

Brain-to-brain Neurofeedback During Naturalistic Dynamic Stimuli to
Reduce Craving in Heroin Addiction

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the <specify NIH Institute or Center (IC) > Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.



INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed: Rita Goldstein

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1 PROTOCOL SUMMARY

Addiction to drugs or alcohol interferes with emotional experience and implementation of self-control. Individuals suffering from intermittent explosive disorder (IED) also have impairments in emotional experience and in self-control and histories of abusing alcohol and other drugs. Hence, in this protocol we study the Impairments in Response Inhibition and Salience Attribution (iRISA) in people suffering from drug addiction and/or IED. Our way to study iRISA is to have individuals with alcohol use disorder, cocaine use disorder, opiate use disorder, and/or individuals with IED undergo neuropsychological (behavioral, cognitive, emotional, personality) and brain and genetic testing.

Specifically, this research project will examine the 1) neuropsychological (NP), 2) brain [Magnetic Resonance Imaging (MRI) and electroencephalography (EEG)], 3) sex differences and 4) genetic correlates of iRISA. The study will screen and recruit 700 individuals with alcohol and/or cocaine use disorder and/or opiate use disorder and/or IED and another 500 healthy controls. After the aforementioned baseline procedures, individuals will take part in computerized cognitive tasks (similar to computer games repeated over 5-15 weeks) to study potential for cognitive enhancement in some subjects. Subjects will then come back every 3-12 months for a follow-up study (same as baseline) to predict and monitor longitudinal trajectories of change (e.g., relapse vs. abstinence or symptom improvement) in brain and behavior. When we refer to relapse in the case of IED, we refer to not abstaining from physical assault on person or property. In drug addicted individuals, relapse is referred to as not abstaining from the use of drugs and/or alcohol except for tobacco.

Due to the development of novel stressors from COVID-19, we continue to monitor iRISA and drug/alcohol use in individuals with substance use disorder (e.g., to cocaine, opiates or alcohol), IED, and control subjects using remote data collection via internet-based questionnaires and cognitive-behavioral tasks (using online platforms including Prolific).



2 INTRODUCTION

2.1 STUDY RATIONALE

Disorders of self-regulation are characterized by chronic and relapsing behavioral tendencies that contribute to poor physical and mental health. Thus the aim of this protocol, to better understand basic mechanisms underlying iRISA, is conceptualized to be relevant and generalizable across a myriad of chronic and relapsing illnesses (where behavior is a contributing factor). Indeed, relapse remains a main challenge in treating any disorder that depends on changing and maintaining health behaviors for prevention or treatment. Relapse and self-regulation are in particular pertinent to the maladaptive conduct in externalizing behavior disorders. **Drug addiction:** is a chronically relapsing disease characterized by repeated periods of drug craving, intoxication, bingeing and withdrawal; multiple attempts by the addicted individual to stop or curtail drug use are unsuccessful. This disease of the brain is endemic nationwide: in 2008, almost 22 million persons aged 12 or older were diagnosed with substance dependence or abuse in the past year (8.9 percent of the population aged 12 or older). These statistics become all the more alarming considering the associated morbidity and mortality rates. For example, drug abuse causes 1.3 million emergency department visits and a staggering cost to the economy at ~\$250 billion annually. Specifically, cocaine, which is one of the substances most frequently associated with drug-abuse-or-misuse deaths, accounted for >90% of emergency room admissions. Alcohol misuse accounts for an estimated 88,000 deaths annually, making it the third leading preventable cause of death in the United States (CDC, 2010) Furthermore, opiates account for the majority of deaths in the United States, with an estimated 130 Americans dying every day from opioid overdose (Rudd et al., 2016). The potential impact of this proposal increases even further if abusers of other psychostimulants (e.g., methamphetamine) are considered. **Intermittent Explosive Disorder:** According to a recent review of the literature, reactive aggression is associated with excessive reactivity to provocation and with negative approach-related emotions such as anger in response to perceived threat (e.g., fist fight instigated by perceived threatening remarks) (Coccaro et al., 2004). Theories of reactive aggression have associated assault behavior with high emotional arousal in tandem with poor response inhibition (Raine et al., 1998; Siever, 2008). Therefore, reactive aggression is conceptualized as having a lower than average threshold for activation of aggressive responses (Nelson and Trainor, 2007). A psychiatric disorder best capturing such poor self-regulation and featuring it as a core problem behavior, is IED. IED is characterized by recurrent episodes of anger attacks and serious acts of physical assault or property destruction in response to disproportionately low provocation (Coccaro, 2004). It has been reported that approximately 1.43 million people die each year from either self-inflicted or interpersonal violence (with a much larger number of nonfatal victims) (WHO, 2007), mostly of unplanned nature (Siever, 2008). In a sample of nearly 10,000 people, the lifetime prevalence of IED was approximately 7% (Coccaro et al., 2004) and in another, the likelihood of IED since age 20 was 8.3%, and the odds of being physically aggressive were 6.6-fold higher if one had a diagnosis of IED versus other diagnoses (O'Leary, 2009). Therefore, in the current protocol, we focus on both addiction and IED as clinical entities in which dysfunctional self-regulation is a hallmark feature: both are prevalent in the population culminating in externalizing harmful



behaviors (e.g., compulsive drug seeking, assault behavior) that evoke serious public health concerns.

A major paradigm shift in this protocol is the integrated brain-behavior study of emotional and inhibitory processes to map features that are common to several psychiatric disorders where maladaptive behavior is a core consequence of impaired self-regulation. We take advantage of our empirically validated theoretically-bound iRISA model, with a choice of psychometrically sound measurements; adding the IED diagnosis, a largely understudied disorder of self-regulation, is a major innovative approach.

2.2 BACKGROUND

Neuropsychological (NP) mechanisms underlying perception of pleasure and behavioral control

The Salience Attribution part of iRISA refers to the individual's ability to process the saliency (importance) of a valued reward or punishment. Basic research suggests that after chronic drug administration the value of a drug reward is increased while that of a non-drug reward is decreased. For example, chronic cocaine in rats produces elevations in threshold for drug reward [number of cocaine infusions, amount per infusion, and intracranial self-stimulation are increased (Ahmed and Koob, 1998; Ahmed et al., 2002)] and reductions in responding for a non-drug reinforcer [saccharin cue (Grigson and Twining, 2002)]. Parallel human studies have generally reached similar conclusions; in addition to the expected increased sensitivity to drug cues, a relatively reduced sensitivity to non-drug rewards has been reported in drug-addicted individuals. For example, cocaine addicted subjects show lower activation of corticolimbic brain areas involved in the experience and perception of pleasure when viewing an erotic video than when viewing a cocaine video (Garavan et al., 2000). In cases of IED, the attribution of salience to a provocation is also disproportionate; IED is characterized by recurrent episodes of anger attacks. The Response Inhibition part of iRISA is akin to self-regulation and engages motor, emotional, cognitive and environmental systems and is phylogenetically one of the most advanced human executive functions (Rubia et al., 2003). Executive functions refer to the unique ability of humans to plan and organize their goals and to make decisions that take long term consequences into account; inhibitory control is one of the major executive functions (Frankle, 2000). Studies have shown that both addicted and violent individuals score lower on tests of executive function (e.g., cognitive control) (Simpson et al., 2001) and that alcohol intoxication further impairs these mechanisms (Pihl., 1998). In the case of drug addiction, relapse ensues and the individual cannot stop using drugs. In the case of IED, relapse can be conceptualized as disproportionate anger concomitant with assault on property and/or others.

Using MRI and EEG to explore the neurobiological mechanisms of iRISA

Neurophysiological and lesion evidence in animal studies suggest that the prefrontal cortex (PFC) is involved in both the perception of pleasure and control of behavior (Rolls and Grabenhorst, 2008), reacting differently to reward depending on the animal's needs and preferences (Tremblay and Schultz, 1999). Thus, basic neuroscience studies suggest that the subjective valuation of reward is mediated by the functioning of the PFC, and especially the orbitofrontal cortex (OFC) as part of the mesocorticolimbic dopaminergic circuit.



Studies of human neurological patients have provided clear parallels with the animal literature. For example, patients with OFC lesions fail to develop anticipatory responses to punishment (Bechara et al., 1999) and show impairments when they need to change their behavior in response to a change in reward contingencies in the environment (Rolls, 2000). These patients may be able to verbalize that the contingencies in the environment had changed but may still be unable to modify their behavior accordingly. In analogous human functional neuroimaging studies in healthy subjects, the OFC has been identified to respond maximally to extremes of a reward range (including best vs. worse outcome) (O'Doherty et al., 2001; Elliott et al., 2003), demonstrating an association with the relative magnitude of reinforcement [monetary, see (Knutson et al., 2000; Breiter et al., 2001)] or the subjective pleasantness (i.e., value) of the rewarding stimulus [liquid food (Kringelbach et al., 2003)].

OFC impairment is documented in populations with addiction and in populations with antisocial behavior and aggression and is therefore a major brain region of interest, though it is not the only one. Other areas of the brain that have extensive connections with the OFC, such as the anterior cingulate cortex (Devinsky et al., 1995), or that are also implicated in anticipation of reward [e.g., nucleus accumbens: NA/midbrain (Breiter and Rosen, 1999)] will also be studied in this project. Limbic system (e.g., amygdala) response to reward and punishment is also examined in this study. These brain areas will be studied with the use of specific functional MRI (fMRI) tasks and complementary resting-state functional connectivity and structural imaging measures.

While fMRI provides high spatial resolution (millimeters) of brain areas activated during *seconds* of mental activity, and is indeed suitable to identify the brain regions involved in reward processing and inhibitory control, the cognitive and emotional substrates of relapse (e.g., anticipation, inhibition, decision-making) occur in bursts of *milliseconds*. Electroencephalographic (EEG) recordings can supplement fMRI by directly reflecting the brain's ongoing (real-time) processing of cognitive and emotional challenges. Thus, signal-averaging techniques can extract time-locked event-related potential (ERP) components from the EEG, yielding high temporal resolution (milliseconds) of neural responses. In particular, components in the ERP such as the P300, ERN, N2, and CNV are known to reflect cognitive brain responses to the types of stimulation paradigms used during fMRI. Therefore, ERPs will offer a powerful complementary analysis to fMRI in the current study (acquired separately).

This protocol will therefore develop and assess NP (cognitive, behavioral, emotional, and personality) stimulation paradigms suitable for both MRI and EEG studies of iRISA, and for cognitive training, in drug addiction and IED.

