NIDA Phenotyping Assessments Battery (PhAB) Feasibility and Validation Study in Non-Intoxicated Drug Users.

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1. LIST OF ABBREVIATIONS

AE   Adverse Event

ADHD   Attention Deficit Hyperactivity Disorder
ANT   Attention Network Task
BCBS   Brief Substance Craving Scale
ASRA Adult Self-Report Symptom Checklist
CARI   Collaborative Advanced Research Imaging (VCU clinic)
CSSR-S   Columbia Suicide Severity Rating Scale
CocUDCocaine Use Disorder
DSM-5 Diagnostic and Statistical Manual of Mental Disorders, Fifth Ed
DTS   Distress Tolerance Scale
FTND   Fagerstrom Test for Nicotine Dependence
FTQ   Family Tree Questionnaire
HC   Healthy Control
IRB   Institutional Review Board
MAIA   Multidimensional Assessment of Interoceptive Awareness
MINI   Mini International Neuropsychiatric Interview
MCQ   Metacognition Questionnaire
MPQ-NEM   Multidimensional Personality Questionnaire-Negative Emotional Temperament
OUD   Opioid Use Disorder
PAB   Phenotyping Assessment Battery
PIB   Platform Instrument Battery
PANAS   Positive and Negative Affect Schedule
PROMIS   Patient-Reported Outcomes Measurement Information System
PSQI   Pittsburgh Quality of Sleep Index
PTSD   Post Traumatic Stress Disorder
SAE   Serious Adverse Event
SST   Stop Signal Task
TAS-20   Toronto Alexithymia Scale
THC   Tetrahydrocannabinol
UPPS-P   Urgency, Premedition, Perseverance, Sensation Seeking, Positive Urgency
VAS   Visual Analog Scale
VCU   Virginia Commonwealth University
WHO-DAS   World Health Organization Disability Assessment Schedule
WHO-QOL   World Health Organization Quality of Life

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3. STUDY SYNOPSIS

Title	NIDA Phenotyping Battery Feasibility and Validation Study in Non-Intoxicated Drug Users
Objective	The primary objective of this project is to validate preliminary findings from the pilot study in order to refine the PhAB into a streamlined, validated deep phenotyping battery for addictions for adoption in future NIDA funded clinical trials. Specific aims to achieve this goal include: 1. To finalize the PhAB battery content by examining levels of redundancy across PhAB measures, in order to further refine the assessment battery; 2. To confirm percentages of participants that can complete the non-MRI portion of the protocol within two study visits; 3. To assess whether PhAB battery profiles and performance measures vary in meaningful ways across substance use conditions, taking into account critical variables such as concomitant substance use, and psychosocial factors (e.g., trauma, depression, anxiety, etc); and 4. To compare effective (directional) brain connectivity (via resting state fMRI and structural scans) between OUD, other relevant populations, and control participants and the relationship between effective brain connectivity and behavioral assessments from the PhAB
Number of Subjects	This project requires a final sample size of 400 subjects (100 non drug-using healthy control subjects, 50 subjects with primary stimulant use disorder, 200 subjects with primary Opioid Use Disorder, and 50 subjects with primary Cannabis Use Disorder).
Inclusion Criteria	In order to participate in this study, subjects must: • Males and females between 18 and 70 years-of-age. • Current DSM-5 primary Substance Use Disorder: Opioid, marijuana, stimulants (individuals with multiple types of substance use (e.g., opioid/marijuana will be included) • Have no contraindications for study participation as determined by medical history and concomitant medications. • Be able to demonstrate an understanding of study procedures and follow instructions including behavioral laboratory testing. • Be able and willing to comply with scheduled visits, and other study procedures. • Be able to read and complete forms and interviews in English. Inclusion Criteria (Non-drug Using Healthy Controls) • Males and females between 18 and 70 years of age. • Have no contraindications for study participation as determined by medical history and concomitant medications. • Be able to demonstrate an understanding of study procedures and follow instructions including behavioral laboratory testing. • Be able and willing to comply with scheduled visits, and other study • Be able to read and complete forms and interviews in English.
Exclusion	General exclusion criteria:

