGo correct trials" minus "Easy NoGo correct trials" (Hard minus Easy), fMRI second-level (random effects) analysis using the SPM8 toolbox for statistical nonparametric mapping (SnPM) showed that there were two clusters with decreased activation after mirtazapine relative to placebo (uncorrected 2-tailed cluster $p < 0.05$, number of voxels in cluster [k] > 340;
cluster-defining threshold = 2.4). These clusters were found in portions of left (L) middle occipital gyrus (g), bilateral (LR) lingual g, and LR calcarine g. In addition, there were three clusters that showed a trend toward decreased activation after mirtazapine relative to placebo (SnPM uncorrected 2-tailed cluster $p < 0.10$, $k > 188$; cluster-defining threshold = 2.4). These clusters were found in LR precentral g, L postcentral g, L middle frontal g, L inferior frontal g (pars opercularis), and Right (R) superior temporal g. Note that, although nonparametric analysis and uncorrected probability levels were used in this pilot data because of small sample size, sufficient numbers of subjects will be recruited so that standard SPM8 parametric analysis with corrected significance levels will be used in this project (see fMRI Power Analysis section). There was no suprathreshold increase in Go- NoGo activation after mirtazapine relative to placebo.

2. * **Describe the study hypothesis and/or research questions. Use lay language whenever possible.**
Cocaine abuse and dependence continue to extract considerable personal, health and societal tolls in the U.S. and the world. The cycling progressive nature of this disorder stymies efforts to stay abstinent with relapse often precipitated by impulsive behavior and craving in the face of exposure to cocaine-associated cues (cue reactivity). The overall goal of this project is to evaluate the role of molecular interactions between 5-HT2AR and 5-HT2CR in behavioral phenotypes that confer risk for cocaine dependence and relapse. Specifically, this project will evaluate the role of the 5-HT2CR:5-HT2AR balance in impulsive action and cue reactivity in cocaine-dependent subjects as compared to non-drug using controls. Brain and behavioral responses to the 5-HT2AR blocking medication mirtazapine will be compared between subjects who have high and low functioning of the 5-HT2CR based on presence of a specific, functionally-relevant single nucleotide polymorphism (SNP) of the 5-HT2CR (Cys23Ser). The 5-HT2CR Cys23Ser SNP is thought to decrease the function of the protein and a preliminary observation indicates cocaine-dependent subjects carrying the CC genotype (Ser23 protein variant) display significantly higher cue reactivity. For Aims 1 and 2, two fMRI analysis methods will be used: 1) a voxelwise whole brain analysis; 2) a region of interest analysis based on proposed integrative circuitry shown in the model below. Because neuroimaging studies have shown that performance of impulsive action tasks and exposure to cocaine-associated cues (cue reactivity paradigms) activate brain regions in brain circuits in humans, impulsive action and cue reactivity may be engendered in related pathways. To explore this hypothesis, we will employ functional magnetic resonance imaging (fMRI)-based dynamic causal modeling (DCM) to ascertain the causal influences of one brain region over another. Employing DCM, we will uncover the effective connectivity within nodes of the neurocircuitry involved in impulsive action and cue reactivity. This project will parallel preclinical work studying the relationship between 5-HT2AR and 5-HT2CR on impulsive action and cue reactivity. Our working hypothesis is that cocaine-dependent subjects that carry the less functional 5-HT2CR SNP will have a greater brain response to a 5-HT2AR antagonist while performing impulsive action and cue reactivity tasks, as shown by regional activation and effective connectivity within a prefrontal-striatal-thalamic circuit.

3. * **Describe the study's specific aims or goals. Use lay language whenever possible.**
Specific Aim 1. To examine the interaction of the serotonin receptor (5-HTR) type-2C Cys23Ser single nucleotide polymorphism (SNP) and a 5-HT2AR antagonist on the functional circuitry underlying impulsive action. We will test the hypotheses that 1) cocaine-dependent subjects displaying the Ser23 5-HT2CR genotype will show the highest fMRI activation and 2) greatest reduction in fMRI activation following the 5-HT2AR antagonist mirtazapine related to levels of impulsivity (Go- NoGo task) relative to controls with the Ser23 polymorphism, cocaine users without the polymorphism, and controls without the polymorphism, supporting a functional balance between 5-HT2AR:5-HT2CR in impulsivity in this patient population.

Specific Aim 2. To examine the interaction of the 5-HT2CR Cys23Ser SNP and a 5-HT2AR antagonist on the functional circuitry underlying cue reactivity. We will test the hypothesis that a functional balance between 5-HT2AR:5-HT2CR in cue reactivity exists in that 1) cocaine-dependent subjects displaying the Ser23 5-HT2CR genotype will present the highest fMRI activation and 2) greatest reduction in fMRI activation following the 5-HT2AR antagonist mirtazapine in the attentional bias task relative to controls with the Ser23 polymorphism, cocaine users without the polymorphism, and controls without the polymorphism.

Specific Aim 3. To explore the effective connectivity involved in the 5-HT2AR:5-HT2CR homeostasis impulsive action and cue reactivity. We will employ effective connectivity analyses using fMRI-based DCM to test the hypothesis that mirtazapine reduces impulsivity (Go-NoGo) and cue reactivity (attentional bias) greater in cocaine dependent subjects with the Ser23 polymorphism compared to controls with the Ser23 polymorphism, cocaine users without the polymorphism, and controls without the polymorphism through an increased prefrontal cortex-striatum (“top-down”) connectivity.

Exploratory Aim. To explore interactions between other 5-HT2CR SNPs and brain activation after a 5- HT2AR antagonist. This exploratory analysis will examine other 5-HT2AR and 5-HT2CR polymorphisms that may need to be included as covariates in the analysis of the relationship between functional imbalance between 5-HT2AR and 5-HT2CR in the prefrontal-striatal-thalamic circuitry.

4. * **Describe the scientific benefit or importance of the knowledge to be gained:**

As the majority of clinical trials run through CARI will involve pharmacotherapies and/or behavioral therapies for substance dependence, it is anticipated that study findings (for those trials) will improve our understanding of pharmacotherapeutic mechanisms in substance dependence, and ultimately allow for development of a clinically useful biomarker to aid in the treatment of substance dependence.

5. * **Describe any potential for direct benefits to participants in this study:**
No direct benefits to subjects are anticipated from taking part in the study.

6. * **Describe any potential for direct social impact in this study . For example, any engagement with specific communities to respond to community-identified needs, or ways the study will strengthen the well-being of the specific communities if applicable:**

7. Upload a supporting citation list if applicable:

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Study Population

1. * **Provide the maximum number of individuals that**

   1. May participate in any study interaction or intervention (Including screening, consenting, and study activities)
   AND/OR
   2. You obtain any data/specimens about (regardless of identifiability)

   at VCU and at other sites under the VCU IRB's oversight. See the help text for additional guidance.
   400

2. **If this is a multi-Center Project, what is the maximum anticipated number of subjects across all sites?**

3. * **Provide justification for the sample size by explaining how you arrived at the expected number of participants and why this number is adequate for answering the research questions:**
   Subjects will consist of 25 male and 25 female subjects with current cocaine dependence and 50 age and gender matched non-drug using control subjects. We expect to recruit and consent approximately 400 subjects to the study. Of these we expect 100 subjects to successfully complete the entire study.

4. * **List the study inclusion criteria:**
   Cocaine Dependent Subjects

   To participate in the study, participants must meet the following criteria.
   1. Be English-speaking volunteers
   2. Be aged between 18 and 60 years
   3. Meet DSM-5 criteria for cocaine dependence
   4. Have a self-reported history of using cocaine
   5. Have hematology and chemistry laboratory tests that are within reference limits (10%) with the following exceptions: hemoglobin and hematocrit within normal limits (for fMRI).
   6. Have a baseline EKG that demonstrates clinically normal sinus rhythm, clinically normal conduction, and no clinically significant abnormalities
   7. Have a medical history and physical examination demonstrating no clinically significant contraindications for study participation, in the judgment of the admitting physician and the principal investigator.
   8. Have no metal fragments or other bodily metal (e.g., pacemaker) or significant claustrophobia that would put the subjects at risk for MRI scanning.

   Non-Drug Using Controls

   To participate in the study, participants must meet the following criteria.
   1. Be English-speaking volunteers
   2. Be aged between 18 and 60 years
   3. Have no past history of Psychiatric or non-Psychiatric medical disorders which could affect the central nervous system as assessed by SCID and physical examination.
   4. Have hematology and chemistry laboratory tests that are within reference limits (10%), with the following exceptions: hemoglobin and hematocrit within normal limits (for fMRI)
   5. Have a baseline EKG that demonstrates clinically normal sinus rhythm, clinically normal conduction, and no clinically significant abnormalities
   6. Have a medical history and brief physical examination demonstrating no clinically significant contraindications for study participation, in the judgment of the admitting physician and the Principal investigator.
   7. Have no metal fragments or other bodily metal (pacemaker) or significant claustrophobia that would put the subjects at risk for MRI scanning.

5. * **List the study exclusion criteria:**
   Cocaine Dependent Subjects

   Potential participants will be excluded from participation in the study if any of the following conditions apply:
   1. Have any history or evidence suggestive of seizure disorder or brain injury.
   2. Have any previous medically adverse reaction to mirtazapine or other antidepressants.
   3. Have neurological or psychiatric disorders, such as (a) psychosis, bipolar illness or major depression as assessed by SCID; (b) organic brain disease or dementia assessed by clinical interview; (c) history of any psychiatric disorder that would require ongoing treatment or that would make study compliance difficult; and (d) history of suicide attempts within the past 3 months and/or current suicidal ideation/plan.
   4. Have evidence of uncontrolled clinically significant heart disease or hypertension, as determined by the PI.
   5. Have evidence of non-psychiatric medical illness including neuroendocrine, autoimmune, renal, hepatic, or active infectious disease.
   6. Use of any medications or drugs that can affect the central nervous system other than cocaine, marijuana, alcohol caffeine and nicotine.
   7. Have a positive HIV test.
   8. Be pregnant or nursing. Other females must either be unable to conceive (i.e., surgically sterilized, sterile, or postmenopausal) or be using a reliable form of contraception (e.g., abstinence, birth control pills, intrauterine device, condoms, or spermicide). All females must provide negative pregnancy urine tests before study entry, weekly during the study, and at the end of study participation.
   9. Have any other illness, condition, or use of psychotropic medications, which in the opinion of the PI and/or the admitting physician would preclude safe and/or successful completion of the study.

   Non-Drug Using Controls

   Potential participants will be excluded from participation in the study if any of the following conditions apply:
   1. Meet DSM-5 criteria for any current or past Axis I disorder.
   2. Meet DSM-5 criteria for an Axis II diagnosis of Borderline or Antisocial Personality Disorder.
   3. Have any history or evidence suggestive of seizure disorder or brain injury.
   4. Have any previous medically adverse reaction to mirtazapine or other antidepressants.
   5. Have evidence of uncontrolled clinically significant heart disease or hypertension, as determined by the PI.
   6. Have evidence of medical illness including neuroendocrine, autoimmune, renal, hepatic, or active infectious disease.
   7. Use of any medications or drugs that can affect the central nervous system other than caffeine or nicotine.
   8. Have a positive HIV test.
   9. Be pregnant or nursing. Other females must either be unable to conceive (i.e., surgically sterilized, sterile, or postmenopausal) or be using a reliable form of contraception (e.g., abstinence, birth control pills, intrauterine device, condoms, or spermicide). All females must provide negative pregnancy urine tests before study entry, weekly during the study, and at the end of study participation.
   10.Have any other illness, condition, or use of psychotropic medications, which in the opinion of the PI and/or the admitting physician would preclude safe and/or successful completion of the study.