Sex differences in addiction

With 5 million current cocaine users aged 12 or older (1.9% of the population), cocaine use is endemic nationwide (from the 2016 National Survey on Drug Use and Health). National studies also show that there is more rapid increase in the use of all drugs of abuse (except alcohol) by women compared with men, comprising a unique public health concern in the US (Lynch, Roth & Carroll, 2002). Certain aspects of drug use and addiction are clearly more severe in women. Using cocaine addiction as an example, compared to men, women are more likely to have an earlier age of cocaine use onset (Van Etten & Anthony, 1999), and they are 3–4 times more likely to become addicted within 24 months of first cocaine use (O'Brien and Anthony, 2005) reporting a



greater difficulty in quitting (Lynch, Roth & Carroll, 2002; Becker & Hu, 2008). Based on the Substance Abuse and Mental Health Services Administration data, women also show more treatment admissions specifically for cocaine, at 8.1 vs. 6.4% for men in 2012. Also, women seek treatment earlier (Anglin, Hser & McGlothlin, 1987; Griffin et al., 1989; Westermeyer & Boedicker, 2000; Brecht et al., 2004) and present a greater severity of abuse when admitted to treatment not recovering as quickly from cocaine abstinence (Griffin et al., 1989) and resuming higher levels of drug use following relapse (Gallop et al., 2007). Abstinent women report higher levels of craving following exposure to cocaine-related cue (Robbins et al. 1999), leading to the hypothesis that women may be more vulnerable to relapse, as indeed supported by treatment outcome studies (Ignjatova & Raleva, 2009). This clinical pattern is consistent with preclinical literature on sex differences in brain function that suggests that chronic drug use may cause sexually dimorphic neuro-adaptive alterations in the cortico-limbic-striatal circuits that contribute to craving and relapse (Lynch et al., 2007). Sex differences in addiction and relapse are also expected based on differential dopaminergic function and structure, and indeed human studies have reported differential pharmacological sensitivity to cocaine (Evans, 2007) and other stimulants (e.g., d-amphetamine). However, relatively little is known about the neurobiological basis of sex differences in human addiction partly because women are greatly underrepresented in imaging studies (and in outcome studies in neuroscience in general). Strikingly, of 869 functional neuroimaging studies relevant to iRISA in addiction and published since 2010 (Zilverstand et al., 2018) (we conducted prior reviews in 2002 and 2011, which spanned the previous two decades), where 105 studies were included in a qualitative synthesis (records were excluded for lack of a control group or absence of whole-brain analyses), only three studies were powered to conduct gender comparisons ($N > 20$ females) (see Figure in specific aims page). Increasing the number of females to be included in this study, both addicted and healthy controls, we will decrease this knowledge gap by elucidating mechanisms underlying iRISA in female addiction. Results could contribute to developing gender-tailored interventions (note their fledgling use to reduce violence and HIV, comorbid with drug use) as exemplified by adapting different cognitive strategies to reduce craving (Andersen, Sawyer & Howell, 2012).

Genetic contributions to iRISA

We will collect and store blood samples to examine the role of genetic and epigenetic indices, and other biomarkers in the selected behavioral phenotype of impaired reward processing and control of behavior in addiction and IED.

Studies of the genetic contributions to poor reward processing and inhibitory control have recently started to identify several functional polymorphisms that alter the transcription, and thus the functions of neurotransmitters, enzymes, and neurotrophic factors regulating approach (e.g., to reward) and withdrawal (e.g., control of) behavior and emotional states essential for survival. In this study we will investigate these genotypic contributions that are particularly pertinent to the development and maintenance of substance abuse or drug addiction (and related psychopathology). For example, we study a variant of the serotonin transporter (*5-HTT*) (Anguelova et al., 2003) gene, which has been associated with impulsivity, alcohol, and polysubstance abuse; the dopamine receptor D4 (*DRD4*) gene's nucleotide variation (the so-called 7-repeat allele), which has been associated with processing of reward salience and poor impulse control, and has been found to be over-represented in opioid dependent, nicotine, and



other drug abusing subjects; the monoamine oxidase A (MAOA) gene promoter located on the X chromosome, which has been implicated in impulsivity and aggression (Manuck et al., 2000; Caspi et al., 2002). We also study any other polymorphism which may be discovered in the future to be associated with any aspect of reward processing, inhibitory control, self-regulation, substance abuse, drug addiction, aggression or IED.

Studying iRISA during COVID-19

The novel coronavirus presents an unprecedented time for research in individuals with substance use disorders and related conditions (e.g., IED). These already vulnerable individuals are positioned to experience unique and unprecedented challenges during the COVID-19 pandemic. Stress, including factors such as loneliness and financial instability, impact the likelihood of relapse and contribute to poorer outcomes in individuals with drug addiction (Sinha, 2001). The unique COVID-19 pandemic is predicted to exacerbate existing mental health conditions (Inchausti et al., 2020) and severity of drug use including craving (Tomova et al., 2020) in these individuals. For example, social distancing, stay-at-home, and shelter-in-place orders could impact the ability of these individuals to access their drugs of choice (e.g., leading to withdrawal) and treatment. Research is therefore urgently needed on the impact of COVID-19 on individuals with substance use disorders and related conditions. We will remotely collect measures from these individuals to better understand the impact of the COVID-19 stressors on iRISA and alcohol/drug use patterns.

2.3 PRELIMINARY STUDIES

MRI

Preliminary results from this protocol (transitioning from Brookhaven National Laboratory; ongoing for over a decade) suggest that cocaine addicted individuals have behavioral and neural impairments in their ability to process relative reward and in control of behavior. For example, using several levels of a generalized (monetary) reinforcer to assess the neurobiology of relative reward processing in drug-addicted individuals on both behavioral (rating scales) and brain (fMRI) tasks, we found that a distinct subgroup within cocaine users exhibited a restricted range of subjective sensitivity to money gradations, reporting \$1000 to be equally valuable as \$10 and 45¢ to be as equally interesting as 1¢ (Goldstein et al., 2007). This compromised subjective sensitivity to different amounts of money in this subgroup of cocaine users was accompanied by compromised graded activation of the left lateral OFC to relative monetary reward compared to controls. We concluded that decreased neural sensitivity to reward in the PFC and a restricted range of variability in the value attributed to reward play a determining role in the ability of drug addicted individuals to use internal cues and feedback from the environment to modify inappropriate (drug-escalated) behavior. This interpretation was further supported by increased involvement of brain areas central to habits (e.g., dorsal striatum), or behaviors that are insensitive to outcomes, in processing the value of money (Konova et al., 2012). Further, we documented a decreased self-reported control of behavior in cocaine addicted individuals which was associated with an objective measure of control and conflict resolution, an executive capacity previously associated with PFC function.



Using a different task (emotionally salient drug Stroop task), cocaine addicted subjects and healthy controls view drug words and matched neutral (household) words while undergoing fMRI. Instructions are to press with speed and accuracy one of four buttons (yellow, blue, red, green) corresponding to the ink color of the word they had just viewed. In this task, although the study groups did not differ on task performance (accuracy or reaction time), the cocaine subjects showed profound anterior cingulate cortex hypoactivations compared with healthy controls throughout the task (Goldstein et al., 2009); we interpreted this finding to represent attention bias to a drug-related context in the cocaine addicted individuals.

EEG

We have validated our fMRI money results using EEG. Using the same sustained attention task and monetary reward quantities for the high, low and no gains (45¢, 1¢ and 0¢) while recording ERPs, we replicated the impact of monetary reward on neural responses (measured here with the P300 ERP component) in healthy young adults (Goldstein et al., 2006). This result was consistent with a large body of literature implicating the P300 in processing reward magnitude and valence [e.g., (Yeung and Sanfey, 2004)]. Importantly, we subsequently replicated these results in 18 healthy individuals matched on age and other demographic factors to 18 cocaine addicted individuals (abstinence 0-4 days) (Goldstein et al., 2008): while in the control subjects the amplitude of the P300 component was higher in the 45¢ condition than the lowest 0¢ condition, a similar P300 response to money was not significant in the cocaine addicted subjects. In parallel, only the control subjects reacted faster to the highest monetary condition (45¢) as compared to the lowest (0¢). Importantly, only in the control subjects these P300 amplitude differentials directly intercorrelated with the respective behavioral adjustments to the monetary incentives (45¢>0¢ with accuracy and 1¢>0¢ with reaction time); in the cocaine addicted subjects, the better the accuracy adjustment for the high monetary condition, the less frequent the cocaine use during the year preceding the study. Our most recent results show that such compromised P300 responses to money characterize both cocaine urine positive (current users, shorter abstinence) and cocaine urine negative (longer abstinence) addicted individuals, who show the most compromised P300 amplitudes (Parvaz et al., 2012b) as potentially driven by structural integrity of the PFC (Parvaz et al., 2012a).

MRI and Clinical Outcome

We have now amassed preliminary evidence of cocaine addicted individuals as they proceed through treatment and follow-up, where these subjects are scanned at baseline and again after 6 months (Moeller et al., 2012). Subjects completed the same drug Stroop task described above, both at baseline and again after 6-months. fMRI analyses revealed that responsiveness increased in the dopaminergic midbrain (encompassing the ventral tegmental area/substantia nigra complex, brain regions where dopamine is produced) from baseline to follow-up. This enhanced midbrain responsiveness was further associated with reduced (behavioral) laboratory and real-world measures of drug seeking over the same six month period. These results support the use of fMRI at baseline to monitor and predict follow-up end-points, and demonstrate our collaborations with residential treatment facilities as described in this protocol.

MRI and Genetics



We showed that OFC gray volume reductions in cocaine addicted individuals were modulated by the monoamine oxidase A (MAOA) genotype (Alia-Klein et al., 2011). The MAOA gene controls the enzyme that regulates metabolism of monoamine neurotransmitters, including dopamine. The low expression variant of this gene is associated with increased risk for aggression and antisocial behaviors (Manuck et al., 2000; Caspi et al., 2002) and alcohol addiction (Samochowiec et al., 1999; Saito et al., 2002). In our study, compared to controls, cocaine subjects with the low-activity MAOA variant, but not carriers of the high-activity allele, showed reduced medial OFC grey matter volumes which were correlated with longer lifetime cocaine use (Alia-Klein et al., 2011). These results suggest a gene $\times$ disease interaction that modulates gray matter volume in the OFC [critical for reward processing (Parvaz et al., 2012a)], perhaps rendering some cocaine subjects more vulnerable to relapse. Other genes contribute to individual differences related to addiction and IED.

Importance of the Knowledge to be Gained

The study aims to help elucidate the underlying neurocognitive mechanisms of addiction and impulsive aggression, especially as pertaining to lack of self-control and impaired pleasure perception. Given that these measures at baseline will be used to predict response to cognitive training and longitudinal outcome, this study could facilitate the development of novel therapies to prevent, treat, or intervene in these disorders.