Criteria	• Current psychosis, mania, or suicidal/homicidal ideation • Meet current DSM-5 diagnosis of any psychoactive substance use disorder other than opioids,marijuana, stimulants, or nicotine. Diagnosis of mild to moderate use disorder for alcohol will not be considered exclusionary for any SUD group. • Have a history of seizures (excluding childhood febrile seizures), or loss of consciousness from traumatic injury for more than 30 minutes. • Have any other illness, or condition, which in the opinion of the PI or study physician would preclude safe and/or successful completion of the study. MRI exclusion criteria: • Metal fragments or implants, and/or history of fear of being in closed spaces for MRI scans. • Currently pregnant or nursing.
Primary Outcome	This study is a feasibility, construct and face validity study. The primary outcome measure is time taken to complete the battery, and rates of successful study completion.
Duration	1 year

3. BACKGROUND AND SIGNIFICANCE

There is profound heterogeneity of subjects in clinical studies of addictions, with patients being diagnosed by the primary substance of use. As a result, utilizing current DSM addictions classification leads to problems with signal detection and hamper the progress of the development of new drugs and treatments for substance use disorders (SUDs). Getting beyond the DSM-5 based definitions is necessary to "fingerprint" addiction phenotypes and endophenotypes, using machine-learning analyses of big data. A detailed in-depth assessment of addiction phenotypes (deep phenotyping) may also include neuroimaging..

In an effort to develop a "fingerprint" for addiction phenotypes, NIDA established a Workgroup to develop a phenotyping battery of tests and self-rated psychometric scales, supplemented by resting state fMRI to be administered to participants in any extramural clinical trial where addictions are assessed. The final phenotyping battery content was determined via consensus from both the selected experts- consultants group and the NIDA workgroup, and as such, the battery requires feasibility and validation study to finalize its content. The NIDA Phenotyping Assessment Battery (PhAB) covers six neurofunctional addiction domains : Metacognition, Interoception, Cognition/Executive Function, Reward/Incentive Salience, Emotion/Negative Emotionality, and Sleep/Circadian Rhythm. The PhAB is meant to be administered during a Phenotyping visit - an extension of a screening visit in any clinical trial addictions protocol. In addition to the PhAB, the group also developed an ancillary set of measures to be administered in conjunction with the PhAB in any addictions clinical trial during the Phenotyping visit. The Platform Instruments include structured interviews, diagnostic measures (e.g., MINI), self report scales of symptom severity (e.g., ASRS-ADHD, VAS-Pain), trauma history (THQ), computer-administered measures of intelligence (e.g., Shipley), and substance use measures (FTND, Timeline Follow-back), etc. Clinical trial investigators would administer these scales and behavioral tasks in addition to protocol nonspecific assessments (e.g., demographics) and medical evaluations (e.g, medical history and physical exams, genotyping, and labs) which could be done at Screening.

4. STUDY OBJECTIVES

The primary objective of this project is to validate preliminary findings from the pilot study in order to refine the PhAB into a streamlined, validated deep phenotyping battery for addictions for adoption in future NIDA funded clinical trials. Specific aims to achieve this goal include:
1. To finalize the PhAB battery content by examining levels of redundancy across PhAB measures, in order to further refine the assessment battery;
2. To confirm percentages of participants that can complete the non-MRI portion of the protocol within two study visits;
3. To assess whether PhAB battery profiles and performance measures vary in meaningful ways across substance use conditions, taking into account critical variables such as concomitant substance use, and
psychosocial factors (e.g., trauma, depression, anxiety, etc); and
4. To compare effective (directional) brain connectivity (via resting state fMRI and structural scans) between OUD, other relevant populations, and control participants and the relationship between effective brain connectivity and behavioral assessments from the PhAB

5. STUDY DESIGN

The study utilizes a four-group cross sectional cohort design. A total of 400 participants (across 4 cohorts) are targeted to complete the study) to include: Healthy Controls (n=100), individuals with CocUD (n=50), individuals with OUD (n=200), and individuals with marijuana use disorder (n=50). The study is anticipated to take 1 year to complete. See Figure 1.