6. * **Will individuals with limited English proficiency be included in or excluded from this research?**
   - ○ Included
   - ● **Excluded - safety concerns if participants are unable to communicate with the study team**
   - ○ Excluded - instruments/measures only validated in English

- ◯ Excluded - no prospect of direct benefit to individual participants
- ◯ Excluded - minimal risk study
- ◯ Excluded - lack of budget/resources for translation and interpretation [provide an explanation in next question]
- ◯ Excluded - other reason [provide an explanation in next question]

7. Justify the inclusion and exclusion criteria if you are either targeting, or excluding, a particular segment of the population / community. Provide a description of the group/organization/community and provide a rationale.
Ethnic and Gender Composition: The procedures described here are those used and have been consistently deemed adequate in previous applications. Study population composition: Women and Minorities: (1) These are clinical studies and (2) are germane to women. (3) Women will not be excluded, and (4) will be included and strive for an approximate 50-50 balance. Our current data have permitted us to conduct meaningful analyses by sex across groups (5).

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Study Procedures

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2. * **Describe the study's specific aims or goals. Use lay language whenever possible.**
Specific Aim 1. To examine the interaction of the serotonin receptor (5-HTR) type-2C Cys23Ser single nucleotide polymorphism (SNP) and a 5-HT2AR antagonist on the functional circuitry underlying impulsive action. We will test the hypotheses that 1) cocaine-dependent subjects displaying the Ser23 5-HT2CR genotype will show the highest fMRI activation and 2) greatest reduction in fMRI activation following the 5-HT2AR antagonist mirtazapine related to levels of impulsivity (Go- NoGo task) relative to controls with the Ser23 polymorphism, cocaine users without the polymorphism, and controls without the polymorphism, supporting a functional balance between 5-HT2AR:5-HT2CR in impulsivity in this patient population.

Specific Aim 2. To examine the interaction of the 5-HT2CR Cys23Ser SNP and a 5-HT2AR antagonist on the functional circuitry underlying cue reactivity. We will test the hypothesis that a functional balance between 5-HT2AR:5-HT2CR in cue reactivity exists in that 1) cocaine-dependent subjects displaying the Ser23 5-HT2CR genotype will present the highest fMRI activation and 2) greatest reduction in fMRI activation following the 5-HT2AR antagonist mirtazapine in the attentional bias task relative to controls with the Ser23 polymorphism, cocaine users without the polymorphism, and controls without the polymorphism.

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3. * **Choose all types of recruitment materials that may be used and upload them below:**
- [ ] E-mail invitations
- [ ] Phone Solicitation scripts (i.e. cold calls or random-digit-dialing)
- [x] **Flyers, Mailed Letters or Newspaper/TV/Radio Ads**
- [ ] TelegRAM announcements
- [x] **Website text**
- [ ] Study-specific web sites (provide the design and text)
- [ ] Social Media
- [ ] EPIC MyChart Patient Portal research study descriptions
- [ ] Psychology Research Participant Pool (SONA) study descriptions
- [ ] Scripts for announcements made to groups
- [ ] Other recruitment material
- [ ] No recruitment materials

4. * **Describe the study procedures/methods for identifying and recruiting participants. Address the following three aspects of recruitment in your response.**

1. Identification of potentially eligible participants or secondary data/specimens of interest.
- What database(s) will be queried to identify secondary data/specimens
- How potential participants' contact information will be obtained

2. Recruitment procedures to invite participation in the study (when applicable):
- How each of the written or verbal recruitment materials and reminders (selected above) will be used
- Who will contact or respond to potential participants
- Locations where recruitment procedures will take place
- The timing and frequency of recruitment attempts

3. Eligibility screening prior to consent and how those activities will be carried out (when applicable)

See the help text for additional guidance.
Potential study participants will be recruited via advertisements and screening procedures described in IRB# HM20000294. At that time, they are asked to participate in the screening evaluation to determine if they are eligible to participate in one of the studies being conducted at CARI. Individuals expressing an interest in participating in the screening evaluation are then consented on the consent form of protocol number HM20000294. Subjects who decline to participate will not be coerced in any way. Written informed consent will be obtained from all subjects. Drug dependent subjects who decline to participate or who do not meet inclusion/exclusion criteria will be referred to treatment options in the community. Once they complete screening evaluation and meet inclusion/exclusion criteria for this study, they will sign an additional study specific consent form to enroll in this study

5. * **Does this study have a separate protocol document (i.e. a multisite or sponsor's protocol) that contains a detailed description of the study's methodology?**

- ○ Yes
- ● **No**

6. * **Since a separate protocol document is not uploaded, describe the proposed research using language understandable to those IRB committee members whose expertise is not scientific. The description must include:**

1. A statement explaining the study design
2. A detailed description of all the procedures that will be followed to carry out the study, preferably in sequential order, and in sufficient detail that the study's methods could be replicated
3. A description of all research measures/tests/interventions that will be used (if applicable)

See the help text for additional guidance
Experimental Design and Methods

Subjects: Subjects will consist of 25 cocaine dependent subjects with the Ser23 HTR2C polymorphism (rs6318 (Cys23Ser / C23S or 68G>C / G68C)) and 25 cocaine dependent subjects with the Cys23 HTR2C polymorphism. In addition 25 non-drug using controls with the Ser23 HTR2C polymorphism and 25 controls with the Cys23 polymorphism will be recruited. Non-drug using controls subjects will have similar age and handedness as the drug dependent subjects. Subjects will be exclusively recruited due to our preliminary data showing group differences on attentional bias based on the HTR2C polymorphism in African American subjects and to reduce heterogeneity. Based on the previously reported prevalence of the Ser23 polymorphism, and our own preliminary data in African American subjects, we expect 13% - 32% of subjects will have at least one Ser23 allele. In order to achieve a balance of subjects with the Ser23 and Cys23 alleles, subjects will be prescreened for the polymorphism according to the schedule below. General inclusion criteria for cocaine dependent subjects includes current cocaine dependence, no current DSM-5 Axis I disorders other than cocaine, marijuana, or nicotine use disorder, or alcohol use disorder (mild to moderate). No past Axis I disorders other than substance abuse/dependence or substance induced mood disorder. No clinically significant non-psychiatric medical disorders. No CNS active prescription medications or other drugs of abuse besides cocaine, marijuana, alcohol, and nicotine.

No metal fragments or implants, and no history of fear of being in closed spaces for MRI scans. Nondrug using controls will have similar inclusion criteria with the addition of any current or past substance abuse or dependence. A detailed list of inclusion and exclusion criteria is provided in the Human Subjects section.

Subject Recruitment: All subjects will be recruited through the VCU CARI facility.

We anticipate needing to screen approximately 400 subjects over 5 years to obtain the required number of subjects for the study. This will necessitate screening approximately one to two subjects per week. Cocaine-dependent subjects are recruited through advertising in local newspapers and word of mouth. As Richmond has a large cocaine using population, we do not anticipate difficulty recruiting the proposed numbers of subjects.

Overview of Procedures: Subjects will undergo initial screening procedures described in IRB protocol # HM20000294. Eligible subjects will then undergo a baseline mock scan and fMRI scan according to procedures described in Table 1.

Subjects who complete the mock MRI scan without claustrophobia will present at the VCU CARI facility at 7:30 a.m. on the day of the actual fMRI scan and undergo an EKG and urine drug screen. Subjects who have a positive urine drug screen (except cocaine or marijuana) or breath alcohol will be rescheduled.

All subjects must have a negative urine drug screen for all drugs of abuse other than cocaine and marijuana and a negative breath alcohol by Breathalyzer at the time of scanning. Subjects with a positive urine drug screen for cocaine will be evaluated by the study physician for cocaine intoxication. Mirtazapine is FDA approved for the treatment of depression and is available for use in patients with depression and cocaine dependence. Previous studies have not reported any serious adverse events of mirtazapine in cocaine-dependent subjects.80 Also, according to clinicaltrials.gov, there are ongoing clinical trials using mirtazapine to treat depression in cocaine dependence. To minimize any risk of the combination of mirtazapine and cocaine, subjects will not be administered mirtazapine who have used cocaine less than 8 hours prior to mirtazapine administration or have any symptoms of cocaine intoxication as determined by a physician. Subjects who smoke cigarettes will be asked to smoke 2 hours before the scan in order to avoid any nicotine withdrawal effects. Subjects who drink caffeinated beverages will be asked to abstain from these beverages prior to the scan. Caffeine and nicotine use will be documented for all subjects.

Subjects who are cleared for drug administration will undergo MRI scans as described below.
Subjects receive placebo or 15mg of mirtazapine prior to the scan. This dose of mirtazapine was chosen because this is the lowest dose that has a clinical effect for depression, and based on our preliminary data that some subjects had sedation after 30mg of mirtazapine. For each subject scans will be repeated after 7 days, with the order of administration randomized across subjects.

Subjects will be monitored for side effects, behavioral effects, and vital signs will be obtained for up to 8 hours after the dose when subjects who have vital signs within normal limits and no side effects will be released. Subjects will return 7 days later for identical procedures. This allows 5 half-lives of mirtazapine between scans to minimize carry-over effects.
The maximum number of hours for subjects to complete the entire research study is about 23 hours.

Face-toFace Interviews/ Surveys

Cocaine Craving Scale: is a 3-item instrument which asks about participant perceptions of their cocaine craving. Participants are asked to rate their current, past week, and worst craving in the past week on a scale ranging from 0 (not at all) to 100 (extremely), using a visual analog scale.

Cocaine Selective Severity Assessment: The Cocaine Selective Severity Assessment (Kampman, 1998) measures early cocaine abstinence signs and symptoms. It is a reliable and valid measure of cocaine abstinence symptoms, and a useful predictor of negative outcomes in cocaine dependence treatment, and requires approximately 5 minutes to complete.

Drug Effect Questionnaire (DEQ): This form utilizes a visual analog scale to measure potential side-effects of mirtazapine. This form is will be administered at different intervals after administration of mirtazapine before and after the fMRI session.

Medical and Laboratory Evaluation:
All subjects will undergo an electrocardiogram (EKG), on all MRI scan session days Urine drug screens will be obtained upon initial evaluation, and on each day of behavioral testing. Urine pregnancy tests will be performed on all female subjects on each day of behavioral and MRI testing. A positive pregnancy test will immediately terminate the subject from additional study procedures.

Monitoring for Drug Usage: Drug and alcohol usage will be monitored by obtaining urine and expired air samples on each day of the study. Subjects will be rescheduled if they have a positive alcohol breathalyzer. Cocaine-dependent subjects will not be excluded from participation if urine testing for marijuana or cocaine is positive on the morning of each test day, since this would eliminate a significant majority of subjects. Presence or absence of marijuana or cocaine in urine on testing days will be included as a covariate in the statistical analyses. Healthy control subjects will be required have negative urine screen on all study session days and will be excluded if there is a positive screen.

Standardized assessments include the following behavioral tasks:

Iowa Gambling Task [Bechara et al. 1997].
This is a computerized version of the original gambling task in which subjects are asked to choose between four decks of cards which result in theoretical monetary rewards at different rates. Each deck (labeled A, B, C, and D) contains 60 cards. Subjects must make 100 choices over the testing session. Healthy controls are able to determine that two decks of cards on the short-term lead to minimal monetary rewards but over the long-term are more advantageous due to large losses in the other two decks of cards. This task has been able to differentiate between patients with frontal cortical lesions and controls [Bechara, Damasio, Tranel, and Damasio1997;Bechara et al. 1998], and drug users and controls [Bechara et al. 2001]. The task takes about 15 minutes to complete. Scoring for the Iowa Gambling Task is based on the total number of cards selected from the advantageous minus the disadvantageous decks across five blocks of 20 cards each. The net score of cards selected ((C+D)-(A+B)) in each of the five blocks will be used as a measure of impulsivity.