2.4 RISK/BENEFIT ASSESSMENT

2.4.1 KNOWN POTENTIAL RISKS

Potential Risks:

Physical:

1. Neuropsychological testing is considered to be of *MINIMAL* physical risk.
2. The MRI scans are considered to be *MINIMAL* risk and include the following: The MRI machine creates a strong magnetic field. If a subject has certain metal objects in their body, for example, metal fragments, non-removable hearing aids, nerve stimulators, or pacemakers, they will not be allowed to enter the magnet area and cannot participate in this part of the study. Subjects may be bothered by feelings of claustrophobia ("feeling enclosed") while in the scanner. Because the MRI makes loud "knocking" noises, the subject will be asked to wear earplugs. While the MRI makes the "knocking" noise, a subject might feel a tingling sensation in their arms or legs, but this is unlikely to occur. The subject may become dizzy or experience a metallic taste in their mouth if they move their head quickly in the magnet. The radio waves produced by the scanner could cause a warm sensation, but this is unlikely. Information collected over 20 years has found no evidence of any long-term risks associated with MRI scanning.
3. EEG recordings are considered *MINIMAL* risk. There is a possibility of temporary reddening or irritation at the sites prepared for the EEG sensors, but when such rare irritations occur they typically improve during the hours after the sensors are removed. Only materials designed specifically for skin preparations are used, and these materials are applied from pre-dispensed



single-subject quantities with single use applicators. During EEG testing the sensors and cap may cause subjects to feel itchy. Any residue of the gel that remains on their hair after the sensors are removed will easily rinse out in their next bath or shower at home. Self-contained shampoo caps approved for hospital use are used to remove the maximum amount of gel before subjects leave the laboratory.

4. The blood sampling for genotyping may result in some momentary discomfort. Risks associated with a blood draw may include bruising, swelling, dizziness, fainting, and infection. To avoid any complications, we will use sterile equipment, and only trained professionals will draw the samples for this test. No physical risks or discomforts are likely to be presented.

5. **Psychological:** (A) Although screened for claustrophobia before MRI onset, some subjects may experience claustrophobia while inside the MRI (note that subject withdrawal due to claustrophobia is expected to be minimal as MSSM has an MRI simulator that allows the acclimatization of subjects to the 'enclosed' MRI environment before subjects actually enter a real scanner). Subjects have the ability to communicate with investigators for the duration of the experiment and may discontinue their participation at any time for any reason. (B) During NP tests and fMRI, money subtraction for errors or decisions made could be frustrating, but such frustration is expected to be transient; in addition, subjects will never lose their own money. (C) Neuropsychological testing and cognitive training are considered to be of low psychological risk, mainly limited to frustration or boredom (experienced in a minority of subjects); subjects are monitored by appropriately trained personnel, and breaks are encouraged for everyone. (D) Interviews involve questions that subjects may consider as sensitive or intrusive. As at any point in the research study, only trained personnel perform these procedures and subjects have the right to terminate any one part or the whole of their participation. Subjects can also request a list of mental health clinics and programs that deal with drug addiction or aggression as appropriate. (E) Psychological risks of genotyping are small. The genetic polymorphisms we will be analyzing do not diagnose any one individual as to their current or future mental or physical health or that of their children. Rather, the information obtained from the DNA serves to study associations in large groups of individuals between addiction and IED and their emotional attributions and control of behavior. Subjects will not receive results of the genetic test because our analysis cannot be used to inform subjects about their own profiles; rather results are experimental and not yet completely understood. No commercial product will be developed from the subjects' DNA sample. There may, however, be risks that are presently unknown. (F) Craving may be elicited in the drug addicted subjects exposed to drug-related stimuli. Anger may be elicited in the IED subjects exposed to anger related material. These are expected to be mild reactions and will be monitored throughout the study by our trained staff and by the subjects' self-reports. Subjects will be discharged only when the post-study craving or anger is reduced to pre-study baseline levels, which is expected to happen within 20 minutes, or to other safe-to-discharge levels as determined by the Principal Investigator, co-PI, and trained personnel. Subjects will be interviewed and debriefed about their experiences. Also, as with all study procedures, subjects may discontinue participation at any given point in time.

6. **Social:** None; **Economic:** None

2.4.2 KNOWN POTENTIAL BENEFITS

NIH Protocol Template for Behavioral and Social Sciences Research



Subjects will not benefit directly from participating in this study; however, they will receive monetary compensation for the study procedures they complete as described in form HRP 503.

2.4.3 PROTECTION AGAINST RISKS

Flyers and advertisements will list a confidential toll-free telephone number to call for more information. Messages left on voicemail will be accessed (by password) only by the Principal Investigator, co-PI or trained personnel who will screen all potential subjects and provide them with comprehensive information about the study, including all possible risks and benefits of participation. Before study onset, the Principal Investigator, co-PI or credentialed personnel will obtain written consent from each subject in compliance with PPHS policies and procedures regarding capacity to provide consent. The consent form will include descriptions of the study procedures, potential risks and benefits, and the list of subjects' rights.

To protect against the physical risks associated with the collection of blood samples, trained professionals use only safe and sterilized equipment and materials. The physical risks associated with MRI scans are minimized by thorough subject screening to ensure that the subject has absolutely no metal in his/her body or on his/her person. MRI scans are conducted in an appropriately safeguarded environment staffed by professionals to minimize the risks of metal objects to come under the influence of the magnet. Women of childbearing age undergo urine test for pregnancy on each MR study day.

Blood Samples: The blood for DNA extraction will be appropriately stored by a credentialed staff member if the subject consented by providing his/her initials next to this option. The samples will be stored with the sample number only. It will not have subject's name, record, or initials on it. Only the Principal Investigator, and co-PI of this study and credentialed study personnel will have the spreadsheet that links the coded sample with identifying information.

All data obtained in this study which is contained in our database will be completely de-identified; ID codes will be used. The key that links subject data to any identifiers will not be accessible to anyone but the Principal Investigator, co-PI and credentialed study personnel. This separate file linking the ID codes with subject names will be kept in a locked cabinet, or stored - password protected - on an encrypted computer, and could be accessed by credentialed personnel of this study only as approved by the Principal Investigator and co-PI. Similarly to all other study materials, the facial recordings data will be protected by separating subject names from their faces, using numerical codes only, and locking (or password protecting) the raw data with access to trained study personnel only.

2.4.4 PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF SUBJECTS

During all communications with the subjects trained personnel guarantee privacy throughout all study procedures. For example, subjects are continuously reminded of their opting-out possibilities, and questions about their level of comfort and the appropriateness of the time (of call/communication) are interspersed throughout all communications with the subjects. In addition, NARC has several spacious testing spaces to guarantee privacy; arrangements have been made to reduce interaction between subjects with other subjects or others who are not part



of the research team (e.g., separate entrance door to NARC's testing space). All examiners are trained to be highly sensitive to all and any subtle indications of needs for privacy.

3 STUDY DESIGN

3.1 OBJECTIVES

The main objective of this study is to examine the 1) NP, 2) brain (MRI, EEG), 3) sex differences and 4) genetic correlates of iRISA in addiction and IED. A second objective is to develop objective ways that will enable the longitudinal prediction of clinical outcome based on this multifaceted data. A third objective is to study whether repeated training on select cognitive tasks would enhance cognition potentially more in those whose longer-term outcome is better. We hypothesize that using our baseline measures we can characterize the subgroups of individuals most responsive to these cognitive exercises as predictive of better clinical outcome and potentially more preserved brain and behavior function at follow-ups. Addressing the COVID-19 pandemic, we will also collect data remotely to provide a perspective on how the pandemic directly affects iRISA and drug/alcohol use in these individuals. We hypothesize that individuals with substance use disorders will be at higher risk for worsening iRISA and drug use patterns (including relapse) due to the many COVID-19 related stressors.

3.2 NUMBER OF SUBJECTS

Planned enrollment for this study is 500 normal healthy volunteers and 700 individuals addicted to cocaine and/or alcohol and/or opiates or individuals who have IED. All subjects are recruited at MSSM. Attrition is expected to be highest (>50%) at the last time point. Note siblings are part of these numbers, classified based on the criteria they would meet (control vs. cocaine/alcohol/opiates and/or IED).

COVID-19 Addendum: Planned enrollment for remote data collection is anticipated to be 1500 research participants.

3.3 STUDY TIMELINES

This project is expected to span ten years, encompassing April 2013 – April 2023. After screening, all subjects undergo a baseline MRI followed by cognitive training sessions (5-15 sessions) followed by additional MR scans and interviews/questionnaires every 2 weeks-12 months for up to five years; brief telephone interviews and reminder phone calls are performed bi-monthly. Completion of all study procedures depends on subject-related factors (e.g., motivation) and other study factors (e.g., time/staff constraints).

COVID-19 Addendum: This arm of the study is anticipated to be ongoing through the duration of the pandemic and its aftermath. Research participants are expected to complete the first several assignments (questionnaires to ascertain demographics, medical history, response to the pandemic and drug use) within about two weeks. After that, we will select the participants who will be administered the next assignments (further questionnaires described below including about mood, stress, personality and tasks tapping various cognitive functions) based upon responses



to the first several assignments. We will also select the participants who will repeat these tasks/questionnaires every 2-4 weeks for a total of ten times.

3.4 ENDPOINTS

Relapse at follow-up study sessions is our most important endpoint. We will use all measures obtained at baseline and throughout the study (MRI, EEG, NP/cognitive performance, clinical interviews, genotype) to predict relapse to drug use or symptom severity/persistence in both the cocaine/alcohol/opiate users and individuals with IED. Subjects who are excluded from any one part of the study but otherwise qualify for the other parts will remain eligible for those parts to increase N for relapse prediction.

4 STUDY POPULATION

4.1 ELIGIBILITY SCREENING

Medical history is ascertained by self-report. Subjects' psychiatric history and current functioning are ascertained by tools validated for use in our populations. These tools, extensively described in the PhenXToolkit <https://www.phenxtoolkit.org/index.php>, are based on commonly used interviews/questionnaires including the Structured Clinical Interview for DSM-5 Axis I Disorders [research version (First et al., 1996; Ventura et al., 1998)]. Using DSM-5 criteria, we also assess related comorbidities including childhood conduct disorder and antisocial personality disorder, which are independently associated with a specific dysfunction of the PFC (Bauer and Hesselbrock, 2001). Also completed are measures specifically designed for a substance-abusing or IED population, encompassing the Addiction Severity Index (McLellan et al., 1992b) and the IED interview (Cocarro, 2004), semi-structured interviews that provide an estimate of the severity of the disorders. Other tools include the Cocaine Selective Severity Assessment Scale (Kampman et al., 1998) that evaluates cocaine withdrawal signs and symptoms 24 hrs. from interview; and the Cocaine Craving Questionnaire (Tiffany et al., 1993).

Drug use is also assessed by means of the Substance Use Calendar (Hersh et al., 1999), similar to the time-line follow-back (Sobell and Sobell, 1992; Fals-Stewart et al., 2000), an instrument that has been validated in drug-abusing samples (Sobell et al., 1980; Hersh et al., 1999; Fals-Stewart et al., 2000) and widely used in assessing cocaine use outcomes in previous treatment studies (Higgins et al., 1994; Carroll et al., 2001; Carroll et al., 2004; Sinha et al., 2006). Treatment Services Review (McLellan et al., 1992a) assesses treatment-seeking status (e.g., participation in treatment and recovery meetings). Cocaine Negative Consequences Questionnaire and measures of cocaine cessation are also assessed. Treatment motivation, which has a unique effect on PFC cue-reactivity in cigarette-smokers (Wilson et al.), and perceived drug use opportunity (Wertz and Sayette, 2001), which is associated with enhanced PFC cue-reactivity (Wilson et al., 2004), are also assessed. Together, these screening tools assess inclusion/exclusion criteria, outcome and possible covariates.