Figure 1
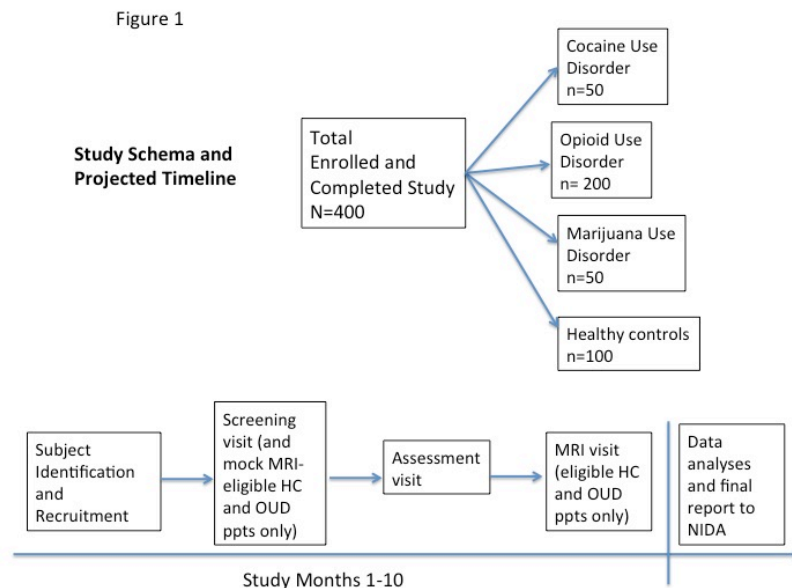
a. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

Inclusion Criteria (Individuals with SUDs)
- Males and females between 18 and 70 years-of-age.
- Current DSM-5 primary Substance Use Disorder: Opioid, marijuana, stimulants (individuals with multiple types of substance use (e.g., opioid/marijuana will be included)
- Have no contraindications for study participation as determined by medical history and concomitant medications.
- Be able to demonstrate an understanding of study procedures and follow instructions including behavioral laboratory testing.
- Be able and willing to comply with scheduled visits, and other study procedures.
- Be able to read and complete forms and interviews in English.

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Inclusion Criteria (Non-drug Using Healthy Controls)
- Males and females between 18 and 70 years of age.
- Have no contraindications for study participation as determined by medical history and concomitant medications.
- Be able to demonstrate an understanding of study procedures and follow instructions including behavioral laboratory testing.
- Be able and willing to comply with scheduled visits, and other study
- Be able to read and complete forms and interviews in English.

b. Exclusion Criteria

General Exclusion Criteria

- Current psychosis, mania, or suicidal/homicidal ideation
- Meet current DSM-5 diagnosis of any psychoactive substance use disorder other than opioids,marijuana, stimulants, or nicotine. Diagnosis of mild to moderate use disorder for alcohol will not be considered exclusionary for any SUD group.
- Have a history of seizures (excluding childhood febrile seizures), or loss of consciousness from traumatic injury for more than 30 minutes.
- Have any other illness, or condition, which in the opinion of the PI or study physician would preclude safe and/or successful completion of the study.

MRI Exclusion Criteria

- Metal fragments or implants, and/or history of fear of being in closed spaces for MRI scans.
- Currently pregnant or nursing.

6. STUDY PROCEDURES

7.1 Time and Events Schedule

The time and events schedule is presented in Table 1 below.