The Kirby Monetary Choice Delay Discounting Questionnaire:
The monetary-choice questionnaire was based on one developed by Kirby et al (1999). Participants were presented a fixed set of 27 choices between smaller, immediate rewards (SIRs) and larger, delayed rewards (LDRs). For example, on the first trial participants were asked, "Would you prefer $54 today, or $55 in 117 days?" The participant indicated which alternative he or she would prefer to receive by circling the alternative on the questionnaire. The order was

contrived such that trial order did not correlate with the SIR or LDR amounts, their ratio, their difference, the delay to the LDR, or the discount rate corresponding to indifference between the two rewards. An estimate of a participant's discounting-rate parameter (k) can be made from the participant's pattern of choices across the 27 questions on the monetary-choice questionnaire. Previous studies have shown that drug users have higher discount rates than controls (Kirby et al., 1999, 2004)

Adjusting Delay Discounting Task:
This task is designed to measure participants' discounting rate when they are presented with the possibility of receiving a hypothetical reward. Each participant completes a program developed by Bickel and Johnson, 2002, where they are presented choices using a choice algorithm running on Microsoft Visual Basic 6.0 program. The participant uses a mouse to choose between available options. During the experiment, the screen displays two large command buttons, one on the left side of the screen and one on the right side, in which the choices are presented. The left button always displays an immediate adjusting reward (e.g., ''$5.00 now''), and the right button displays a delayed reward (e.g., ''$10.00 in 1 week''). Participants are exposed to a series of choices where the future reward magnitudes are $10, $25, $100, $250, $1000 or $2500 (for delayed rewards) at delay periods of 1 day, 1 week, 1 month, 6 months, 1 year, 5 years or 25 years. The computer program varies the smaller, immediately available amounts across trials according to the algorithm. However, the larger delayed amount stays the same until an indifference point is determined. After an indifference point is determined, the delay for the larger reward increases to the next duration. When all indifference points for a magnitude at each delay is found, the magnitude changes and the delay returns to the first delay (1 day) again. Participants are randomly assigned to complete the assessment in either ascending or descending order of delays. Choice presentations end once indifference points have been determined for each magnitude at each delay. Cocaine-dependent subjects reliably discount higher than controls in this task as evidenced by higher indifference values (Heil et al., 2006).

Stop-Signal Task:
The SST measures motor impulsivity, which is defined as the inability to inhibit a precued response. The current test is adapted from the task developed by Fillmore et al. (2002). In this task, subjects are required to make quick key responses to visually presented go signals and to inhibit any response when a visual stop signal is suddenly presented. The go-signals are four 1.5-cm letters (A, B, C, and D), presented one at a time in the center of a computer monitor. Subjects are required to respond to each letter as quickly as possible by pressing one of two adjacent keys on the computer keyboard using the index and middle fingers of the preferred hand. One key (the period key) is pressed to indicate that either 'A' or 'C' appeared, and the adjacent key (the forward slash key) is pressed to indicate that either 'B' or 'D' appeared. A letter was displayed for 500 ms and the computer screen is blank for a 2.5-s inter-stimulus interval before the next letter is displayed. This provides a 3-s period in which the subject can respond to the letter. A single test consists of 176 trials in which each of the four letter stimuli are presented equally often. A stop-signal occurs on 27% of the 176 trials (i.e. 48 trials) during a test. The stop-signal is a 500-ms, 900-Hz tone generated by the computer at a comfortable listening level. Subjects are required to withhold any response on trials in which a stop-signal is sounded. Stop-signals are presented 12 times, at each of four delays after the onset of a letter: 50, 150, 250, and 350 ms. The order of letters, stop-signals, and delays is random. Trials always begin with a 500-ms preparation interval in which a fixation point (#) appears in the center of the computer screen. A test is completed in approximately 10 min. The stop-signal task has been reliably shown to increase stop signal reaction time in cocaine users (Li et al., 2006)

Eye-tracker Attentional Bias Task:
Participants will be instructed to look at (pro-saccade) or look away from (anti-saccade) a presented image. The testing session will include four counterbalanced blocks (two cocaine and two neutral image blocks), with 36 pro- or 36 anti-saccade trials in each block. Rates of pro-saccades during anti-saccade trials will be used as an indicator of attention bias (Lane et al., in prep). MiraMetrix S2 Eyetracker (Vancouver, BC) will be used to measure performance on counterbalanced blocks of trials in which participants will be instructed to look at (pro-saccade) or look away from (anti-saccade) a presented image. First, a nine-point calibration procedure will be performed for each subject to map the eye-fixation position to screen coordinates. All trials have the following structure: (1) orienting stimulus (cross hair; jittered 300-400ms to avoid anticipation effects); (2) cue = images, counterbalanced either to the left or right; (3) image cue removed from screen, followed by inter trial interval (1600ms). For the pro-saccade trials, the participant is instructed to look at the image; for anti-saccade trails, they are told to look away from the image and fixate on the blank screen on the opposite side. Participants will begin with a brief training session (16 pro-, 16 anti- saccade trails), in which the image shown will be a grey box. The testing session will include four counterbalanced blocks (2 pro, 2 anti, latin-square design), with 36 pro- or 36 anti-saccade trials in each block. Trials with blinks (which render accurate measurement invalid) are captured, ended, and then the trial is reinserted randomly at the end of the block. Thus each subject completes the same number of valid trials and no data are lost in the session. Rates of prosaccades during antisaccade trials will be used as an indicator of attentional bias.

The Attentional Bias (modified Stroop task) task (-- et al.,)
This is a widely-used implicit task in which the subject is presented with words printed in color, and asked to discriminate the color of each stimulus and to ignore the meaning of the words. There are ten cocaine-related words (e.g., "cocaine", "crack"), and ten neutral words consisting of household features (e.g., "table", "kitchen"). The word sets are matched in length or frequency of use using typical procedures. Subjects are instructed that words written in different colors (blue, green, or red) will be presented on the screen, one after the other, and that their task is to indicate the color in which the word is written as quickly and as accurately as possible, ignoring the meaning of the word itself. A new word is presented 500 ms after a response (or 500 ms after the timeout of 3 sec). In this block design protocol, a block (60 s) of neutral words alternates with a block (60 s) of cocaine words and each run is approximately 10 min. Subjects first respond to a practice sequence (50 trials) of letter strings (e.g., HHHH). Within each Stroop task, the program randomly determines the presentation order of words and colors for each participant under the constraint that the same color does not appear on two consecutive trials. This task will be used during the baseline and will also be used in the fMRI study.

Brain Imaging Measures

MRI Sessions. Each MRI scanning session consists of a 90-minute period in which the person is in the scanner for two 40-minute periods with a 10 minute break in between. The 90-minute period consists of a T1 weighted spin echo 3-plane localizer (scout), followed by 2 runs of the first fMRI task, 2 runs of the second fMRI task, , a high resolution T1 weighted 3D-MPRAGE scan (256 x 256 acquisition and reconstruction matrix, in-plane resolution 0.94 mm, 170 sagittal slices, 0.94 slice thickness, flip angle 6.0 degrees, TFE shots 119; TFE duration shot / acquisition (ms) = 2236.6 / 2188.4; minimum inversion delay 1133.3 ms; TR 8.55 ms, TE 4.0 ms, total duration 5 min 56 s). This is followed by a 3D time-of-flight arteriogram, and a pulse-gated phase-contrast velocity quantitative flow (QFLOW) scan with the slice positioned normal to the interior carotid artery and the vertebral artery, and then a pseudo-continuous arterial spin labeling (PCASL) perfusion scan. A QUASAR perfusion series that incorporates QUIPSS II will also be acquired for verification of the quantitative rCBF with the PCASL results. The PCASL images will be analyzed off-line using in-house developed software (P. Narayana and Y. Zhou, personal communication), which uses the phase contrast velocity QFLOW results to calculate whole-brain blood flow in order to normalize the PCASL rCBF data (Aslan et al., 2010). The QUASAR/QUIPSS II data will be analyzed off-line according to the methods in Petersen et al. (2010). The scanning is concluded by a 3D-FLAIR and a T2-weighted fast spin echo scan for diagnostic purposes to be read by the radiologist to rule-out incidental brain abnormalities

fMRI Behavioral Tasks:
a. The Go-NoGo (Response Inhibition) fMRI task (- - -) is a rapid presentation stochastic event-related fMRI design containing two levels of difficulty. The stimulus array consists of two boxes containing (a) diagonal lines in the same direction for Go trials, (b) diagonal and horizontal lines for Easy NoGo trials, and (c) diagonal lines in opposite directions for Hard NoGo trials. The two boxes are presented simultaneously side by side on the screen for 500 ms, followed by a blank screen jittered randomly for 1900 ms, 2100 ms, or 2300 ms. NoGo trials occur randomly throughout the run. One run lasts approximately 10 min and consists of 224 trials: 168 (75%) Go; 28 (12.5%) Easy NoGo; and 28 (12.5%) Hard NoGo. Easy NoGo activation is defined as the parameter estimate of the Easy NoGo stimuli on which the subject responded correctly minus the parameter estimate of the Go stimuli on which the subject responded correctly. fMRI activation is similarly defined for the Hard NoGo contrast of interest. The difference in activation (Hard NoGo minus Easy NoGo) will also be analyzed.

b. The Attentional Bias (modified Stroop task) fMRI task is a widely-used implicit task in which the subject is presented with words printed in color, and asked to discriminate the color of each stimulus and to ignore the meaning of the words. There are ten cocaine-related words (e.g., "cocaine", "crack"), and ten neutral words consisting of household features (e.g., "table", "kitchen"). The word sets are matched in length or frequency of use using typical procedures. Subjects are instructed that words written in different colors (blue, green, or red) will be presented on the screen, one after the other, and that their task is to indicate the color in which the word is written as quickly and as accurately as possible, ignoring the meaning of the word itself. A new word is presented 500 ms after a response (or 500 ms after the timeout of 3 sec). In this block design fMRI protocol, a block (60 s) of neutral words alternates with a block (60 s) of cocaine words and each fMRI run is approximately 10 min. Subjects first respond to a practice sequence (50 trials) of letter strings (e.g., HHHH). Within each Stroop task, the program randomly determines the presentation order of words and colors for each participant under the constraint that the same color does not appear on two consecutive trials.

Statistical Analyses. Power Analysis: fMRI Power Analysis.

The power analysis for fMRI data (second level "Random Effects" SPM8 between-group general linear model analysis) used the model and equations in the papers by Friston et al.; brain signals are modeled by continuously distributed Gaussian kernels of random height and of width (f) in proportion to W, where W is the smoothness of the random field.