These measures may be modified to assess heroin cravings and severity of use in people with Opioid Use Disorder (OUD).



We will also use the Severity of Opiate Dependence Questionnaire (Sutherland, 1986) measuring opiate use, physical and affective symptoms of withdrawal including craving; the Opiate Dependence Questionnaire (Sutherland, 1986) is also administered. The Opiate Treatment Index (Darke et al., 1992; Adekan et al., 1996; Darke et al., 1991) is a structured interview to measure effectiveness of drug treatments (on drug use, HIV risk-taking behavior, social functioning, criminality, health status, and psychological adjustment).

The following blood tests will also be performed once to determine study eligibility: Comprehensive Metabolic Panel, T4 (free/total), TSH, HIV AB Screen, Hepatitis B AB, Hepatitis C AB, CBC & PLT.

Completion of these tools depends on subject-related factors (e.g., motivation) and other study factors (e.g., time/staff constraints).

COVID-19 Addendum: Questionnaires and tasks will be made available on a rolling basis for the online platforms to be completed depending on the same factors (subjects' motivation, time commitment).

4.2 INCLUSION CRITERIA

Together, these medical and psychiatric screens determine that subjects meet the following eligibility criteria. **Inclusion criteria:** **(A)** Ability to understand, give informed consent and perform the tasks; **(B)** males and females 18-64 years of age at the time of enrollment in the study; and **(C)** DSM diagnosis for alcohol and/or cocaine use disorder and/or OUD and/or IED or otherwise problematic cocaine, opioid, or alcohol use as clinically determined.

Control subjects: *Healthy subjects are recruited to establish norms across all measures, scanned/tested at the same time intervals as the cocaine/alcohol and IED subjects. Inclusion criteria are the same as inclusion criteria A-B above; exclusion criteria are also the same (A-F) in addition including (G) maladaptive pattern of substance use and/or aggressive behaviors [unless limited to teenage years or other structured environment (e.g., school, military service)] and excluding nicotine or caffeine dependence; and (H) urine positive for any drugs on any study day.*

COVID-19 Addendum: Subjects recruited for remote data collection will meet these inclusion criteria: **(A)** ability to read the consent form and accept or decline study participation by clicking the "I agree" or "I do not agree" button; **(B)** males and females at least 18 years of age at the time of enrollment in the study; **(C)** having used cocaine and/or opiates more than once any time in their life.

4.3 EXCLUSION CRITERIA

Exclusion criteria: **(A)** present or past history of a neurodevelopmental (e.g., autism), neurological (including history of migraines or seizures), or a psychotic disorder; **(B)** head trauma with loss of consciousness for more than 30 min; **(C)** use of medications (current or in the last 6 months) with known CNS effects which may alter cerebral function, with the exception of psychotropics for the treatment of pain/depression/anxiety/PTSD (e.g. SSRIs) or as otherwise determined by the Principle Investigator; **(D)** current medical illness and/or evident infection; **(E)** being pregnant or nursing (for women for MRI; i.e., we will not enroll women into the study who are currently



pregnant or nursing; however, if women who are already consented into the study become pregnant during the follow-up periods, they will not be excluded at follow-up from non-MRI procedures including interviews); **(F)** contraindications to the MRI environment (if participating in the MRI component); and **(G)** positive urine drug screen on any day for any individuals not meeting criteria for cocaine and/or opioid addiction.

To increase generalizability of results, we do not exclude cocaine/alcohol/opiate or IED subjects for history of other drug addiction (e.g., marijuana) or other psychiatric disorders at high comorbidity with cocaine/alcohol/opiate addiction and IED (e.g., depression, post-traumatic stress disorder). Additionally, note that we do not exclude subjects based on their court-mandated status. As such they may be receiving treatment as part of the disposition of a criminal case, but in no case will they be “detained” at the facility. The individuals recruited from this population are not considered prisoners under OHRP regulations as these potential participants are not detained in the facility and can leave on their own accord.

Note: pregnancy is exclusionary for MRI. However, if a woman who participated in the baseline MRI session comes back for the behavioral tasks and to follow-up on relapse status, she will not be excluded (if MRI data already obtained when non-pregnant). Additional MRI will not be performed. *COVID-19 Addendum*: Pregnant women will not be excluded from completing the remote arm of the study.

4.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Trained personnel from the NARC research group provide educational talks to staff and patients in group settings in affiliated organizations (e.g., Phoenix House) soliciting participation in research in addition to disseminating knowledge. After these talks, interested individuals approach our personnel for further information and voluntary enrollment in research.

We also post flyers and receive phone calls from interested individuals. Any flyers that will be used for recruitment will be submitted to the IRB for review and approval before use. We will post similar advertisements on online forums, like Craig'slist and Facebook. Physical flyers will be posted broadly throughout the city and surrounding areas. Due to the sensitive nature of such advertisements, in public spaces flyers for people who use crack or cocaine will be posted alongside flyers for healthy controls, so that any onlookers will not know which flyer a person is responding to. (This strategy will not be necessary in addiction treatment centers or in online, private forums like Craig'slist.)

ResearchMatch will be used as a method for identifying and contacting potential subjects. The study specific announcement is included with this submission.

The NARC research group will also partner with BuildClinical, a technology company that uses social media, software, and machine-learning to target advertisements for our particular study population. With input from the study team about eligibility criteria (including indications, demography, and geography), BuildClinical utilizes machine-learning and data mining to identify specific groups across a multitude of online platforms, and applies algorithms to point interested candidates to the research study. Additional information about the BuildClinical algorithm and targeting methods, along with the BuildClinical advertising materials, study landing page, and



study screening form, are included in the study IRB page (see “BuildClinical Overview,” “BuildClinical Ad Copy,” “BuildClinical Landing Page,” and “BuildClinical Screening Form”).

Our study population is very difficult to identify, recruit, and maintain on-study. Partnering with BuildClinical will enable the study team to target this population more precisely, and to specifically engage individuals such as women with heroin and/or cocaine use disorder, a population that is continuously understudied in addiction clinical research and imaging and neuroscience outcome studies. Our study also aims to recruit healthy control subjects from the same communities where our opiate/cocaine/alcohol or IED subjects reside in order to match the groups on demographic variables; supplementing past recruitment methods with BuildClinical software will enable us to continue this healthy control recruitment strategy and demographically match our two groups.

BuildClinical will develop and post digital ads on search engines, health websites, and social media platforms. Participants who click an ad will be directed to a custom study landing page, where they will complete a screening form. Results from the forms will be transmitted to the research team, who will then follow up with potential participants. All such advertisements and participant-facing materials are attached in this submission and will be IRB-approved before they are implemented in recruitment.

Additionally, we will use a video explaining a number of our procedures to help recruit participants (and to help with the consenting process).

Thus, subjects are recruited by advertisements (in local newspapers, subways, bulletin boards and online), word-of-mouth and our collaborating institutes: **(A)** the Clinical Neuroscience Research Unit of the Connecticut Mental Health Center, supported by Yale University School of Medicine and the State of Connecticut (www.yalestress.org). **(B)** Phoenix House, the nation’s leading nonprofit provider of substance abuse prevention and treatment services (phoenixhouse.org/National/About/PhoenixFacts.html). **(C)** Samaritan Village (<http://samvill.org/pages/about-us.php>), another leading nonprofit substance abuse services organization. And **(D)** Mount Sinai’s Adult Outpatient Psychiatry Department (primary provider of mental health care for many area residents). We will also establish recruitment from the Bronx Veteran’s Administration Medical Center (providing mental health services to individuals with substance abuse disorders) and a network of several community-oriented hospitals in New York, including Beth Israel and St. Luke’s-Roosevelt Hospital, home of the Addiction Institute of NY.

In addition to these methods, we will receive referrals from other researchers. These referrals will include only research participants who explicitly opt to be contacted by other researchers to participate in additional studies. We will receive referrals from study GCO # 00-0952. We do intend to receive direct referrals from other researchers. Information will be shared through secure methods. We will not receive any referrals from other protocols until those protocols receive IRB approval to provide referrals.

Research participants enrolled in the study are also encouraged to spread the word and refer friends/acquaintances. They will be compensated (\$20) for this if the person they referred meets study inclusion criteria and agrees to participate. Participants enrolling in the sex differences portion of the study will be eligible for compensation for child care in order to increase accessibility to study participation.



Healthy control subjects are recruited from the same communities where our opiate/cocaine/alcohol or IED subjects habitually reside; this allows us to carefully match the groups on many of the demographic variables (e.g., sex, race, age, education, IQ, socio-economic status) that may affect our measures of interest. When a complete match is impossible, we statistically control for possible covariates. We will also use ResearchMatch.org and other resources available at MSSM to facilitate recruitment in our study. An effort will also be directed at recruiting siblings of our opiate/cocaine/alcohol and/or IED subjects. Word-of-mouth and explanation efforts would be used for this purpose. Example flyers for subject recruitment are attached.

All potential subjects are screened by telephone by a trained research assistant. Subjects are then invited on site and thoroughly interviewed as described below.

COVID-19 Addendum: Individuals participating in the COVID-19 remote data collection will be recruited through online forums (e.g., the Prolific online workforce) and by using our usual recruitment methods (described above). Recruitment materials on the Prolific platforms will include language directly from the study consent form. Questionnaires and tasks will be placed on online platforms (e.g., Prolific).

5 PARTICIPANT DISCONTINUATION/WITHDRAWAL

Subjects may be withdrawn from the study if they no longer meet eligibility criteria, if we find it is in their best interest to remove them, or if they do not or cannot follow study procedures. Subjects may also be withdrawn from specific study components (e.g., fMRI due to medical contraindications), but can still complete the other study procedures for which they are eligible.

COVID-19 Addendum: The study will be administered through online platforms (e.g., Prolific). Prolific workers receive an ID when they sign up with the website, which is linked to their personal profile in order to receive cashout payments. Prolific worker IDs will be only collected for the purposes of distributing compensation. Prolific worker IDs will not be shared with anyone who is not a member of the research team, and before any data sharing they will be removed from the data set. These worker IDs are not direct identifiers. The platforms themselves will not allow us to access participant direct identifiers. Messaging and rescheduling participants is built into both platforms using these anonymized participant IDs. Subjects may withdraw from the study at any time and may contact the study team through the anonymized messaging system in Prolific if they would like their data destroyed.