Table 1. Schedule of Assessments

	Screening	Assessment visit	MRI visit
Informed consent	X		
Demographics	X		
MINI-DSM5	X		
C-SSRS	X	X	X
Medical survey	X		
Prior/concomitant medications	X	X	X
Vital signs	X	X	X
Urine toxicology screen	X	X	X
* Physical exam	X		
* Laboratory blood draw	X		
* MRI contraindication and safety checklist	X		
Pregnancy test (females)	X	X	X
Alcohol breathalyzer	X	X	X
Expired CO	X	X	X
Locator form	X	X	X
**Mock MRI scan	X		
**Adult self-report symptom checklist (ASRA)	X		
**Recent Life Events Questionnaire (Adults)	X		
Timeline Follow-Back, Drug, Alcohol & Tobacco		X	
**Computerized Shipley-2	X		
Fagerstrom (FTND)		X	
Brief Substance Craving Scale (BSCS)		X	
PTSD Checklist for DSM5 (PCL5)		X	
WHOQOL BREF		X	
**Family Tree Questionnaire	X		
**Trauma History Questionnaire (THQ)	X		
Positive and Negative Affect Schedule (PANAS)		X	
Toronto Alexithymia Scale (TAS-20)		X	
**Relationship Scale Questionnaire (RSQ)	X		
MPQ-NEM		X	
WHO-DAS		X	
**VAS-Pain	X		
Attentional Network Test (ANT)		X	
Hypothetical Purchase Task		X	
Stop Signal Reaction Task		X	
	Screening	Assessment visit	MRI visit
Visual Digit Span (backward recall)		X	
5-Trial Adjusting Delay Discounting		X	
Emotional Go/Nogo Task		X	
SUPPS-P		X	
Cue Interference Task-Attentional Bias Line Counting		X	
Distress Tolerance Scale		X	

PROMIS-Depression Scale 4a		X	
PROMIS-Anxiety Scale 4a		X	
Buss Perry Aggression Questionnaire		X	
Snaith-Hamilton Pleasure Scale		X	
Metacognitions Questionnaire (MCQ-30)		X	
MAIA		X	
Pittsburgh Sleep Quality Index-Revised		X	
Debriefing Questionnaire		X	
Adverse Events		X	X
MRI scan			X
Edinburg Handedness Questionnaire	X		
^ Opioid Craving Scale	X	X	X
^ Opioid Intoxication Scale	X	X	X
24 Hour Survey			X
Resting State Questionnaire			X

Note: Many of the assessments are available for download through the Millisecond Test Library (www.millisecond.com). Millisecond Software, LLC, is a provider of software for psychological testing. All tests in the Millisecond Library are free with an Inquisit license or with the Inquisit Lab free trial.

* Denotes procedures that will be completed only for individuals who are eligible for screening for MRI portion of the study (Healthy Controls and individuals with OUD).

** If time is available, this task will be completed at Screening Visit, otherwise, the task will be completed at the Phenotyping Assessment Visit.

^ The Opioid Intoxication Scale will also be completed with individuals who test positive for opioid use during the mock scan and/or MRI visit(s). The Opioid Craving Scale will also be administered to individuals with OUD at each visit.

7.2 Subject Recruitment and Consenting

Subjects will be recruited from participants included in the CARI screening repository (VCU IRB# HM20000294, Keyser-Marcus (PI)) and from local advertising. Individuals who have previously completed the CARI universal screening protocol (through HM20000294) and are determined to be eligible for an on-site screening visit, will be contacted to determine study interest. Interested individuals will be scheduled for an on-site screening visit.

Individuals who present for the screening visit will undergo the informed consent process. The consent procedure fully apprises individuals of rights and responsibilities of study participants. Consent is conducted by study personnel in a private office. During the consenting process, potential participants will be given the opportunity to ask questions throughout and have all of their questions answered prior to making a decision regarding whether or not to participate. All consent and study procedures and materials will be approved by the VCU IRB. All subjects will provide informed written consent prior to any data collection. During the informed consent process it will be made clear to all subjects that this is not a treatment study. A community resource brochure will be offered to all study participants, regardless of group assignment. The resource brochure includes information on substance abuse treatment providers in the Richmond area.

7.3 Screening

The screening assessment will take place during the same visit as the consent/enrollment into the study. It is estimated to take between 60 and 90 minutes for subjects to complete screening procedures.