The standard deviation (sigma), of the kernel corresponds to the height (i.e., intensity) of the measured signal. The kernel is then convolved with an uncorrelated random process representing noise. The new process representing signal+noise has zero mean and variance 1 + sigma^2. We estimate signal height to be the voxel t value which is determined by the desired effect size (d) (7, formula 2.5.4, p.67). In this analysis, we have conservatively assumed that the degrees of freedom are reduced by the presence of up to four additional potential covariates (e.g., demographic and/or behavioral variables). We used the observed values of field smoothness (W), underlying signal width (f) prior to smoothing, and 3D brain volume (R) from our pilot event-related Go-NoGo fMRI study (see Preliminary data). Based on the observed effect size (d = 0.83) for the second-level (Random Effects) within-group activation of mirtazapine vs. placebo in the event-related fMRI pilot study for Go-NoGo, we have calculated the predicted effect size d = 0.57 for the between group comparison using the conversion formula in Cohen,7 formula 2.5.6, p.71), but this is probably inflated due to the small sample. Therefore for fMRI power analysis we have conservatively used a more modest effect size of 0.25. For an effect size d = 0.25 and Random Field Theory family-wise error-corrected 2-tailed alpha = 0.05 at the cluster level of inference, observed 3D search volume = 188579 voxels, observed field smoothness W = [4.9 4.9 4.3] voxels (FWHM), width of signal prior to smoothing (relative to W) f = 0.909 (calculated based on observed width after smoothing and known spatial smoothing kernel), and minimum cluster spatial extent k = 23 voxels that was computed to achieve the above alpha at a cluster-defining voxel height threshold u = 4.5, we have calculated that a sample size of 25 subjects in each group would achieve a power of at least 89 percent for the event related Go-NoGo fMRI between-group activation comparison. We expect the power to be greater than this for the block design Attentional Bias fMRI study, since we have observed effect sizes greater than 0.83 for the within-group activation of mirtazapine relative to placebo in the pilot Attentional Bias fMRI study, and block design is generally more efficient than event-related design, leading to higher t values given the same residual error variance.

7. * **The IRB only reviews research activities, so indicate which of the study activities are:**

- Being performed exclusively for research purposes (i.e. they would not otherwise be done apart from this study) VERSUS.
- Alterations of routine activities/procedures (e.g. the study is altering the timing, frequency, method, location, amount, etc.) VERSUS.
- Being done for other purposes and whose data/results will be used secondarily in the study (e.g. standard medical or psychological tests, routine education practices, quality improvement initiatives, etc.).
all procedures in the study are being performed exclusively for the purpose of research

8. If applicable, describe alternatives (research or non-research) that are available to potential participants if they choose not to participate in this study:
Standard (normal) care in the community may include being in the hospital or outpatient treatment and may involve group or individual therapy. Potential participants who indicate they are treatment seeking are eligible to participate in other treatment studies at the clinic or will be referred to other treatment (if available), if they do not wish to take part in this project. The research staff members will help subjects find alternatives. Costs of other treatment will be the subject's responsibility.

9. Upload any supporting tables or documents (e.g. protocol documents, figures/tables, data collection forms, study communications/reminders):

Upload ALL instruments/guides that will be used or that participants will experience (i.e. see, hear, complete), including measures, scripts/questions to guide interviews, surveys, questionnaires, observational guides, etc,:

Upload ALL recruitment and screening materials, including such as ads, flyers, telephone or in-person scripts, letters, email invitations, TelegRAM announcements, and postcard reminders, screening scripts, screening forms, and screening measures:

VCU Office of Research and Innovation

Date: Friday, October 15, 2021 9:30:57 AM Print Close

ID: HM15289 **HM15289**

View: SF2 - Bio-Medical Drug / Biologic / Supplement / Other Compound Details

HM15289 - Frederick Moeller
5-HT2AR: 5HT2CR Balance in Brain Connectivity in Cocaine Dependence

Bio-Medical Drug / Biologic / Supplement / Other Compound Details

1. * **List all drugs and/or biologics:**

	Drug	Manufacturer	Types	FDA Labeling	IND Holder	IND Number
View	Mirtazapine	American health packaging	Investigational Drug/Biologic/Supplement used as drug	Yes	Not Required	IND Exempt

2. * **Will the Investigational Drug Service (IDS) pharmacy be utilized:**
Yes

3. * A. For each drug/biologic listed above**, upload an investigator's drug brochure or package insert/FDA labeling.**

B1. <u>For drug products that require an IND</u>, upload at least one of the following documents for verification of the IND number:
- External sponsor's protocol including IND number and signed Form FDA 1572 for the VCU Principal Investigator
- Communication from the external sponsor verifying the IND number and signed Form FDA 1572 for the VCU Principal Investigator
- VCU sponsor-investigator's FDA IND protocol including IND number
- Communication from the FDA with verification of the IND number

B2. *For drug products that qualify for IND exemption* under under 21 CFR 312.2(b), upload one of the following documents for each applicable drug:
- A document explaining, with protocol-specific information, how the drug's use in this study meets the relevant critieria for IND exemption under 21 CFR 312.2(b).
- The completed "Determination of IND Exemption for Marketed Drugs" form available on the VCU Faculty-Held IND or IDE website at go.vcu.edu/indide.
- External sponsor's protocol including IND exemption information
- Communication from the external sponsor verifying the IND exemption
- Communication from the FDA with verification of IND exemption

C. <u>If the Investigational Drug Service Pharmacy (IDSP) is not utilized</u>, upload the IDSP management plan approval.

Bio-Medical Project Drugs

1. * **Drug:**
   Mirtazapine
2. * **Manufacturer:**
   American health packaging
3. * **Select all types that apply:**

- [ ] FDA Approved and being used as approved
- [ ] Marketed Drug/Biologic Exempt from IND
- [x] **Investigational Drug/Biologic/Supplement used as drug**
- [ ] Supplement
- [ ] Over the Counter Medication
- [ ] Other (Drug or Compound Not Listed Above)

4. * **Will the doses of drug administered and the dosing schedule match FDA approved labeling:** ***(if not, include all doses and dosing schedules in the Methods)***

- (●) **Yes**
- ( ) No
- ( ) Not Applicable

5. * **Select who holds the Investigational New Drug (IND) application for the drug/biologic:**

- ( ) External to VCU Sponsor or Investigator
- ( ) VCU Sponsor-Investigator
- ( ) VCU Sponsor who is not the Investigator
- (●) **Not Required**

6. **Indicate the drug's IND number, if applicable. If the drug qualifies for IND exemption, enter "IND Exempt":**
   IND Exempt

HM15289 - Frederick Moeller
5-HT2AR: 5HT2CR Balance in Brain Connectivity in Cocaine Dependence

Sample Collection Details

1. * **Select all of the types of samples that will be collected as part of this study.**

- [ ] Amniotic Fluid
- [x] **Blood**
- [ ] Buccal Smears
- [ ] Saliva
- [ ] Tissue
- [x] **Urine**
- [x] **Other**
- [ ] None of the Above

2. * **If Other, please describe the type of sample being collected:**
Expired air samples to measure breath alcohol level

3. * **Select all of the methods of blood collection that will be utilized in this study:**

- [x] **Individual Needle Stick(s)**
- [ ] Indwelling Catheter Placed Solely for This Study
- [ ] Indwelling Catheter Placed for Other Reason(s)
- [ ] Blood Collected at the Same Time as Non-Research Blood Collection(s)
- [ ] Other

4. * **In order to collect urine, will an indwelling catheter be placed solely for the research study:**

- ○ Yes
- ● **No**

5. * **Describe how the sample will be collected and the collection schedule. For each type of sample, include information about**

- The procedures that will be followed to collect the sample
- The role(s) of the individuals who will collect the sample
- The volume/size range of the sample
- The timing and frequency of sample collection
A 12-lead electrocardiogram will be used to determine safety during the study. Blood specimens, if not already collected during screening protocol procedure (IRB# HM 20000294, PRE-SCREEN, Keyser-Marcus, (PI)), (about 30 cc) will be collected for genetic testing. Blood draws will occur during the screening process (IRB # HM20000294), and will be performed by either the study nurse or one of the study physicians. Drug and alcohol usage will be monitored by obtaining urine and expired air samples

6. * **Will genetic testing or analyses be conducted on any of the samples:**

- ● **Yes**
- ○ No

7. * **What are the intended research areas that this DNA will be collected for:**
To evaluate the role of molecular interactions between 5-HT2AR and 5-HT2CR in behavioral phenotypes that confer risk for cocaine dependence and relapse. Polymorphisms in the genes encoding the 5-HT2AR and 5-HT2CR receptor subtypes are been evaluated as genetic predictors of treatment for cocaine dependence.

HM15289 - Frederick Moeller
5-HT2AR: 5HT2CR Balance in Brain Connectivity in Cocaine Dependence

Costs to Participants

1. * **Select all categories of costs that participants or their insurance companies will be responsible for:**

- [x] **Participants will have no costs associated with this study**
- [ ] Study related procedures that would be done under standard of care
- [ ] Study related procedures not associated with standard of care
- [ ] Administration of drugs / devices
- [ ] Study drugs or devices
- [ ] Other

HM15289 - Frederick Moeller
5-HT2AR: 5HT2CR Balance in Brain Connectivity in Cocaine Dependence

Compensation

1. * **Describe any compensation that will be provided including:**
   1. **total monetary amount**
   2. **type (e.g., gift card, cash, check, merchandise, drawing, extra class credit)**
   3. **how it will be disbursed**

   Non-drug using controls will be compensated $20 for the practice scan, additional $5 for each task completed (up to $15) and earn bonus money based on task performance (up to $15). They will earn $75 for each scanning session additional $5 for each task completed (upto $15) and earn bonus money based on task performance while inside the scanner (upto $15). They will receive $30 for each behavioral task session and earn bonus money based on task performance (up to $10). In addition a study completion bonus of $75 will be provided. In addition, reimbursement for transportation costs (mileage at current VCU approved rate) will be provided for participants who need to travel more than 20 miles to the study site.
   If subjects complete the entire study procedures they will receive approximately $415 dollars. Participants will be paid in the form of vouchers. These vouchers can be exchanged for cash or a check that will be mailed directly to them (choice of either option).

   Prior to receiving compensation cocaine dependent subjects will meet with a designated staff member to discuss plans for use of the payment consistent with a drug free lifestyle. if subjects complete the entire study procedures they will receive approximately $415 dollars.

2. **If compensation will be pro-rated, explain the payment schedule.**

3. * **Will Social Security Numbers be collected for compensation purposes only?**
   - (●) **Yes**
   - ( ) No

	Group	Types	Waivers	Roles	Roles - Other	Electronic Signatures	Consent	Coercion	Decision	Re-Consent
View	Cocaine dependent subjects	Written/Signed Consent for Genetic Testing Signed Consent by Participant	No Waivers Requested	Co/Sub-Investigator Research Coordinator Research Assistant Trainee/Student(working on project)			Cocaine dependent subjects who respond to advertisements or referrals by phone or in person complete an initial screening process (IRB# HM20000294) asking questions about general inclusion and exclusion criteria at the VCU CARI facility. If subjects appear to meet general inclusion criteria, the research assistant will meet with the potential subject once they have completed the screening protocol in private. At that time, they are asked to participate as volunteer in this study. Subjects who decline to participate will not be coerced in any way. Written informed consent will be obtained from all subjects who agree to research study. Drug dependent subjects who decline to participate or who do not meet inclusion/exclusion criteria will be offered treatment options in the community.	The informed consent process involves a detailed verbal description of the study procedures, and how it is used to determine eligibility for participation in the study being conducted at CARI. Staff will emphasize that participation in the study is voluntary. Further, they will be told that they may drop out at any time without penalty or loss of benefits to which they are otherwise entitled. Participants will be informed of procedures for ensuring their confidentiality, including; the use of numbers, codes and/or pseudonyms rather than participants' names;; and the placement of all data in locked files. Participants will be informed that, despite participant confidentiality protections, research staff, under current state law, are required to report certain communicable diseases, and any incidents of sexual or physical abuse of a child or elder. Participants will be given the contact numbers of both the Principal Investigator and IRB Chair to answer questions about the study or one's rights as a human subject. A copy of the signed form is made and given to the client, another copy is held in the Principal Investigator's records, and the original signed consent is kept in a separate, locked file accessible to the Institutional Review Board (IRB) upon request.	The research staff member will meet with the prospective subject in a private room. After receiving a brief overview of the study, the subject will be left alone to review the consent form. After about 5-10 minutes, the research staff member will return and obtain the written consent from individuals who express an interest in participating. Prospective subjects may also take home a copy of the consent form to review before signing it.	N/A