Prolific's data security systems protect participant data and confidentiality. Prolific's security systems use encrypted HTTPS connections that are secured by Transport Layer Security. Participants are anonymized by the platform and are assigned a unique 24-character worker ID that is not disclosed to the researchers. Researchers are unable to access any of the participants' identifiable information but are able to contact researchers with any questions or concerns through Prolific's anonymized internal messaging service. Furthermore, participants are free to opt out of any study at any time. While personally identifiable information is disclosed to Prolific, none of that data is disclosed to the study team. Instead, the research team has access to anonymized demographic data that can be used for screening purposes. Participants are informed of this before they disclose any demographic data to Prolific. Worker IDs are used by the study team in



order to process payments to study participants. This is all completed securely through the platform. Prolific does not receive any responses to any data collected by the study team. More information on data protection and privacy at Prolific can be found here: <https://researcher-help.prolific.co/hc/en-gb/articles/360018895214-Prolific-Practices-and-Security-Systems>.

6 STUDY ASSESSMENTS AND PROCEDURES

Urine screen for drug toxicology and pregnancy (in premenopausal women) are performed each study day.

Blood samples for genetic and epigenetic assays and other biomarkers are drawn from all consenting subjects at each blood draw visit. A needle will be used to collect up to approximately 2 ml of blood per kg of body weight from the participant's arm at each blood collection visit—an amount which is within NIH safety guidelines for clinical research (Peplow et al., 2019). The amount drawn will not exceed the lesser of 50 ml or 3 ml per kg of body weight at each blood collection visit, and collection may not occur more frequently than 2 times per week.

Hair samples used to test for drugs and other materials/chemicals (e.g. hormone levels, metals) will be taken from consenting subjects at each hair sampling visit. Stainless steel scissors will be used by trained study personnel to collect 0.2 grams (40-50 strands) of hair, collected as close to the scalp as possible. The sample will be placed directly into a clean Coin Envelope and sealed with the glue flap to be transported for analysis. Hair samples are optional and opting out will not affect a person's ability to participate in this study.

We may review mental health and alcohol/substance use records from treatment facilities where participants are, or were, in treatment, for information to confirm eligibility.

Psychiatric screens and interviews are performed in all subjects. Impairments of Response Inhibition and Salience Attribution (iRISA) mechanisms will be evaluated by several different non-invasive measures that probe into daily behavior (as measured by interviews, self-reports), personality [e.g., self-report questionnaires (Tellegen and Waller, 1997)] and task performance (e.g., timed computerized tests, outside or inside an imaging environment inclusive of MRI or EEG). Voice and/or facial recordings will be collected on an as needed basis during several of these procedures. Other tests, not directly associated with iRISA, such as memory and intelligence testing, are administered in this study as in other studies (Frankle, 2000) to rule out covariates and ensure intact general intellectual functioning. This is especially important since we also use neuroimaging to assess brain functioning (Bigler, 2001).

Baseline study procedures may be repeated several times for the duration of this protocol as determined by subject availability and other constraints. Reminder phone calls will be made; subjects will receive monetary remuneration irrespective of their relapse status.

COVID-19 Addendum: Subjects will be recruited via online platforms (e.g., the Prolific workforce) and our usual recruitment strategies. Recruited subjects will perform tasks and answer questionnaires remotely (described below). Subjects will be compensated for all completed tasks and questionnaires.

In addition to the fully-remote COVID-19 arm of the study, planned in-person study visits may be performed remotely in cases where public health events or personal sickness prevent in-person



meeting, in order to minimize risk to participants. The necessity of switching to remote work will be determined by the PI and Co-Is, in consultation with public health and hospital requirements where relevant. All efforts will be made to continue in-person where possible. Accommodations for remote procedures are discussed below. Remote study visits will utilize secure, Mount Sinai-authorized videoconferencing platforms, such as Zoom.

6.1 . NEUROPSYCHOLOGICAL PROCEDURES

Neuropsychological testing is a series of paper and pencil or computerized tests that assess abilities such as attention, memory, and motor coordination. These NP interviews, tests, and questionnaires are listed and described below. All NP procedures are conducted by trained personnel (e.g., Study Coordinators and research assistants – RAs - with appropriate training) and supervised by the Principal Investigator and co-PI (NY State licensed clinical psychologists). Some tasks are modified to fit the population of drug addiction and/or IED (e.g., more preparation time is allowed, fluency/how fast a person can say words is examined for drug-related or anger-related stimuli) or to increase focus on reward processing and inhibitory control. Note that these assessments take several hours (e.g., clinical interviews and questionnaires around 1-3 hours; cognitive baseline testing around 2-4 hours; cognitive training around 1-3 hours), depending on individual subjects' processing speed, and that as many components are completed depending on time constraints. Individual computerized tasks may take anywhere from 5-20 minutes.

If public health events or personal sickness prevent in-person meeting, as many of the items described below as possible will be performed remotely. Following the remote consent procedure described below, neuropsychological tests, interviews, tasks, and questionnaires will be performed over videoconference, with research staff either interviewing the participants or sending secure links to questionnaires for the participants to complete by themselves. All study items included in a study visit day will be completed with the research staff person available on videoconference. REDCap will be utilized for questionnaire completion, as is already in place for in-person assessments. Memory, attention, and cognitive inhibitory control tests, and computerized tasks including the Attention Network Test and Iowa Gambling Task, will be completed by participants using secure experiment presentation software (e.g., Inquisit, ePrime). All data collected remotely, including audio/video recordings when required in a task, will be anonymized and stored on password-protected computers to which only the study team has access, similarly to the data that is stored for in-person visits.

Because switches to remote work are made to decrease risk to participants, such changes to the protocol will not be considered major study deviations.

The domains assessed and the specific assessments that comprise each domain are as follows:

- **The SCID** is a semi-structured interview that includes assessment of DSM-5 based axis I psychopathology including alcohol and drug use and axis II personality assessment (e.g., antisocial personality disorder) (First et al., 1996). The axis I interview will be administered via TeleSage's secure, online NetSCID program. The axis II interview will be administered via software provided by Multi-Health Systems, Inc.



- **Mini International Neuropsychiatric Interview (MINI) 7.0.2 (2016).** The MINI is a widely used psychiatric structured diagnostic instrument in the format of a structured interview. The MINI comprises modules for 17 psychiatric diagnoses. Questions are phrased to allow only "yes" or "no" answers. Examples are provided to facilitate responses, and they are read word for word by the person administering it (Sheehan et al., 2016).
- **Life History of Aggression** is a semi-structured interview that assesses the degree of aggressive behavior that has characterized a patient's life-long experience (Coccaro et al., 1997).

6.1.1 ADDICTION AND DRUG USE

- **Addiction Severity Index** to obtain basic demographic and employment information, medical status, alcohol and drug use in the past 30 days and lifetime, legal status and lifetime involvement with the criminal justice system, family and social status (McLellan et al., 1992b).
- The **Cocaine Selective Severity Assessment Scale (CSSA)** to assess withdrawal symptoms (Kampman et al., 1998).
- The **Short Opioid Withdrawal Scale (SOWS)** to assess signs and symptoms of opioid withdrawal (Gossop, 1990).
- **Questionnaires/interviews** specific to the study to obtain information on factors which may affect results of the NP assessment, such as number of hours of sleep the night before, caffeine intake and consumption of medications, drugs of abuse and cravings using the Cocaine Craving Questionnaire (Tiffany et al., 1993) and/or the Heroin Craving Questionnaire (HCQ) (Heinz et al., 2006), and the Severity of Dependence Scale (Gossop et al., 1992), etc.
- **Short Michigan Alcohol Screening Test (SMAST)** is a 13-item questionnaire that requires a 7th grade reading level, and only a few minutes to complete. It was developed from the Michigan Alcoholism Screening Test. Evaluation data indicate that it is an effective diagnostic instrument, and does not have a tendency for false positives, as does the Michigan Alcoholism Screening Test (Selzer et al., 1975).
- **South Oaks Gambling Screen (SOGS)** offers a convenient means to screen clinical populations of alcoholics and drug abusers, as well as general populations, for pathological gambling (Lesieur and Blume, 1987).
- **Fagerstrom Test for Nicotine Dependence (FTND)** assesses intensity of physical addiction to nicotine (Heatherton et al., 1991).
- **Timeline Followback Calendar (CL-90)** a walk back calendar that assesses drug use in the past 90 days (Miller and Del Boca, 1994).
- **Treatment Services Review (TSR)** assesses health services utilization (McLellan et al., 1992a).



- **Cocaine Negative Consequences Checklist** to assess awareness of negative consequences from cocaine use (Michalec et al., 1996).
- **The Negative Consequences of Chronic Heroin Use** to assess the effect of long-term opiate use on life functioning (Moses et al., 2018).
- **Severity of Opiate Dependence Questionnaire** to measure opiate use, physical and affective symptoms of withdrawal including craving (Sutherland, 1986).
- **The Opiate Treatment Index** is a structured interview to measure effectiveness of drug treatments (on drug use, HIV risk-taking behavior, social functioning, criminality, health status, and psychological adjustment) (Darke et al., 1992; Adelekan et al., 1996; Darke et al., 1991).

6.1.2 IED AND AGGRESSION

- **Assessment for Intermittent Explosive Disorder.** An appropriate diagnostic interview was developed by Coccaro and colleagues and will be used in our study (IED-IR). This interview includes specific criteria available in the Diagnostic and Statistical Manual-IV, assessing the frequency of explosive events as well as a qualitative description of the event (Coccaro, 2004).
- **Assessment of Physical Aggression.** The Life History of Aggression is a semi-structured interview that assesses the frequency of aggressive behavior across the lifespan starting at age 13 consisting of questions on physical assault, verbal aggression, and destruction of property (Coccaro et al., 1997).
- **The Buss-Perry Aggression Questionnaire** (the most frequently used self-report measure of aggression) makes distinctions between Physical and Verbal aggression (as well as Hostility and Anger) with its subscales (Buss and Perry, 1992).
- **Personal History Questionnaire (PHQ)** asks respondents questions about the frequency with which they fought with siblings, friends, parents, and dating partners from grade school through high school (Canli and Amin, 2002).
- **Borderline Personality Organization Scale.** Three subscales (reality testing, use of primitive defenses, and identity disturbances) to dimensionally measure an individual's level of Borderline Personality Organization (Oldham et al., 1985).
- **Attitudes Toward Women Scale** measures how women are perceived on a societal level. Scores reflect the degree to which the respondent holds liberal or traditional views (Spence et al., 1973).
- **State-Trait Anger Expression Inventory (STAXI-II)** to assess state and trait anger expressions (Spielberger, 1988).
- **Levenson's Self-Reported Psychopathy Scale.** Measures the domains of manipulation/callousness and impulsivity (Levenson et al., 1995). **Conflict Tactic Scale (CTS-II)** is a questionnaire for individuals with a partner and their relationship including aggression toward each other (Straus, 1979).



- **Life Experience Questionnaire (LEQ)** is a checklist of life events that have emotional impact such as death of a parent, divorce, etc (Canli and Amin, 2002).
- **Childhood Trauma Questionnaire (CTQ)** is a self-report inventory that provides brief, reliable, and valid screening for histories of abuse and neglect (Bernstein et al., 1994).