Screening assessment used to determine study eligibility will include (may not in that particular order as in below):
     A Demographics Questionnaire will be used to assess standard sociodemographic information, including age, racial/ethnic background, sex, educational attainment, employment status, occupation, and marital status.

     Participant Locator Form The Participant Locator form collects information (e.g., name, address, telephone number, email) for the participant and phone numbers for up to three other people whom the participant states are familiar with his or her whereabouts and who might assist with contact efforts if study personnel are unable to reach the participant.

     The Mini International Neuropsychiatric Interview V 7.0.2 (MINI) (Sheehan et al, 1998) will be used to collect diagnostic information used to make eligibility determinations. DSM-5 diagnoses (including Cocaine Use Disorder and Opioid Use Disorder) will be ascertained for all subjects. Interviews will be conducted by experienced research personnel who have successfully completed standardized training in the administration and scoring of the MINI.

     Columbia Suicide Severity Rating Scale (C-SSRS). (Posner et al., 2009) is an interview measure used to assess suicidal ideation and behavior. The *Baseline* version is used during screening and collects information related to lifetime suicidal ideation and behavior. The *Since Last Visit* version assesses suicidal ideation and behavior in the time since the last patient visit, and will be used at the subsequent study visit.

     The CARI Medical Survey will be used to collect information regarding medical history on all potential subjects, and the Concomitant Medications form will be used to collect information regarding current over-the-counter and prescription medications used by potential participants. Vital signs to be assessed include oral temperature, sitting blood pressure, pulse, respiratory rate, and weight. Urine specimens will be collected for pregnancy testing (females only), as well as urine drug screen for cocaine (benzoylecgonine), opiates and opioids, benzodiazepines, amphetamine, methamphetamine, and THC. Breath alcohol and carbon monoxide (for recent tobacco use) levels will also be obtained.

     Upon completion of the screening assessments listed above, individuals who screen as ineligible will be compensated for their time and effort and informed that they are ineligible to participate in the study. Individuals who are deemed eligible for the study will go on to complete a portion of the Platform Battery (listed below) assessments during this visit, if time permits. If the participant has to leave prior to completing these assessments, they will be completed at the Phenotyping Assessment Visit.

MRI Eligibility Screening

Individuals in the Healthy Control and Opioid Use Disorder groups will also be eligible to screen for the MRI portion of the study. The MRI screening consists of the following:

Medical and Laboratory Evaluation, which will include a physical examination (including neurological exam and medical history), MRI safety screening, and a blood draw for complete blood count (CBC).

Mock MRI scanning session: Healthy control and OUD subjects who are deemed eligible for MRI scanning, based on results of the physical exam and MRI screening checklist, will also complete a mock MRI scanning session. During the mock session, participants are allowed to practice tasks in a MRI Simulation Device (mock MRI machine). During the computer demonstration prior to the simulator sessions, subjects are allowed up to 10 min of practice (with interaction permitted with the research assistant), until it is clear that the procedures are understood and that the majority of the practice responses are correct. During simulator sessions, tasks are projected by an LCD projector on a screen that the subject views using mirror-prism glasses. The subject listens to a recording of MRI sounds during the simulator sessions. Participants will also complete the Edinburgh Handedness inventory in order to determine their dominant hand across a number of tasks. Self report of recent drug use will also be collected. Participants will also complete the 24-hour Survey at both the mock MRI scan visit and the MRI scan visit, in order to document consumption of caffeinated beverages, alcohol and tobacco use in the past 24 hours. The Opioid Intoxication Scale will also be completed with individuals who test positive for opioid use during the mock scan and/or MRI visit(s). The Opioid Craving Scale will also be administered to individuals with OUD at each visit. Finally, the Resting State Questionnaire will be administered following the MRI scan.

Upon completion of the screening visit, CARI research staff will inform participants of their eligibility to complete the study. Eligible participants are then scheduled to return to the clinic to complete the study assessment visit. Individuals who are not eligible will be notified of their ineligibility, compensated $30 (non MRI candidates) or up to $70 ($70 for MRI candidates who complete the mock scanning session, or $50 for MRI candidates who do not complete the MRI scanning session), and thanked for their time.