	Group	Types	Waivers	Roles	Roles - Other	Electronic Signatures	Consent	Coercion	Decision	Re-Consent
View	Healthy Contol subjects	Written/Signed Consent for Genetic Testing Signed Consent by Participant	No Waivers Requested	Co/Sub-Investigator Research Coordinator Research Assistant Trainee/Student(working on project)			Healthy control subjects who respond to advertisements or referrals by phone or in person complete an initial screening process (IRB# HM20000294) asking questions about general inclusion and exclusion criteria in the CARI facility. If subjects appear to meet general inclusion criteria, the research assistant will meet with the potential subject once they have completed the screening protocol in private. At that time, they are asked to participate as volunteer in this study. Subjects who decline to participate will not be coerced in any way. Written informed consent will be obtained from all subjects who agree to research study.	The informed consent process involves a detailed verbal description of the study procedures, and how it is used to determine eligibility for participation in the study being conducted at CARI. Staff will emphasize that participation in the study is voluntary. Further, they will be told that they may drop out at any time without penalty or loss of benefits to which they are otherwise entitled. Participants will be informed of procedures for ensuring their confidentiality, including; the use of numbers, codes and/or pseudonyms rather than participants' names;; and the placement of all data in locked files. Participants will be informed that, despite participant confidentiality protections, research staff, under current state law, are required to report certain communicable diseases, and any incidents of sexual or physical abuse of a child or elder. Participants will be given the contact numbers of both the Principal Investigator and IRB Chair to answer questions about the study or one's rights as a human subject. A copy of the signed form is made and given to the client, another copy is held in the Principal Investigator's records, and the original signed consent is kept in a separate, locked file accessible to the Institutional Review Board (IRB) upon request.	The research staff member will meet with the prospective subject in a private room. After receiving a brief overview of the study, the subject will be left alone to review the consent form. After about 5-10 minutes, the research staff member will return and obtain the written consent from individuals who express an interest in participating. Prospective subjects may also take home a copy of the consent form to review before signing it.	N/A

2. Upload any consent / assent documents:

Consent Groups

1. * **Enter a descriptive name for this consent / assent group:**
   Cocaine dependent subjects

2. * **Select all that apply to this consent / assent group:**

	Name
☑	**Signed Consent by Participant**
☐	Signed Parent/Guardian Permission or Legally Authorized Representative Consent
☑	**Written/Signed Consent for Genetic Testing**
☐	Signed Assent by Child or Decisionally Impaired Adult
☐	Verbal Assent by Child or Decisionally Impaired Adult
☐	Short Form Consent (limited applicability)
☐	None of the Above (select waiver below)

3. * **Select all electronic signature platforms that apply to this consent / assent group:**
   - ☐ Not using electronic signature platforms
   - ☐ DocuSign Part 11 (FDA regulated studies)
   - ☐ DocuSign (standard platform for non-FDA regulated studies)
   - ☐ REDCap e-Consent
   - ☐ Other electronic signature platform

4. **If Other is selected, explain:**

5. * **Select any waivers that apply to this consent / assent group:**

☑	**No Waivers Requested**
☐	Waiver of All Consent or Some Elements in Consent Form
☐	Waiver of Parental Permission or Legally Authorized Representative Consent
☐	Waiver of All Assent by Child or Decisionally Impaired Adult
☐	Waiver of Signature on Consent/Permission Forms (waiver of documentation of consent)
☐	Exception from Informed Consent (for emergency research only)

6. * **Select all study team role(s) that will obtain consent / assent from this group:**

☐	Principal Investigator
☑	**Co/Sub-Investigator**
☐	Medical or Psychological Responsible Investigator
☐	Lead Student/Trainee Investigator (leading their own project)
☑	**Research Coordinator**
☐	Research Nurse
☐	Consultant
☑	**Research Assistant**
☐	Pharmacist
☐	Statistician
☐	Regulatory Coordinator
☑	**Trainee/Student(working on project)**
☐	Other
☐	N/A: Requesting Waiver of Consent

7. * **Describe the consent procedures used for this group. Include when, where, and how consent / assent will be obtained both initially and, if applicable, during ongoing participation in the study:**
   Cocaine dependent subjects who respond to advertisements or referrals by phone or in person complete an initial screening process (IRB# HM20000294) asking questions about general inclusion and exclusion criteria at the VCU CARI facility. If subjects appear to meet general inclusion criteria, the research assistant will meet with the potential subject once they have completed the screening protocol in private. At that time, they are asked to participate as volunteer in this study. Subjects who decline to participate will not be coerced in any way. Written informed consent will be obtained from all subjects who agree to research study. Drug dependent subjects who decline to participate or who do not meet inclusion/exclusion criteria will be offered treatment options in the community.

8. * **Describe the process for minimizing any potential perception of undue influence to participate when there is a pre-existing relationship between the participant and the researcher (e.g. treatment provider/patient; instructor/student; supervisor/employee, etc.):**

The informed consent process involves a detailed verbal description of the study procedures, and how it is used to determine eligibility for participation in the study being conducted at CARI. Staff will emphasize that participation in the study is voluntary. Further, they will be told that they may drop out at any time without penalty or loss of benefits to which they are otherwise entitled. Participants will be informed of procedures for ensuring their confidentiality, including; the use of numbers, codes and/or pseudonyms rather than participants' names;; and the placement of all data in locked files. Participants will be informed that, despite participant confidentiality protections, research staff, under current state law, are required to report certain communicable diseases, and any incidents of sexual or physical abuse of a child or elder. Participants will be given the contact numbers of both the Principal Investigator and IRB Chair to answer questions about the study or one's rights as a human subject. A copy of the signed form is made and given to the client, another copy is held in the Principal Investigator's records, and the original signed consent is kept in a separate, locked file accessible to the Institutional Review Board (IRB) upon request.

9. * **How much time will participants be given to make a decision:**
   The research staff member will meet with the prospective subject in a private room. After receiving a brief overview of the study, the subject will be left alone to review the consent form. After about 5-10 minutes, the research staff member will return and obtain the written consent from individuals who express an interest in participating. Prospective subjects may also take home a copy of the consent form to review before signing it.

10. **If applicable, describe the procedures for consenting children upon entering adulthood or participants who are no longer decisionally impaired:**
    N/A

Consent Groups

1. * **Enter a descriptive name for this consent / assent group:**
   Healthy Contol subjects

2. * **Select all that apply to this consent / assent group:**

	Name
☑	**Signed Consent by Participant**
☐	Signed Parent/Guardian Permission or Legally Authorized Representative Consent
☑	**Written/Signed Consent for Genetic Testing**
☐	Signed Assent by Child or Decisionally Impaired Adult
☐	Verbal Assent by Child or Decisionally Impaired Adult
☐	Short Form Consent (limited applicability)
☐	None of the Above (select waiver below)

3. * **Select all electronic signature platforms that apply to this consent / assent group:**
   - ☐ Not using electronic signature platforms
   - ☐ DocuSign Part 11 (FDA regulated studies)
   - ☐ DocuSign (standard platform for non-FDA regulated studies)
   - ☐ REDCap e-Consent
   - ☐ Other electronic signature platform

4. **If Other is selected, explain:**

5. * **Select any waivers that apply to this consent / assent group:**

☑	**No Waivers Requested**
☐	Waiver of All Consent or Some Elements in Consent Form
☐	Waiver of Parental Permission or Legally Authorized Representative Consent
☐	Waiver of All Assent by Child or Decisionally Impaired Adult
☐	Waiver of Signature on Consent/Permission Forms (waiver of documentation of consent)
☐	Exception from Informed Consent (for emergency research only)

6. * **Select all study team role(s) that will obtain consent / assent from this group:**

☐	Principal Investigator
☑	**Co/Sub-Investigator**
☐	Medical or Psychological Responsible Investigator
☐	Lead Student/Trainee Investigator (leading their own project)
☑	**Research Coordinator**
☐	Research Nurse
☐	Consultant
☑	**Research Assistant**
☐	Pharmacist
☐	Statistician
☐	Regulatory Coordinator
☑	**Trainee/Student(working on project)**
☐	Other
☐	N/A: Requesting Waiver of Consent

7. * **Describe the consent procedures used for this group. Include when, where, and how consent / assent will be obtained both initially and, if applicable, during ongoing participation in the study:**
   Healthy control subjects who respond to advertisements or referrals by phone or in person complete an initial screening process (IRB# HM20000294) asking questions about general inclusion and exclusion criteria in the CARI facility. If subjects appear to meet general inclusion criteria, the research assistant will meet with the potential subject once they have completed the screening protocol in private. At that time, they are asked to participate as volunteer in this study. Subjects who decline to participate will not be coerced in any way. Written informed consent will be obtained from all subjects who agree to research study.

8. * **Describe the process for minimizing any potential perception of undue influence to participate when there is a pre-existing relationship between the participant and the researcher (e.g. treatment provider/patient; instructor/student; supervisor/employee, etc.):**
   The informed consent process involves a detailed verbal description of the study procedures, and how it is used to

determine eligibility for participation in the study being conducted at CARI. Staff will emphasize that participation in the study is voluntary. Further, they will be told that they may drop out at any time without penalty or loss of benefits to which they are otherwise entitled. Participants will be informed of procedures for ensuring their confidentiality, including; the use of numbers, codes and/or pseudonyms rather than participants' names;; and the placement of all data in locked files. Participants will be informed that, despite participant confidentiality protections, research staff, under current state law, are required to report certain communicable diseases, and any incidents of sexual or physical abuse of a child or elder. Participants will be given the contact numbers of both the Principal Investigator and IRB Chair to answer questions about the study or one's rights as a human subject. A copy of the signed form is made and given to the client, another copy is held in the Principal Investigator's records, and the original signed consent is kept in a separate, locked file accessible to the Institutional Review Board (IRB) upon request.

9. ° **How much time will participants be given to make a decision:**
   The research staff member will meet with the prospective subject in a private room. After receiving a brief overview of the study, the subject will be left alone to review the consent form. After about 5-10 minutes, the research staff member will return and obtain the written consent from individuals who express an interest in participating. Prospective subjects may also take home a copy of the consent form to review before signing it.

10. **If applicable, describe the procedures for consenting children upon entering adulthood or participants who are no longer decisionally impaired:**
    N/A

Risks, Discomforts, Potential Harms and Monitoring

1. * **Describe the risks of each research procedure to participants or others. For each identified risk, provide an assessment of the anticipated seriousness and likelihood of the risk. Some examples of possible risks include but are not limited to:**
   - **Physical risks (e.g. bodily harms or discomforts, side effects, etc.)**
   - **Psychological risks (e.g. emotional, mental, or spiritual harms or discomforts, changes to thoughts, beliefs, or behaviors, etc.)**
   - **Research data risks (e.g. loss of confidentiality and privacy)**
   - **Social or legal risks (e.g. impacts on relationships or reputation, legal or criminal justice actions for self or others, etc.)**
   - **Financial risks (e.g. impacts on income, employability, or insurability, loss of services, etc.)**
   - **Other risks (e.g. unforeseeable risks of experimental procedures, risks related to particular study designs (randomization, washout, placebo, withholding care/services, deception), etc.)**

   See the help text for additional guidance.