6.1.3 MOOD AND PERSONALITY

- **Beck Depression (BDI) and Beck Anxiety (BAI) Inventory** survey symptoms of depression in the last 2 weeks (Beck, 1996).
- **Positive and Negative Affective States (PANAS state and trait measure).** The scale consists of a number of words that describe different feelings and emotions where scoring varies from 1 to 5 (Watson et al., 1988).
- **The Frontal Systems Behavioral Scale (FrSBe)** to assess distinctive behavioral problems putatively associated with damage to the different prefrontal cortical systems of the brain: apathy, disinhibition, and executive dysfunction (Grace and Malloy, 2001).
- **Conners' Adult ADHD Rating Scales (CAARS)** to assess indicators of restlessness, impulsivity, and self-concept (Conners, 1999).
- **BIS BAS Scales.** Measures personality in terms of reinforcement sensitivity (i.e., individual differences in behavioral inhibition and behavioral activation (Carver and White, 1994).
- **Multidimensional Personality Questionnaire (MPQ)** to assess personality traits (e.g., aggression, negative and positive emotionality, control of behavior) (Tellegen and Waller, 1997).
- **Sensitivity to Reinforcement of Addictive and other Primary Rewards (STRAP-R)** asks participants to respond how much they like and want addictive drugs and other primary reinforcers (food and sex) in several different contexts (Goldstein et al., 2010).
- **The Anger Rumination Scale** consists of nineteen items ($\alpha = .83$) to assess the tendency to focus on angry moods, recall anger related events, and think about consequences (Sukhodolsky et al., 2001).
- **The Psychological Entitlement Scale** consists of nine items (e.g., "If I were on the Titanic, I would deserve to be on the first lifeboat!"; $\alpha = .83$), rated on scales ranging from 1 (strong disagreement) to 7 (strong agreement) (Campbell et al., 2004).
- **The Anger Behavior Scale** consists of twenty-three items (e.g., "I discuss my anger to show how wrong others are"), rated on scales from 1 (almost never) to 4 (almost always) (Gerwin et al., 2006; Chambers, 1999).
- **Sensitivity to Reward and Sensitivity to Punishment Questionnaire (SRSPQ)** to assess sensitivity to environmental reward and punishment (Torrubia et al., 2001). **The State vs. Trait Loneliness** developed from the UCLA loneliness scale, to assess acute and chronic loneliness (Shaver et al., 1985).



- **The Perceived Stress Scale (PSS)** to assess perceived life stress in the past month (Cohen & Williamson, 1988).
- **The Brief Irritability Scale (BITe)** to assess irritability (Holtzman et al., 2015).
- **The Sort Boredom Proneness Scale (SBPS)** to assess state and trait boredom (Struk et al., 2015).
- **The Financial Well-Being Scale** to assess financial stress (Prawitz et al., 2006).
- **Epworth Sleepiness Scale** to assess state sleepiness at time of assessment (Johns, 1991).
- **Pittsburgh Sleep Quality Index** to assess sleep quality (Buysse et al, 1989).
- **WHO Quality of Life** to measure health-related quality of life (WHOQOL, 1993).
- **Substance Use Risk Profile Scale** to assess personality risk for substance abuse (Woicik PA et al., 2009).
- **The Five Facet Mindfulness Questionnaire** to assess elements of mindfulness that impact wellbeing (Baer et al., 2006).
- **The Ways of Savoring Scale** to assess savoring within mindfulness practice (Jose P.E. et al., 2012; Chadwick E.D., 2012).
- **Our own COVID-19 questionnaire** to assess exposure to the virus and its impact on a person's life and drug use (e.g., financial stability).
- **Menstrual History Questionnaire** to assess several factors related to the menstrual cycle (Nurses' Health Study, 1988).
- **Menopause Rating Scale** to assess menopausal symptoms (Heinemann et al., 2004).
- **The Survey of American Family Finances** to assess financial strain of subjects (Pew, 2015).
- **The Contemplation Ladder** to assess readiness to change substance use (Biener & Abrams, 1991).
- **The Conflict Tactics Scale** to assess history of family violence (Strauss, 1979).
- **The Lifetime of Experiences Questionnaire** quantitatively assesses life experiences (Valenzuela et al., 2007).
- **The Creature of Habit Scale** to measure habits and tendencies in everyday life (Ersche et al., 2017).
- **The Stanford Acute Stress Reaction Questionnaire (SARSQ)** to measure development of acute distress and predict the development of post-traumatic stress disorder (Cardeña et al., 2000).

Many of these interviews/questionnaires have been standardized by PhenX, led by RTI International and funded by the National Human Genome Research Institute (NHGRI), to integrate genetics and epidemiologic research. The PhenX Toolkit provides standard measures



related to complex diseases, phenotypic traits and environmental exposures. Use of PhenX measures facilitates combining data from a variety of studies, and makes it easy for investigators to expand a study design beyond the primary research focus. All Toolkit content is publicly available at no cost: <https://www.phenxtoolkit.org/>. We will use select standardized measures available in this Toolkit, which assess the domains described above.

6.1.4 MEMORY, ATTENTION AND COGNITIVE INHIBITORY CONTROL TESTS

We use a computerized cognitive testing available through Cambridge Cognition as described in <http://camcog.com/cantab-tests.asp>. The CANTAB® battery is considered the gold standard cognitive assessment system for academic research. It was originally designed by researchers at the University of Cambridge, used in academic research for more than 20 years. More details can be found in <http://camcog.com/cantab-for-academic-research.asp>. We may also use (in addition or instead of CANTAB) the tests provided by the NIHToolbox <http://www.nihtoolbox.org/Pages/default.aspx>. NIH Toolbox is a multidimensional set of brief measures assessing cognitive, emotional, motor and sensory function from ages 3-85, meeting the need for a standard set of measures that can be used as a “common currency” across diverse study designs and settings. These tests are freely available for NIH funded researchers.

In addition, the following measures may be used:

Other/demographic measures:

- **Modified Edinburgh Handedness Inventory** which assesses dominant handedness by having subjects mime several everyday activities (Oldfield, 1971).
- **Ishihara’s Color Blindness Test** in which subjects look at pictures and are asked to identify the numbers they see printed in different colors (Ishihara, 1979).
- **Socioeconomic status** using the Hollingshead Index, which asks about education and profession (Hollingshead, 1975).

Intellectual ability:

- **Matrix Reasoning** from the Wechsler Abbreviated Scale of Intelligence, in which subjects choose segments which best complete different pictures (Wechsler, 1987).
- **Wide Range Achievement Test III** Reading subtest in which subjects read a list of increasingly difficult words (Wilkinson, 1993).

Learning, memory, and inhibitory control:

- **Immediate and delayed verbal memory: California Verbal Learning Test** in which subjects are asked to repeat lists of words (Delis et al., 2000);
- **Attention Network Test** a computerized task in which subjects respond as quickly as possible to neutral visual cues in different directions on the screen (Fan et al., 2005);
- **Iowa Gambling Task** a computerized task in which subjects simulate playing a card game for amounts of play-money, selecting cards from ‘decks’ that present advantageous and disadvantageous reinforcement schedules (Bechara et al., 1997);



- **Verbal Fluency** in which subjects list as many words as they can that begin with a specific letter (e.g., B) or within certain semantic categories (e.g., food, drug-related) (Benton, 1968).
- **Free Talk Task** in which participants speak for ten minutes into a recorder about the negative impacts of drug use and the positive impacts of quitting using drugs on their lives.
- **Weather Prediction Task** is a computerized probabilistic category learning task which assesses the strength of individuals' stimulus-response associations (or habit learning) (Knowlton et al., 1994).
- **Working Memory:** In the Digit Span Forwards and Backwards (Wechsler, 1997), participants recall back a sequence of numbers in the normal order or reverse order.
- **The Two-Step Decision Task** in which participants choose between multiple slot machines to determine which seems to be the most advantageous option (Daw et al., 2006).
- **The Stop Signal Reaction Time** task (SSRT) that measures inhibition based upon choice reaction time responses (Logan GD et al., 1984; Verbruggen et al., 2019).
- **The Monetary Incentive Delay** task (MID) that measures anticipation for monetary rewards and reaction time (Knutson et al., 2001).
- **The Choice Task** that serves as an objective marker of addiction severity in which participants choose viewing drug vs. non-drug pictures (Moeller et al., 2009)

6.1.5 EMOTIONAL FUNCTIONING

- **Point Subtraction Aggression Paradigm (PSAP)** is a safe laboratory paradigm (not dependent on self-report) to evoke and quantify aggressive responding. Subjects are told they are playing online against another person. They are provoked when money is being deducted by the "other person," and they have the option to retaliate or to protect themselves from subtractions without retaliating. Subjects can earn up to \$7 in this game (Cherek et al., 2004);
- **Levels of Emotional Awareness Scale (LEAS)** an open-ended NP test of emotional intelligence/processing (Lane et al., 1990).
- **Delay Discounting task** a test of individual's propensity to choose smaller immediate over larger delayed rewards (Petry 2003).
- **Loss Aversion** task is a measure of an individual's sensitivity to the prospect of losing objects or money as compared with the possibility of gaining the same objects or amounts of money (Tversky & Kahneman, 1992).

6.1.6 DECISION-MAKING RISK TASKS

Kirby Delay Discounting Task (KDDT) (Kirby et al., 1999) assesses temporal discounting. Participants complete a series of questions that require choosing between a smaller, immediate reward versus a larger, later reward in a specified amount of time. Ambiguity Risk Task (Levy et



al., 2012) assesses how participants make decisions under known risk and under unknown (ambiguous) risk by playing a probability computer game. Social navigation Task (Tavares et al 2015) is an interactive social cognitive role-playing computer task where participants make choices in social situations that are guided by power and affiliation.

6.1.7 COGNITIVE TRAINING

We will use the tests described above and below (in the next section) for cognitive training (i.e., repeated over 5-15 times). During cognitive training, psychophysiological measures (GSR, EEG, MRI) may be recorded. For example, EEG-based neurofeedback training using a Brain-Computer Interface (BCI) system will involve a variety of tasks including the P300 Speller and emotion regulation.

We may also use the tests available through <http://www.lumosity.com/>. These tests were chosen by neuroscientists and cognitive psychologists from institutes such as Stanford and Berkley to improve several cognitive functions using computerized, personalized, engaging and fun computer games.

Computer-assisted delivery of cognitive-behavioral therapy for addiction (CBT4CBT), developed by Kathleen Carroll of Yale <http://videocast.nih.gov/summary.asp?Live=7170&bhcp=1>, may also be used.

6.1.8 ECOLOGICAL MOMENTARY ASSESSMENTS

Additional daily information will be collected from some participants in the form of Ecological Momentary Assessments (EMAs) (Shiffman, 2009a, 2009b) using smartphones; to be completed based on subject availability and motivation. Low-cost smartphones (e.g., old iPhones) will be provided if participants do not have their own devices. These will include frequent (e.g., daily) reports on drug craving, sleep quality, mood, and menstrual cycle. Objective measures in the form of select cognitive tasks will also be incorporated into the EMAs. Secure links to the objective measures described above will be delivered via Redcap, and presented using secure experiment presentation software (e.g., Inquisit). No personally identifying information is held on these devices. Only de-identified data will be transmitted.