Note: Individuals who have already completed the Phenotyping portion of the protocol, and have been recontacted and reconsented to participate in the MRI portion of the study will complete a MRI screening visit, which will consist of the same MRI screening procedures listed above.

7.4 Phenotyping Assessment Visit

As described above, the Assessment Visit will consist of the the remaining measures included in the Platform Instrument Battery, and all of the measures included in the Phenotyping Battery. It is estimated to take approximately 3.5 - 4 hours to complete both (with scheduled rest breaks included). Upon arrival to the clinic, participants will first complete biological measures, which includes vital signs (oral temperature, sitting blood pressure, pulse, respiratory rate, and weight), urine and breath samples. Urine specimens will be collected for pregnancy testing (females only), and urine drug screen for cocaine (benzoylecgonine), opiates and opioids, benzodiazepines, amphetamine, methamphetamine, and THC. Breath alcohol and carbon monoxide (for recent tobacco use) levels will also be obtained.

7.4.1 Assessment Measures

<u>Platform Instrument Measures</u>. Platform instruments will not be administered in the fixed sequence as in below. Efforts will be made to administer as many of the Platform Instruments marked with an asterisk (*) at the time of the Screening Visit (as time permits). Otherwise, they will be administered during the Phenotyping Visit.

* <u>Computerized Shipley-2</u>. Brief, but robust measure of cognitive functioning and impairment that assesses both crystallized and fluid cognitive ability (Shipley, Gruber, Martin, and Klein, 2009). Estimated time to complete 20 minutes. The Shipley-2 has been shown to be psychometrically sound, with moderate to high test-retest reliability correlations (.74 to .94) across a 1-2 week delay, and good internal consistency, discriminative validity, and strong concurrent validity with WAIS-III, PIQ, and VIQ (with correlations ranging from .62- .87).

* <u>Adult Self-Report Symptom (ASRA) Checklist (ADHD)</u>. A brief self-administered inventory consisting of 18 questions which aids in assessing symptoms of ADHD/ADD. Estimated time to complete is 1-5 minutes. It has demonstrated high rates of internal consistency for both self-report and rater-administered versions (Cronbach's alpha 0.88, 0.89, respectively) and high concurrent validity with the rater administered ADHD RS (Adler, Spencer, et al, 2006)

* <u>Recent Life Events Questionnaire (Adults)</u>. (Brugha, Bebington, et al, 1985), Is a 21-item self-administered scale used to assess recent (past 12 months) life events, as well as their current impact on the respondent.

* <u>Family Tree Questionnaire (FTQ) for Substance Use.</u> A self-report family history measure that assists in identifying of first- and second-degree relatives with alcohol and other substance use-related problems (Mann, Sobell, Sobell, & Sobell, 1985). Reliability studies have demonstrated good test-retest reliability, and validity studies have shown criterion and concurrent validity of the instrument.

* <u>Trauma History Questionnaire (THQ).</u> A 24-item self report measure of physical and sexual abuse (ever in lifetime), which includes items related to crime-related events and general disaster/trauma. Respondents are asked to provide the frequency of the event and their age at the time of the event. The THQ has been found to be psychometrically sound with regard to both reliability and validity (Hooper, Stockton, Krupnick, & Green, 2011)

* <u>Relationship Scale Questionnaire (RSQ)</u> A 30-item self-report questionnaire that assesses attachment style. Subjects rate on a 5 point scale, the extent to which each statement describes them in close relationships from "Not at all like me" to "Very much like me". (Griffin and Bartholomew, 1994). Previous research has suggested that the RSQ demonstrates good test-retest reliability and internal consistency (Guédeney, Fermanian, & Bifulco 2010).