   Potential Risks: The primary risks to participation in this study are those related to the single dose of mirtazapine and the risk of MRI and psychological measures. Other risks include psychological (anxiety related to being in the MRI scanner), social risks associated with potential loss of confidentiality, and legal related to potential disclosure of drug related information.

   Risks of mirtazapine administration: Mirtazapine is medication approved by the FDA for the treatment of depression. Mirtazapine possible side effects include nausea, dry mouth, constipation, dizziness and feeling drowsy, and worsening of suicidal ideation and elevation of liver enzymes.

   Placebo: There are no known serious health risks to treatment with placebo.

   Risk of mirtazapine combined with cocaine: Mirtazapine is FDA approved for the treatment of depression and is available for use in patients with depression and cocaine dependence. Previous studies have not reported any serious adverse events of mirtazapine in cocaine dependent subjects (ref). Also, according to clinicaltrials.gov, there are ongoing clinical trials using mirtazapine to treat depression in cocaine dependence.

   Potential Risks Not Due To Study Medications
   1. Potential risks to participating in this study not involving medication include: unauthorized disclosure of confidential information; discomfort or embarrassment related to urine collection ; possible unwanted encounters with friends or associates.
   2. fMRI: Some individuals become anxious due to claustrophobia during MRI scans. This risk will be minimized by having all subjects undergo a “mock” MRI scan using a simulator prior to the actual scan. Subjects with significant claustrophobia during the mock scan will be excluded from the actual MRI study.
   3. Individuals who have pacemakers, metal or electromechanical implants or metallic foreign bodies can be injured if they undergo an MRI scan. These individuals will be carefully screened out prior to participation in the MRI experiment by careful history and physical examination, and completion of a standard screening checklist for MRI.
   4. Phlebotomy: There is the potential risk of pain and bruising at the site of the blood draw for the HIV test and for the blood chemistries and complete blood count. There is also a slight risk of infection. This risk will be minimized by having blood drawn by a trained phlebotomist.
   5. Some subjects who are allergic to tape adhesive may have an allergic reaction to the ECG electrode adhesive. This risk will be minimized by only leaving the electrodes in place for the shortest period necessary to obtain an ECG.

2. * **Describe how each of the risks/harms/discomforts identified above will be minimized:**
   Participants will be evaluated by study physician to screen for physical or psychiatric illnesses or medication interactions that would prevent safe study participation. In order to reduce the potential risk of allergic reaction to the ECG electrode adhesive, electrodes will be left in place for the shortest period necessary to obtain an ECG. Mirtazapine risk of side effects will be minimized by 1) use of a single low dose of mirtazapine 2) screening out any subjects with evidence of suicidal ideation or liver disease. Social and legal risks associated with disclosure of confidential information will be minimized through the use of a 5 digit number to code all information obtained, storage of all information in a locked file cabinet, and obtaining a certificate of confidentiality from NIH to protect against subpoena of research information. All participants will be provided with a 24-hour phone number through which the study physician may be contacted to answer questions or to provide direction in case of emergency.

3. * **Describe any potential risks or harms to a community or a specific population based on study findings (e.g. information that could be stigmatizing or derogatory):**
   N/A

4. **Where appropriate, discuss provisions for ensuring necessary medical, professional, or psychological intervention in the event of adverse events to the subjects:**
   Evaluation of any acute psychiatric consequences from participation in this research will be provided by the study physicians. Treatment for medical and psychiatric consequences of participation in this research is available in the community, and subjects will be referred to appropriate treatment facilities as needed.

5. * **Describe criteria for when the investigator would withdraw an individual participant from the study; such as safety or toxicity concerns, emotional distress, inability to comply with the protocol, etc.:**
   Research participation may be stopped at any time by the study doctor without the subject's consent. The reasons might include:
   • the study doctor deems it necessary to protect the subject due to health or safety concerns;
   • the subject fails to follow study instructions; or
   • administrative reasons require the subject's withdrawal.

6. * **Summarize any pre-specified criteria that would trigger the investigator/sponsor/monitoring committee to stop or change the study protocol due to safety concerns:**
   N/A

   Data and Safety Monitoring
   Data and safety monitoring is a system for checking the study’s data at regular intervals over the study period to identify and address issues that could affect the safety of research participants. This requirement is in accordance with 45 CFR 46.111.

   The purpose of data and safety monitoring plan is to set forth study team procedures for monitoring/addressing:
   - Participant safety (physical, psychological, etc.)
   - Data validity
   - Early stopping (termination) based upon changes in risks and benefits.

7. * **Indicate if this study will have a Data Safety Monitoring Board (DSMB) or a Data Safety Monitoring Plan (DSMP): [Required for all greater than minimal risk studies]**
   - [x] **DSMB**
   - [x] **DSMP**

☐ No DSMB/DSMP [Note: This response is not applicable for greater than minimal risk studies]

8. * **Describe the composition and affiliations of the DSMB:**
The board will consist of physicians and faculty that are knowledgeable in clinical research but have no funding or other potential conflicts of interest with this research protocol. The DSMB will consist of clinical scientists recruited from VCU and outside VCU faculty that are not affiliated with this research program but who have the necessary scientific and clinical expertise to evaluate risks and benefits of this research.

Previous members of the DSMB have since retired or transferred employment from VCU, and were unable to make themselves available to attend the meetings and meet the requirements of DSMB membership. Subsequently, a new DSMB panel has been assembled to provide oversight of the project through its completion. They include:

Georgia Thomas, MD
VCU Department of Internal Medicine

Justin Canada, PhD
Assistant Professor
Division of Cardiology – VCU Pauley Heart Center
Department of Internal Medicine

Dave L. Dixon, PharmD, FACC, FCCP, FNLA, BCPS, BCACP, CDE, CLS
Associate Professor and Vice-Chair of Clinical Services
Department of Pharmacotherapy & Outcomes Science
Director, Center for Pharmacy Practice Innovation

Salvatore Carbone, PhD
Assistant Professor
Department of Kinesiology & Health Sciences
College of Humanities and Sciences

9. * **Describe the frequency or schedule for DSMB review of data:**
The DSMB will meet annually to review data and study procedures.

10. * **Describe what data (blinded or unblinded) the DSMB will review.:**
A DSM Board (DSMB) will be formed to provide additional, independent oversight of data related to patient safety. This committee will perform the following activities: (a) review the research protocol and plans for data and safety monitoring; (b) evaluate study progress, including data quality, participant recruitment rates, retention rates, outcome and adverse experience data, and risk versus benefit profile; (c) make recommendations to terminate the trial because of safety concerns; and (d) protect the confidentiality of the trial data and the results of monitoring. The DSMB will be blind to study medication, unless they believe that termination of the trial is warranted, at which time the blind will be broken.

11. * **Describe your Data Safety Monitoring Plan for monitoring the study's data to ensure the safety of participants. This plan should include (but is not limited to) the following elements:**
1. Who will monitor data
2. What data and/or processes will be reviewed
3. When and how frequently monitoring will occur
4. What report/documentation will be submitted to the IRB at the time of continuing reviews

See the help text for additional guidance.

This plan describes the general data and safety monitoring procedures for the proposed study.
1. The Principal Investigator will be responsible for knowing the policies of the local IRB. The PI will adhere to IRB policies and maintain accurate documentation of IRB correspondence and reports (e.g., annual report). The PI will be responsible for documentation and handling of all possible study-related adverse events. There are data collection and safety monitoring systems in place that will be available for the proposed study. These include staff training, manual driven processes, weekly audit of data collection/entry, medical screening with results reviewed by on-site physician, use of standardized assessments, continued medical monitoring during treatment, procedures to monitor medication compliance (e.g., riboflavin). The P.I. will assure that the above systems are in place and functioning properly for the duration of the study.

2. Adverse events (AE) will be reported to the IRB on an annual basis. Serious adverse events will be reported immediately (verbally within 24 hours) to the IRB, the DSMB, and to the National Institute on Drug Abuse (NIDA), which is the funding agency for this project. A written report will follow as soon as possible but in no more than three days. The written report will be in the format required by the IRB and will contain information regarding the date of the AE, description of the AE, severity rating (Grade 1 to 4), assessment of cause, whether the AE indicates an increased risk for current or future subjects, and whether changes to the informed consent form are necessary.

3. The DSMB will meet annually, and as needed if situations arise that require DSMB input.

4. Documentation regarding all AEs that occurred during the continuing review period (including previously reported SAE and UP summaries), as well as protocol violations and deviations will be included in the continuing review

HM15289 - Frederick Moeller
5-HT2AR: 5HT2CR Balance in Brain Connectivity in Cocaine Dependence

Privacy

Privacy refers to an individual's right to control how others view, record, or obtain information about them. When privacy is violated it can involve such things as

- Being asked personal questions in a public setting;
- Being publicly identified as having a particular characteristic or diagnosis;
- Being seen entering a place that might be stigmatizing;
- Being photographed, videotaped or observed without consent;
- Disclosure of personal information to unauthorized people

Privacy is not the same as confidentiality because privacy protections apply to people, and confidentiality protections apply to data. Confidentiality protections should be described on the Data Confidentiality page of this form, not here.

Instructions for this page:

Select all the applicable ways that the research team will protect participants' privacy throughout the course of the study. Not all will be applicable to every study.

To elaborate on any response, also click the "Other Protections" checkbox to provide further explanation in the last free-text question.

Read the entire page before filling out the form.

1. * **Protections when conducting one-on-one in-person interventions or interactions (for groups see Q2 below):**

- ☐ Conducting study activities in locations that maximize privacy (limited people around, closing doors, drawing drapes around beds, monitoring voice volume, etc.)
- ☐ Verifying identity before discussing personal information.
- ☐ Asking the participant if they are comfortable answering questions in that location
- ☐ Asking the participant if they are comfortable with having other people present (if any)
- ☐ Moving away from other people when conducting activities in public spaces or offering a private space
- ☐ Offering other options of ways to respond to sensitive questions (i.e. pointing, clicking, or writing) if uncomfortable verbally responding
- ☐ Using generic signs on research rooms and spaces, particularly for research on stigmatizing or sensitive topics
- ☐ Other protections not listed in this question – describe below
- ☐ N/A – study has no in-person interventions or interactions with participants

2. * **Protections when conducting group interventions or interactions:**

- ☐ Conducting study activities in locations that maximize privacy (limited people passing by, closing doors, monitoring voice volume, etc.)
- ☐ Moving to a more private area to answer questions or to discuss concerns
- ☐ Discussing privacy with the participants and the importance of not talking outside the group about what other people say during the group session
- ☐ Allowing participants to use a pseudonym or limiting use of individuals' names during the group activity
- ☐ Asking everyone in a public group setting (e.g. classrooms, workshops) to turn something in (blank or filled) so participants do not have to self-identify when turning in materials
- ☐ Collecting paper forms in a closed box or envelope rather than passing to others or leaving in an open area
- ☐ Limiting participant identifiers that would be visible on paper documents (i.e. using study IDs instead of direct identifiers)
- ☐ Allowing people to distance themselves from other participants during group activities
- ☐ Offering other options of ways to respond to sensitive questions (i.e. pointing, clicking, or writing instead of speaking)
- ☐ Using generic signs on research rooms and spaces, particularly for research on stigmatizing or sensitive topics
- ☐ Ensuring non-participating individuals are not captured on recordings or in photos
- ☐ Other protections not listed in this question – describe below
- ☐ N/A – study has no group interventions or interactions

3. * **Protections when conducting remote interventions or interactions (e.g. phone, text, video-conference, tele-health, online, etc.):**