6.2 FMRI/EEG TASKS

The fMRI and EEG recordings will be conducted separately while a person is engaged in select iRISA tasks. All tasks are based on standard NP tasks modified to fit the fMRI or EEG environment and the study goals. Tasks typically measure reaction time (button press) and accuracy, and subjective preferences, and typically require cognitive (e.g., reading, color naming, implicit or explicit recall, attention, decision making, appraisal/reinterpretation) and/or motor responses (e.g., forcefully gripping a handle). The tasks present neutral or abstract objects [such as fractal images or shapes] or disease-specific (i.e., drug- or IED-related) images (e.g., objects, people), videos, or words/verbal scenarios. For example, the modified Stroop task (described above in **Preliminary Studies** section), a classical task of inhibitory control, consists of neutral words (e.g., furniture), color words, drug-related words (e.g., cocaine, vodka), threat words (e.g., murder), or other emotional words (e.g., sad, happy). These tasks measure subjects' cue reactivity to different



categories of stimuli, particularly emotionally charged stimuli (images and words). The participants' ability to regulate emotional responses to these stimuli is also assessed through reappraisal and inhibitory control tasks (e.g., the stop signal reaction time task). Thus, several of these tasks specifically study the ability to inhibit a response under an emotional context by asking a subject to inhibit a response to certain stimuli (e.g., a 'go' picture/stimulus instructs the subject to press a button on a computer pad while a 'no go' stimulus instructs the subject to refrain from responding; this may be accomplished under differing monetary reward contingencies or emotional states) or by measuring reaction time to different stimuli (e.g., reaction time is longer when color naming a word than a non-word because of the inability to inhibit reading of the word; it is also longer for emotional than neutral words). Some of the tasks will involve monetary loss or perceived/relative loss (note that subjects never lose their own money: money lost will be the potential money the subject *could have earned* in case of no errors or based on subjective preference as determined by objective choices or money earned on a previous task or at the start of the study; these tasks are designed such that every subject will err and/or experience monetary loss). Participants may receive feedback on their performance, derived from their neural response (neurofeedback).

In these fMRI/EEG environments, we also use pictures from the International Affective Picture System (IAPS) (Lang et al., 2008), cocaine/heroin/other drug cue pictures or segments from cocaine/heroin/other drug or violence related videos (Volkow et al., 2006) and negative images from the IAPS. The IAPS, a set of over 700 positive, negative, or neutral pictures developed by the NIMH Center for the Study of Emotion and Attention at the University of Florida at Gainesville, provides normative ratings for emotional valence and arousal for each picture. These pictures are therefore widely used in imaging studies of affective neuroscience. With this set of stimuli, which we will show in the EEG and/or fMRI environments, we are able to study brain reactivity and ratings (rating each picture in terms of arousal and valence, ratings of subjects' preferences, performance and confidence) of the pictures. During some of these tasks, subjects' facial expressions or eye movements will be recorded with optical devices.

Thus, several tasks for fMRI/EEG are used in this protocol. Subjects perform the number of tasks that does not exceed the time allowed in the magnet (about 2 continuous hours in a sitting) or their motivation to participate in the experiment, whichever comes first. Throughout the course of the study, women with cocaine and/or opiate use disorder, and women who are in the healthy control group, may be asked to complete an MRI scanning session during each of the two different phases of their menstrual cycle. For comparison purposes, other subjects may also be asked to complete follow-up MRI sessions in a similar timeframe. For remuneration, see consent form. These tasks include training outside of the MR scanner or before EEG to ensure that the subject is familiar with the task or has achieved stable performance. An additional training is usually also performed inside of the scanner to allow the subject to adapt to the scanner environment before performance is assessed. Furthermore, if necessary, behavioral components (e.g., ratings of stimuli, implicit recall, timed reading) are administered outside the scanner/EEG to validate the core NP components measured by the task, and the same/similar tasks may also be given during behavioral testing (outside of MRI/EEG) for preliminary data collection/psychometric properties purposes.



Siemens 3T MAGNETOM Skyra fMRI: The Siemens 3T MAGNETOM Skyra at MSSM is the latest FDA approved 3 Tesla human MRI scanner. It has a short and open bore (173 cm system length with 70 cm Open Bore Design). The magnet is equipped with actively shielded echo-planar capable Siemens (SONATA) whole-body gradient coils and Siemens CASCADE gradient amplifiers. This gradient system delivers 45 mT/m with risetimes of 200 T/m/sec for each axis for increased resolution, throughput and reduced susceptibility distortions in echo-planar imaging acquisitions. The parallel receiver has 128 RF channels and is capable to interface with up to 204 coil elements. This system is equipped with the latest fMRI/DTI packages as well as 2D and 3D Chemical Shift Imaging Package. Other features include: Zero Helium boil-off and Tim 4G, the fourth generation of Total imaging matrix Technology [204x128] (that provides up to 204 coil elements with up to 128 channels), and a dedicated high performance Time 4G Head and Neck 20 Channel coil that is included with DirectConnect technology.

EEG: EEG is recorded in a quiet room after (approximately 1 hour) preparations for recording. Subject's skin is gently cleansed with alcohol and lightly abraded with a cotton swab. A small amount of skin prep (NuPrep gel) is applied at the following sites: **(A)** behind each ear (mastoid processes), **(B)** approximately 1 cm beyond each outer canthus, and **(C)** on the forehead. A small EEG electrode (Ag/AgCl) filled with an electrolyte gel is adhered to each cleansed and dried skin area with an adhesive tape. An elastic cap (NeuroScan Quik-Cap) is placed to cover the scalp (but not the face or ears). A blunt cannula is inserted through the cap's integral electrodes to reach through the hair to the scalp and is used to fill up to 64 electrodes with electrolyte. All electrode leads are neatly bundled to a connector box and impedance of each site is kept below 20 kilohms. All materials used were commercially developed and approved for standard multiple subject use in research and clinical settings. Between subjects, materials are cleaned with NeuroScan's approved virucidal germicide (Metrex Envirocide). After hookup and training, the subject's EEG and eye movements are recorded as they perform the computerized tasks. A break between tasks is encouraged (without electrode removal). After the complete study, electrodes are removed.

Psychophysiological measures: Using commercially available and MRI compatible products, we also collect Skin Conductance Response (SCR)/Galvanic Skin Response (GSR: the dynamically changing electrical resistance of the skin) and heart rate during MRI, EEG and/or cognitive tasks.

6.3 BLOOD COLLECTION

Blood samples for genetic and epigenetic assays, other biomarker assays, and for eligibility determination will be drawn from all consenting subjects at each blood draw visit. A needle will be used to collect up to approximately 2 ml of blood per kg of body weight from the participant's arm at each blood collection visit – an amount which is within NIH safety guidelines for clinical research (Peplow et al., 2019). The amount drawn will not exceed the lesser of 50 ml or 3 ml per kg of body weight at each blood collection visit, and collection will not occur more frequently than 2 times per week.

Blood collection will occur over the course of study participation, during the baseline assessments and at follow-up visits depending on participant availability and practicality.



For eligibility determination, the following blood tests will be performed: Comprehensive Metabolic Panel, T4 (free/total), TSH, HIV AB Screen, Hepatitis B AB, Hepatitis C AB, CBC & PLT. The clinical research coordinators and research team will be automatically alerted to any abnormal tests, and will forward those results to the medical professionals on the study team for review. The medical professionals will discuss clinically significant test results with the participants, and recommend follow-up with participants' personal care physicians if necessary, before the participants continue on the study or are withdrawn.

To determine hormonal levels (for progesterone and estradiol), genetic and epigenetic patterns, and to determine peripheral biomarkers, blood collection will be performed several times over the course of the study. Estradiol (LCA) and Progesterone will be determined during several phases of the menstrual cycle. To profile DNA genetic variation, an assessment will be performed using an appropriate technology (e.g., SNP array or WGS). In addition to DNA variation, follow-up sample collection will allow for the assessment of dynamic changes in molecular markers using genomic approaches. For example, such assessments can include gene expression analysis using RNA-seq and epigenome regulation analysis using ATAC-seq. Given that these molecular markers (gene expression and epigenome regulation) are determined by genetic DNA variation and environmental factors, this critical longitudinal assessment will enable utilization of the powerful within/between subjects design for data analysis. Subjects will not receive the results of the genetic tests. These analyses cannot be used to inform subjects about their own profiles, because the results are experimental and not yet completely understood.

Institute of Genomics and Multiscale Biology (IGMB) at MSSM

All blood samples are handled by and analyzed at the Institute of Genomics and Multiscale Biology (IGMB) at MSSM. The Institute of Genomics and Multiscale Biology (IGMB) at MSSM is a "core technology institute," which enables Mount Sinai Researchers to carry out cutting-edge genomic-based basic and translational research that brings state-of-the-art, high-throughput genomic technologies under one roof to provide a centralized resource to carry out large scale genomic studies. IGMB has three core units: The Genomics Core, the Proteomics/Metabolomics Core, and the Computational Genomics Core. Each core has state-of-the-art equipment, technical and analytical infrastructure manned and run by highly skilled and knowledgeable technical and scientific staff to facilitate sophisticated genomic, proteomic and metabolomic research. Quantitative PCR analysis for small-scale gene expression quantitation and detection of single nucleotide polymorphisms (SNPs) is available using an Applied Biosystem 7900HT with associated robotics for accurate reaction set-up using a Biomek FX for automated liquid handling. Automated, high throughput nucleic acid purification from blood, tissue or bacteria are performed in a 96 well format using a Qiagen Universal BioRobot. To assess the quality of nucleic acids, the Genomic Institute has an Agilent Bioanalyzer 2100. Genome wide approaches (GWAS) may also be used. The results of the GWAS testing may in the future be shared with the NIH GWAS repository. The information will be made anonymous and the link between the de-identified code and subject identity will never be shared. The following demographic information will be shared along with the genetic information: age, sex, race, education and other group membership such as study diagnosis.

Specimen Banking



Fractions of whole blood like white blood cell subsets, whole blood cell lysates and blood plasma will be frozen and stored in locked freezers or locked storage compartments until analyses are performed in the laboratory (i.e., RNA sequencing). They will not be labeled with any identifiers, but only with the study number and specimen type (i.e., SN#1/monocytes or SN#2/plasma). The Principal Investigator and Co-investigator will have access to the specimens. We will utilize the specimens for analyses including, but not limited to, fluorescence cytometric staining of whole blood cellular composition, RNA sequencing, ELISA assays, rt-PCR analysis and microarray analysis.

There are no plans to release tissue to other investigators independent of this study at this time, but in the future if we have collaborators this may change. Subjects have the option to allow us to keep their sample so that we can, in the future, analyze their samples for yet-to-be-discovered polymorphisms or to use pooled DNA (Craig et al., 2005) to be associated with NP and fMRI indices. Subjects will have the option to have their blood samples stored in a de-identified manner or to keep it linked to their identity and to be contacted for future use of the sample. Subjects will also have the option to give their sample to other researchers at Mt. Sinai. These options were adapted from Mt. Sinai boiler-plate HIPPA language.

6.4 SAFETY ASSESSMENTS

N/A This study is minimal risk.

7 STATISTICAL CONSIDERATIONS

Because this design is a mixed (split-plot) multivariate design, power is different for the between and the within subjects factors. To detect moderate effect sizes between the groups, a sample size of 240 in each group will provide a power of 0.80 at $\alpha = 0.05$ even for multiple dependent variables (e.g., NP, fMRI, ERP) (Stevens, 1992). To detect significant correlations (e.g., between NP performance and fMRI or EEG measures, or clinical variables), this relatively large sample size (total $N=480$) will allow us enough power (e.g., >0.80) to detect even small effects (such as $r=0.20$), which are often characteristic of studies employing genetics. The statistical analyses to be conducted will include the following:

- Simple ANOVAs to compare the groups on demographics and other relevant factors;
- Mixed ANCOVAs to detect a between groups effect (differences in activation of the brain regions/performance on the tasks between the groups), within group effects (differences between experimental conditions within a group and correlations with individual variables), and interaction effects (between task and group). These will be followed by post-hoc tests to localize the significant differences.

Within each diagnostic group, we stratify by polymorphism groups and compare them on the NP, fMRI and ERP measures. For example, we use independent sample t-tests to compare the frequency of two polymorphism groups (e.g., low vs. high MAOA) and general linear models for more groups and interactions. This power analysis is based on conservative measures of effect sizes to reflect the paucity of data studying genetic contribution to addiction and behavioral control using neuroimaging studies.



8 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

8.1 INFORMED CONSENT PROCESS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention. The following consent materials are submitted with this protocol: the consent form and the COVID-19 Addendum consent form.

8.1.1 CONSENT PROCEDURES AND DOCUMENTATION

During telephone recruitment screening to determine eligibility for enrollment, verbal consent will be obtained and documented (see appendix phone screening articles 1-3) using internal firewall procedures to ensure subject anonymity. Two staff will perform the telephone screening from separate areas. The staff member who places the phone call returned from the recruiting voicemail will request and document verbal consent, following the attached script. Subjects who affirm consent by saying 'yes' to their interest in being included in the study will then be forwarded anonymously to a second staff member. Following the attached anonymous screening script, the second staff member- who will not know the caller's name or recruitment category- will evaluate the caller's responses without making any notes or records, solely to determine whether the caller is ineligible for recruitment. On determination of enrollment suitability, the call will be returned to the originating staff member with only the determination of whether and which screening should be scheduled. No criterion details will be recorded or exchanged by either staff. On arrival for on-site enrollment and screening, the volunteer will be fully consented, as follows:

Consenting will occur in dedicated NARC research spaces that are private and free from distraction. Before the study begins, the experimenter/study coordinator will fully explain the nature of the research, highlight particularly important portions of the consent form to ensure subject understanding, and answer any questions that subjects may have. Consent will also be reaffirmed before every additional follow-up session. Consent will be obtained by study personnel with human subjects training that includes obtaining informed consent. Study personnel have appropriate training in the consenting process, and will explain to research participants all pertinent information. We will follow the guidelines set forth in the "SOP HRP-090 Informed Consent Process for Research."

This study does not involve children or cognitive impaired adults. Subjects have to understand and speak English at a level that would allow them to perform the behavioral and imaging tasks used in this study.

Our study does not entail a waiver of consent.

When necessary, consenting may take place remotely. Consenting procedures will align with the in-person practices described above as much as possible, and will also follow the Mount Sinai SOP, HRP-093, "Consent at a Distance". Secure, Mount Sinai-authorized consenting and videoconferencing platforms will be utilized, such as HIPAA-compliant Zoom and REDCap e-consenting.



When consenting remotely, research staff will schedule a videoconferencing appointment with prospective subjects at the time of telephone prescreening. Following the telephone prescreening, the participant will be emailed a link to the appointment. At the remote appointment, research staff will meet with prospective participants on video where possible. During the visit, research staff will send the prospective subject a blank copy of the consent, open up the informed consent document, and share their screen with the participant, in order to review all aspects of the informed consent with the participant, as described above. The REDCap e-consenting framework will be utilized for the participant to sign the consent and receive a copy of their consent.

At the participant's next in-person visit, a focused review of the consent form will occur at the beginning of the visit. Participants will be invited to ask any questions, and the conversation will be documented in the research record.

COVID-19 Addendum: Due to the remote nature of this arm of the study, subjects will consent for the study remotely using the standard PPHS consent form. Consenting will occur without staff presence and in the remote location of the subjects. Consent will be provided before initiation of the questionnaires and tasks on the online platforms. Prolific has an anonymized internal messaging system that allows for participants to contact the research team anonymously with any questions or concerns about the research or the consent process. Participants will be encouraged to use this system for any and all communication with the research team. We are attaching a waiver of alteration of the consent process and a waiver of documentation because we will not collect any identifiers in this study. The signature would be the only link between the participants and the study and not requesting signatures will help protect participants' privacy. During no point in the consent process or in the study will we collect any information that could identify research participants, including name, e-mail, IP address, or geographic location. Instead, we will collect worker ID numbers, which are anonymized. Only Prolific will have access to identifiers for worker ID numbers, which will be locked up in their system. We will keep worker ID numbers locked in our data security system as well. If participants decide to sign the consent form, they will sign using their worker IDs and will not provide any contact information, including name, email, etc. All contact with research participants will occur anonymously through Prolific's messaging forum.

Participants will be provided information about the study prior to registering for the study on Prolific. All information about the study will come directly from the consent form. If participants are interested, they will choose to enroll and then will initiate the consent process.

After completion of each section of the study, participants will be offered an opportunity to ask any questions, express concerns or provide feedback to the study team. This will occur using a debriefing sheet that pops up after completion of the study embedded into Prolific's anonymous messaging forum. The debriefing document is attached to the submission. The debriefing will also include an option to request to destroy data.

We are altering the consent process for the remote arm of this study because it involves no more than minimal risks to subjects and is qualitatively similar to other remote studies that use waivers of documentation in lieu of full consent forms. In addition, the consent form used for the remote study arm excludes explanation on protected health information, neuroimaging, and collection and storage of genetic material. The aspects of the full study that make it ineligible for waivers of documentation, including collection of protected health information and neuroimaging, will **not** be



administered in the remote arm of the study. The remote arm necessitates the use of a waiver of documentation because:

1. **The research involves no more than minimal risk to the subjects:** The research does not involve more than minimal risk to research participants. The data collected is anonymized and we will not have access to individual identifiers. Furthermore, the type of data we are collecting includes anonymous surveys and behavioral tasks that are on par with other remote studies that are exempt from using full consent forms and pose no more than minimal risk to research participants.
2. **The waiver or alteration will not adversely affect the rights and welfare of the subjects:** The full consent form with the waiver of documentation used for the remote survey arm only will have no adverse effect on the participants.
3. **The research could not practicably be carried out without the waiver or alteration:** It will be burdensome and ineffective to administer the study requiring oral explanation of a full consent form. Research participants are completing online surveys and tasks and there will be many participants working simultaneously. Other aspects of the study for which the full consent form is necessary do not apply. Our proposed n is 1500 in a short period of time and it would not be feasible or necessary to run a full consent orally explained for those participants.
4. **Whenever appropriate, the subjects will be provided with additional pertinent information after participation (If not applicable please briefly explain why):** There is **no** pertinent information from the initial full consent form that is applicable to the remote study arm. We are not collecting any identifiable data or administering any tasks that are predicted to be higher than minimal risk.

8.1.2 CONFIDENTIALITY AND PRIVACY

All data obtained in this study that is contained in our database will be coded; ID codes will be used. The key that links subject data to any identifiers will not be accessible to anyone but the Principal Investigator, co-PI and trained study personnel. This separate file linking the ID codes with subject names will be kept in a locked cabinet, or stored - password protected - on an encrypted computer, and could be accessed by credentialed personnel of this study only as authorized by the Principal Investigator and co-PI. Before being granted access to data, all study personnel are required to complete the Collaborative IRB Training Initiative (CITI) Courses, which train individuals on how to conduct responsible research (including maintaining subject confidentiality). Additional training is as required to fulfill necessary study obligations; weekly laboratory meetings led by the Principal Investigator and co-PI reinforce the necessity of protecting confidential data. All data forwarded to collaborators is completely de-identified, without any links to subject identifiers. De-identified data is stored on the group's server and individual PCs.

A Certificate of Confidentiality is provided by the National Institute on Drug Abuse (NIDA) before start of the study; the Certificate protects subjects' data from being used in any court proceedings.

8.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

NIH Protocol Template for Behavioral and Social Sciences Research



There are no plans to release tissue to other investigators independent of this study at this time, but in the future if we have collaborators this may change. Subjects have the option to allow us to keep their sample so that we can, in the future, analyze their samples for yet-to-be-discovered polymorphisms or to use pooled DNA (Craig et al., 2005) to be associated with NP and fMRI indices. Subjects will have the option to have their blood samples stored in a de-identified manner or to keep it linked to their identity and to be contacted for future use of the sample. Subjects will also have the option to give their sample to other researchers at Mt. Sinai. These options were adapted from Mt. Sinai boiler-plate HIPPA language.

De-identified data may be shared with collaborators at other institutions who will contribute to data analysis. Information will be sent using secure file sharing methods, and may include demographic data, psychological and behavioral assessments, and brain imaging results. Potential collaborators include, but are not limited to: Guillermo Cecchi, PhD and Carla Agurto, PhD (IBM); Conor Liston, MD, PhD (Weill Cornell Medical College); the ENIGMA Addiction working group (University of Vermont); Elisa Tatti, PhD (CUNY School of Medicine); Anna Konova, PhD (Rutgers University); Karolina M. Lempert, PhD (Adelphi University); James E. Hubbard Jr, PhD (Texas A&M University); Junqian (Gordon) Xu, PhD (Baylor College of Medicine); Travis Baker, PhD (Rutgers University); Ken Norman, PhD and Uri Hasson, PhD (Princeton University); Roi Reichart, PhD (Technion at the Israel Institute of Technology); Francisco Castellanos, PhD and Luís Martinez Agulleiro, PhD (NYU Grossman School of Medicine); and their trainees/staff. Within the Mount Sinai system, collaborators will include, but are not limited to, Panagiotis Roussos, MD, PhD, Yasmin Hurd, PhD, Chinwe Nwaneshiudu, MD, Muhammad Parvaz, PhD, and Scott J. Russo, PhD, and their trainees/staff.

8.1.4 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	Medical Monitor or Independent Safety Monitor
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