- ☐ Conducting study activities in locations where study staff can maximize their own privacy (limited people around, closing doors, monitoring voice volume, etc.)
- ☐ Leaving/sending generic messages that avoid using study and participant identifiers, such as names, study titles, clinics, study topics, etc.
- ☐ Obtaining permission prior to sending text messages
- ☐ Advising the participant to move to a location where they are comfortable answering questions and will not be overheard
- ☐ Advising online participants to complete the activity at a time and location where they will be comfortable answering questions
- ☐ Ensuring non-participating individuals are not captured on recordings or in photos
- ☐ Offering other options of ways to complete the activity (i.e. online, paper, phone) if more privacy is desired
- ☐ Offering a way to save and return later to the online activity if privacy is compromised
- ☐ Other protections not listed in this question – describe below
- ☐ N/A – study has no remote interventions or interactions with participants

4. * **Protections when mailing study materials to/from participants:**

- ☐ Obtaining permission to mail study materials

- [ ] Confirming/verifying the accuracy of addresses before mailing items
- [ ] Ensuring the participant is able to personally receive mailed materials and has a way to protect their own privacy if they do not want others to know they are receiving research communications (i.e. notifying participants of when to expect it)
- [ ] Using return address labels and document headers that avoid study identifiers, such as study names, clinics, study topics, etc.
- [ ] Avoiding or limiting use of participant identifiers and health information on mailed documents (i.e. using study IDs instead of direct identifiers)
- [ ] Providing a return mailing address label or pre-addressed envelope to ensure returned items are sent to the correct address
- [ ] Communicating receipt of mail from participants and/or asking them to notify you when they mail it to ensure study documents are not lost in transfer
- [ ] Offering other options of ways to complete the activity (i.e. by phone or online) if desired
- [ ] Other protections not listed in this question – describe below
- [ ] N/A – not mailing any materials to/from participants

5. * **Protections when analyzing or disseminating study data** *Applicable to all studies*:

- [ ] Working only in locations where the study team can ensure privacy (not working in close proximity to non-study personnel, closing doors, closing/putting away documents/files before leaving, etc.)
- [ ] Securing physical materials only in locations that ensure privacy (access limited to authorized study personnel)
- [ ] Only sharing data/specimens in accordance with the Sharing Plan outlined in this smartform
- [ ] Obtaining explicit parental permission before disseminating or sharing recordings or photos of children
- [ ] Blurring/redacting/hiding faces and other identifiable features/marks (tattoos, scars, birthmarks, distinctive voice, etc.) in recordings or photos prior to disseminating or sharing
- [ ] Other protections not listed in this question – describe below

6. * **If "other protections" was selected in one or more of the questions above, describe all the other way(s) that the research team will protect participants' privacy. See the help text for additional guidance.**

Collection of all confidential information and consenting will be done alone and in private with the subjects in one of the interview rooms at the VCU CARI research facility. Only information that is necessary for the safe conduct of the research will be collected. All subjects will be given a 5 digit subject number which will be used in documentation of all study material collected from the subjects. In addition a certificate of confidentiality has been obtained from the National Institute on Drug Abuse to protect confidential information obtained for individuals who go on to enroll in the study.

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5-HT2AR: 5HT2CR Balance in Brain Connectivity in Cocaine Dependence

Data Confidentiality and Storage

Confidentiality refers to the way private, identifiable information about a participant or defined community is maintained and shared. It describes how the study's research materials (data, specimens, records, etc.) are protected from unauthorized access.

Instructions for this page:
Select all the ways that the research team will keep the study materials and data confidential throughout the course of the study. Not all will be applicable to every study.
To elaborate on any response, also click the "Other Protections" checkbox to provide further explanation in the last free-text question.

Read the entire page before filling out the form.

1. * **Protections for paper research materials:**
   - ☐ Maintaining control of paper documents at all times, including when at an off-campus location
   - ☐ Limiting or avoiding use of participant identifiers on paper documents (i.e. using study IDs instead of direct identifiers)
   - ☐ Storing paper documents in a secure location accessible only to authorized study personnel
   - ☐ Promptly transcribing, scanning, or abstracting data from paper into electronic platforms with destruction of the paper copy
   - ☐ Proper destruction of paper records (and obtaining prior permission when required) in accordance with VCU Records Management policies
   - ☐ Other protection not listed in this question – describe below
   - ☐ N/A – no paper research materials

2. * **Protections for research specimens:**
   - ☐ Maintaining control of specimens at all times, including when at an off-campus location
   - ☐ Storing specimens in a secure location accessible only to authorized study personnel
   - ☐ Labeling specimens with subject ID or other coded information instead of direct identifiers
   - ☐ Final destruction of specimens will be devoid of any identifiable information
   - ☐ Other protection not listed in this question – describe below
   - ☐ N/A – no research specimens

3. * **Protections for electronic files/data - See https://ts.vcu.edu/about-us/information-security/data-management-system/**
   - ☐ *Required for all studies* Use VCU-approved methods of data storage, transmission, and transfer (see https://dms.vcu.edu)
   - ☐ Remotely accessing VCU network storage to store data when at off-campus locations
   - ☐ Ensuring unauthorized individuals who might share a device do not have access to study materials (e.g. individual logins, separate accounts)
   - ☐ Using VCU-approved data collection tools and apps (e.g. REDCap) and storing exported analysis files in VCU-approved storage locations (see https://dms.vcu.edu)
   - ☐ When using non-VCU-approved electronic data collection tools, storage locations, data transfer platforms, and mobile apps (e.g. Dropbox, Box, Survey Monkey, Fitbits, novel apps):

     • consulting with VCU Information Security on proper data management (see https://ts.vcu.edu/askit/essential-computing/information-security/);

     • advising participants about the terms of use and privacy policies of those sites/apps;

     • limiting or avoiding use of identifiers; and

     • removing data promptly from the external location after transferring it to a VCU storage location
   - ☐ De-identifying the research data by replacing subjects' names with assigned subject IDs
   - ☐ Storing the study's linkage key in a password-protected and VCU-approved storage location (see https://dms.vcu.edu)
   - ☐ When analyzing particularly sensitive information, using computers that are unconnected from the internet.
   - ☐ Proper destruction of electronic records (and obtaining prior permission when required) in accordance with VCU Records Management policies
   - ☐ Other protection not listed in this question – describe below

4. * **Protections for computers and research devices/apps provided for participant use by the study:**
   - ☐ Transferring data promptly from the device/app to a VCU storage location
   - ☐ Setting strong passwords on computers and research devices (when applicable)
   - ☐ When providing devices or mobile apps to children, informing parents about the settings and how to manage them (if applicable), internet access, and any other installed apps on the device
   - ☐ Other protection not listed in this question – describe below
   - ☐ N/A – no computers or devices/apps being provided for participant use

5. * **Protections for email/online communications**
   - ☐ Only using VCU/VCU Health email addresses for study-related communications
   - ☐ Only using VCU/VCU Health–approved methods of teleconferencing or video conferencing (e.g. Zoom) (for studies involving HIPAA, contact VCU or VCU Health Information Security [as appropriate] about HIPAA-compliant systems)
   - ☐ Other protection not listed in this question – describe below
   - ☐ N/A – no email/online communications

6. * **If "other protections" was selected in one or more of the questions above, specify where this study's paper and electronic research data and/or physical specimens will be stored and how they will be secured from improper use and disclosure.**
   Confidentiality will be protected in several ways. All information collected solely for research purpose will be kept in locked, restricted access files. Subject records will be coded and filed by a number code. A "Waiver of Some or All Elements of Consent or Parental Permission" will be obtained in order to collect the names and phone numbers of someone who can serve as a secondary contact for the subject. This could include family members. RedCAP may be

used to store some of the collected data measures. RedCAP user permissions will be assigned to prevent research staff from having access to subject contact data. Subject identities will not be revealed in any publication of the data. Individual subject information will be transferred to outside sources only with the express written request of the subject. Subjects will receive a copy of their signed consent form. In addition, for each study in which eligible participants can be randomized, a Certificate of Confidentiality has been obtained from the National Institute on Drug Abuse to protect study information

7. * **If research data that contains any of the 18 HIPAA identifiers will be released to person(s) or group(s) outside of the VCU study team or the PI's department, identify the data recipient(s) along with their VCU department or other institutional or organizational affiliation(s).**
n/a

8. * **Select all identifiers that will be collected as part of this study (including for recruitment, data gathering, data analysis, etc.), even if the data will eventually be anonymized:**

- [x] **Names**
- [x] **Geographic Locators Below State Level**
- [x] **Social Security Numbers**
- [x] **Dates (year alone is not an identifier)**
- [ ] Ages over 89 (age under 89 is not an identifier)
- [x] **Phone Numbers**
- [ ] Facsimile Numbers
- [x] **E-mail Addresses**
- [ ] Medical Record Numbers
- [ ] Device Identifiers
- [x] **Biometric Identifiers**
- [ ] Web URLs
- [ ] IP Addresses
- [ ] Account Numbers
- [ ] Health Plan Numbers
- [x] **Full Face Photos or Comparable Images**
- [ ] License/Certification Numbers
- [ ] Vehicle ID Numbers
- [ ] Other Unique Identifier
- [ ] No Identifiers
- [ ] Employee V#

9. * **If the study will code (i.e. de-identify) the research data by replacing subjects' names with assigned subject IDs, explain the following aspects of the coding process:**

- The process for how subject IDs will be generated/assigned (e.g. random, sequential)
- Whether there will be a key that links the subject ID with direct identifiers.

If a key will be created, describe
- The place where the key will be stored
- The role(s) of all individuals who will have access to the key
- When the key will be destroyed

See the help text for guidance.
The permanent subject identification number is assigned sequentially by study staff at the first clinic visit in the context of the CARI PRESCREEN registry. The subject key is maintained as a database in REDCap with access limited to authorized staff only (PI and designees). The original subject key will be maintained indefinitely in support of the registry.
For the purpose of the present study, participants will be recruited directly from participants in the CARI PRESCREEN registry (Keyser-Marcus, PI), and will retain their CARI subject ID number (assigned by the registry). However, a separate subject key will be created for the present study and will be maintained on Redcap and destroyed when the final study analyses are completed.

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Date: Friday, October 15, 2021 9:35:09 AM Print Close

ID: HM15289 **HM15289** View: SF2 - Data Retention

HM15289 - Frederick Moeller
5-HT2AR: 5HT2CR Balance in Brain Connectivity in Cocaine Dependence

Data Retention

1. * **Select all of the ways that individually identifiable information obtained during pre-screening and/or screening will be handled for individuals who DO NOT qualify for the study:**
   - ☐ Immediately destroy the information and identifiers (no data collected)
   - ☐ Immediately destroy the identifiers connected with the data (anonymization)
   - ☐ Store until the end of study & then destroy
   - ☑ **Use as "screening failure" data by members of the study team**
   - ☐ Provide to others outside of the research team (with the participant's permission)
   - ☐ Request permission from participant to maintain and use the identifiable information
   - ☐ Other
   - ☐ N/A - study does not require screening procedures

2. * **Will participants be able to withdraw their data (paper, electronic, or specimens) from the study (e.g. ask that it be destroyed or returned) if they no longer wish to participate? (FDA-regulated studies should select No - see help text)**
   - ○ Yes
   - ● **No**

3. * **What will happen to the research materials (e.g. data, specimens, documents, etc.) when the research has been completed?**
   - ○ Stored indefinitely with identifiers removed
   - ● **Stored indefinitely with identifiers attached**
   - ○ Destroyed at the end of study once the minimum time required for data retention has been met per VCU Data Retention Policy and/or sponsor retention requirements
   - ○ Destroyed when notified by sponsor but not less than the minimum time required for data retention per VCU Data Retention Policy
   - ○ Other

4. **If "stored indefinitely with identifiers attached", explain why identifiers are necessary:**
   consent form is stored with the study documents

HM15289 - Frederick Moeller
5-HT2AR: 5HT2CR Balance in Brain Connectivity in Cocaine Dependence

Sharing Plan

This page addresses times when investigators may be required to share information about participants or may desire to share their research information/specimens with the aim of advancing science. This page creates a plan for when and how information/specimens could be shared.

Try to anticipate all reasonably foreseeable sharing so that the consent document can also reflect that information. However, it is acceptable to amend this page later and explain either how re-consent of previously and currently enrolled participants will occur or why re-consent should not be required.

The IRB reviews this page against the consent document (if one exists) to demonstrate the ethical principle of Respect for Persons by confirming that plans for sharing do not go against what participants would understand about the use of their data/specimens.

The IRB also ensures there are adequate protections for the privacy of participants and the confidentiality of participants' data/specimens when data is shared with others.

1. * **Is it likely investigators could discover information about child/elder abuse or neglect that would require mandatory reporting by the investigators or staff?**

   The Code of Virginia requires that most medical personnel and all employees of institutions of higher education report suspected child/elder abuse or neglect.

   - (●) **Yes**
   - ( ) No

2. * **Is it likely investigators could discover a previously unknown reportable disease or condition that would require mandatory reporting by the investigators or staff (i.e., HIV , coronavirus, hepatitis, etc.)?**

   ( ) Yes ( ) No

3. * **Will the sponsor or investigator obtain a Certificate of Confidentiality for this study?**

   Certificates of Confidentiality (CoC) are issued by the National Institutes of Health (NIH), the FDA and CDC to protect identifiable research information from forced disclosure. All human subject research studies regardless of funding can qualify to receive a CoC. A CoC is automatically issued for research that was ongoing on December 13, 2016. or initiated after that date. For more information, see https://humansubjects.nih.gov/coc/

   - ( ) No - Will not obtain CoC for this study
   - (●) **Yes - CoC has been obtained or issued automatically**
   - ( ) Yes - CoC request is pending
   - ( ) Yes - Plan to submit request for CoC and will amend study/ICF once status of request is known

4. * **Select the way(s) that individual-level information or biospecimens (including DNA) may be used by the VCU PI or VCU study team for other future research projects (i.e. analyses beyond/apart from the aims of this study)?**
   See help text for definitions.

   - [ ] Will use directly identifiable information or specimens.

     ('Directly identifiable' means that identifiers like name, medical record number, social security number, etc. are included in/attached to the dataset/specimens. Maintaining identifiable data for future research is treated as a registry by the VCU IRB. The IRB must approve the new research use in an amendment to this study or as part of a new study before the project is initiated. You will be asked more questions about this on a later page)

   - [ ] Will use de-identified or indirectly identifiable information or specimens.

     ('De-identified' means that a linkage/key code exists that links identifiers to data/specimens. When the researcher holds both the data and the key, the VCU IRB considers the subjects to be readily identifiable. Maintaining identifiable data for future research uses is treated by the IRB as a registry. The IRB must approve the new research use in an amendment to this study or as part of a new study before the project is initiated. You will be asked more questions about this on a later page)

   - [ ] Will use anonymized information or specimens.

     ('Anonymized' means that 1) no linkage/key codes exist that link identifiers to data/specimens; and 2) subjects cannot be readily identified, i.e. no direct or indirect identifiers or identifiable combinations of variables. The VCU IRB considers uses of anonymized data/specimens to not be human subject research.)

   - [ ] Will use aggregate results (summary-level results), not individual-level information or specimens.

     (The VCU IRB considers uses of aggregate data to not be human subject research because there are no individual subjects.)

   - [ ] Will contribute to an existing registry or repository

     (You will be asked more questions about this on a later page.)

   - [ ] Will not use information/specimens for purposes beyond this study.
   - [x] **Not sure and will submit an amendment when known**
   - [ ] Other use(s) of individual-level information in a way not listed above

5. * **Select the way(s) the VCU PI/study team may share individual-level information or biospecimens (including DNA) with other researchers who are not on this study team (i.e. for analyses beyond/apart from the aims of this study).**
   See help text for definitions.

Will share directly identifiable information or specimens with other researchers.

☐ *('Directly identifiable' means that identifiers like name, medical record number, social security number, etc. are included in/attached to the dataset/specimens. Maintaining identifiable data for future research uses is treated by the VCU IRB as a registry. The data recipient's use of identifiable data would require them to obtain IRB review. You will be asked more questions about this on a later page.)*

Will share de-identified or indirectly identifiable information or specimens with other researchers.

☐ *('De-identified' means that a linkage/key code exists that links identifiers to data/specimens. The VCU researcher maintains the key but does not share it with any other researchers. The recipient's use of de-identified data/specimens may not be human subject research if there is documentation that the key will never be shared with the recipient, but they should check with their own IRB about review requirements. You will be asked more questions about this on a later page.)*

Will share anonymized information or specimens with other researchers.

☐ *('Anonymized' means that 1) no linkage/key codes exist that link identifiers to data/specimens; and 2) subjects cannot be readily identified (i.e. no direct or indirect identifiers or identifiable combinations of variables). The VCU IRB considers uses of anonymized data/specimens by other researchers to not be human subject research, but the recipient should check with their own IRB about review requirements.)*

Will only share aggregate results (summary-level results), not individual-level information or specimens.

☐ *(The VCU IRB considers uses of aggregate data to not be human subject research because there are no individual subjects. The data recipient should check with their own IRB about review requirements.)*

☑ **Will contribute to an existing registry or repository (You will be asked more questions about this on a later page.)**

☐ Will submit data to an NIH genomic data repository (You will be asked more questions about this on a later page.)

☐ Will not share information/specimens with other researchers.

☐ Not sure and will submit an amendment when known

☐ Other sharing of individual-level information with other researchers

6. * **The Principal Investigator certifies that after the study has been closed with the VCU IRB, the following conditions will be met whenever individual level research information and/or specimens are used or shared:**

- The identities of participants who are represented in the dataset/specimens will not be readily ascertainable or otherwise re-identifiable by the recipient;
- If a linkage/code key is created, it will be maintained at VCU and not shared with the recipient under any circumstances;
- The PI will have no knowledge that the remaining information could be used alone or in combination with any other information to identify the individuals represented in the data; and
- The PI agrees to abide by this sharing plan even after the study has been closed with the VCU IRB.

● **Yes**

○ No

○ N/A - No sharing will occur

7. If the Certificate of Confidentiality has been obtained by the PI, upload it here:

HM15289 - Frederick Moeller
5-HT2AR: 5HT2CR Balance in Brain Connectivity in Cocaine Dependence

Existing Registry/Repository Details

1. **Provide name(s) of the registry/repository, if applicable.**
   Pre-Requisite Evaluation and Screening for CARI Research Eligibility and ENrollment (PRE-SCREEN)

2. * **Site having overall responsibility for the management of this registry/repository**
   - (●) **VCU**
   - ( ) Non-VCU

3. **If registry is located at VCU, provide IRB number(s) for the registry/repository:**
   HM20000294

4. **If VCU is not responsible for the management of this registry/repository describe the organization and/or individual who is responsible:**

5. * **Describe the research materials (data elements, specimens, recordings, etc.) that this study will contribute to the registry/repository:**
   DNA samples

6. * **List and describe any identifiers (including linkable codes) that will accompany data or samples to the registry/repository.**
   Samples and data will be labeled only with the participant ID, which is assigned by study staff, and the data in which the data/sample was collected. Keys to the break the code will be maintained on REDCap, in a separate database with limited access.

7. **If the participant gives specific permission for future use of this data/specimens in the informed consent, address 1) what are the stipulations/conditions, if any (e.g., research only on diabetes) and 2) describe how the registry/repository has a mechanism to capture, utilize, and respect these conditions?**
   The consent form allows participants to stipulate whether their blood/tissue samples may be stored and use in the future for 1) future research about drug or alcohol use, and 2) future research about other health problems. These responses are then captured on a future use case report form (CRF), which is entered into the repository and allows our investigators to accurately identify participant stipulations regarding future use of their genetic data.

8. **If there is not a mechanism to capture the participants data use stipulations, explain why this is not necessary.**

9. * **If participants will be able to access their data and/or samples from the registry/repository for personal use, explain how this will occur.**
   n/a

10. * **Explain how participants are allowed to request the data/samples be destroyed/removed from the registry/repository or why it is not allowed:**
    Participants are instructed to contact the study PI in writing (e.g., email or letter) to request that their samples be destroyed/removed from the registry.

HM15289 - Frederick Moeller
5-HT2AR: 5HT2CR Balance in Brain Connectivity in Cocaine Dependence

Pertinent and Incidental Findings

1. * **Is it likely investigators could discover a participant's previously unknown condition (e.g. pregnancy, disease, suicidal thoughts, wrong paternity, genetic results, or other findings that may be of importance to health or well-being) or if a participant is engaging in illegal or reportable activities:**
   - (●) **Yes**
   - ( ) No

2. * **Describe what possible pertinent or incidental findings stemming from research-only procedures may be discovered.**
   It is possible that individuals may disclose child or elder abuse in the context of the interviews (although this type of information is not covered in the interviews). Individuals are made aware of the limits to confidentiality during the consenting process and that child or elder abuse must be reported. In addition to reportable activities noted above, laboratory findings, the physical examination, and/or the ECG may reveal a medical condition that was not previously known to the participant.

3. * **Explain what actions or procedures research personnel should take to inform the PI of such a discovery :**
   Participants will be informed that, despite participant confidentiality protections, research staff, under current state law, are required to report certain communicable diseases, and any incidents of sexual or physical abuse of a child or elder. Evaluation of any acute psychiatric consequences from participation in this research will be provided by the study physicians. Treatment for medical and psychiatric consequences of participation in this research is available in the community, and subjects will be referred to appropriate treatment facilities as needed.

   If, during administration of the Cocaine Severity Rating Scale or at any other instance, a participant indicates suicidal ideation, the following measures will be taken. One of the study psychiatrists (Drs Moeller and Steinberg) will meet with any participants expressing current suicidal ideation to assess if it is clinically significant. If the psychiatrist feels that the suicidal ideation is clinically significant and in need of immediate treatment, subjects will be referred to the emergency room at VCUHS for evaluation for potential admission to the psychiatric unit.

4. * **Will findings be disclosed to participants and/or any other person/group outside of the study team?**
   - (●) **Yes**
   - ( ) No

5. * **Describe a communication plan addressing:**
   1. What criteria will be used to determine which pertinent and/or incidental findings will be communicated, including the following for health related findings:
   --- The reliability of the tests/images, such as being done in a CLIA-certified lab,
   --- Whether the meaning and significance of the findings are known,
   --- Whether the findings reveal a significant risk of a serious health condition,
   --- Whether there is an accepted treatment for the health condition revealed by the findings, and
   --- The risks both of knowing and not knowing the findings, including risks to family members from genetic testing results.
   2. What information will be provided during the consent process about the plans for communicating pertinent and/or incidental findings;
   3. Whether the participants will be given the option of refusing communication of some or all types of pertinent and/or incidental findings to themselves, their family members, and/or any other individuals or groups; and
   4. To whom and by whom the findings will be communicated, when, and how.
   In the event that test results indicate medically significant incidental findings in the opinion of the study physician, then the participant would be notified by a member of the medical personnel on the study (e.g., study physician or nurse practitioner) and referred to their personal physician or treatment facility for appropriate follow-up care. All of their test results will be provided to the participant or their physician after obtaining a signed CARI Research Participant Medical Record Request Form.