* <u>Visual Analog Scale for Pain (VAS-pain)</u>. 100mm visual analog scale used to obtain patient rating for current magnitude of pain experienced, with endpoints defining extreme limits such as 'no pain at all' and 'pain as bad as it could be' (Wewers & Lowe, 1990)

<u>Timeline Follow Back for Drug, Alcohol, Tobacco use</u> (Sobell and Sobell, 1996). Structured interview that queries quantity of daily drug,alcohol and tobacco use over a specified time period. Using a calendar, respondents provide retrospective estimates of their tobacco, alcohol

and/or drug use. This method has demonstrated solid psychometric properties across a variety of populations (Robinson, Sobell, Sobell, & Leo, 2014).

Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al, 1991; available in the Millisecond Test Library). A widely used 6-item self-report questionnaire designed to measure nicotine dependence, The items are summed to yield a total score of 0-10, with higher scores indicating greater nicotine dependence.

Brief Substance Craving Scale (BSCS; available in the Millisecond Test Library). The BSCS is a 16 item, self-report instrument assesses craving intensity and frequency of craving for cocaine and other substances of abuse over a 24-hour period. Items are rated on a five-point Likert-type scale (Somoza, Dyrenforth, Goldsmith, Mezinskis, & Cohen, 1995).

PTSD Checklist for DSM5. (PCL5; available in the Millisecond Test Library) A 20-item questionnaire based on DSM5 criteria for PTSD,with each item being assigned a severity score of 0-4, yielding a total symptom severity score ranging from 0-80 The PCL5 has been shown to exhibit strong internal consistency ($α$ = .94), and test-retest reliability (r = .82), as well as convergent and discriminant validity (Blevins, Weathers, Davis, Witte, & Domino, 2015).

WHO QOL Bref. (available in the Millisecond Test Library). A 26-item questionnaire assessing quality of life in 4 domains: physical, psychological, social and environmental (WHOQOL Group, 1998). Reliability and validity data indicate that the WHOQOL-BREF has good to excellent internal consistency, item–total correlations, and discriminant validity and construct validity (Skevington, Lotfy, & O'Connell, 2004)

Positive and Negative Affect Schedule (PANAS-20; available in the Millisecond Test Library). A 20-item measure assessing positive and negative affect, on a scale from 1 to 5 (Watson et al.1988). Reliability and validity reported by Watson (1988) was moderately good, with the Cronbach alpha coefficient ranging from 0.84 to 0.90, and test-retest correlations ranging from 0.39-0.71 over a 8-week time period.

Toronto Alexithymia Scale (TAS-20; available in the Millisecond Test Library). A 20-item self-report questionnaire to assess emotional awareness. The measure is divided into three subscales: Difficulty Describing Feelings, Difficulty Identifying Feelings, and Externally-Oriented Thinking. Items are rated on a 5 point Likert-type scale, from 1 (strongly disagree) to 5 (strongly agree). The TAS-20 demonstrates good internal consistency (Cronbach's alpha = .81) and test-retest reliability (.77, p<.01), as well as adequate levels of convergent and concurrent validity (Bagby, Parker & Taylor, 1994).

Multidimensional Personality Questionnaire- Negative Emotional Temperament (MPQ-NEM). (Tellegen,1995). A 40-item scale on the MPQ that assesses individual trait differences in affective reactivity: primary scales of Stress Reaction, Alienation, and Aggression. High scores on the MPQ NEM factor indicate greater anxiety, anger, and related negative emotions and behavior. The MPQ has strong psychometric properties and good behavioral genetic data from twin studies (McGue, Bacon, & Lykken, 1993).

WHO Disability Assessment Schedule (WHO-DAS; available in the Millisecond Test Library). A 12 item generic assessment for health and disability linked to ICF (International Classification of Functioning, Disability and Health). A Normative data for the 12 item version of the WHODAS

2.0. found that scores of 10–48 accurately identify individuals with a clinically significant disability (Andrews, Kemp, Sunderland, VonKorf, & Ustun, 2009).

Levenson Self-Report Psychopathy Scale (LSRP; available in the Millisecond Test Library). A 26 item self-report scale, in which respondents rate each item on a scale from 1 (strongly disagree) to 4 (strongly agree. Items included in the scale reflect both primary psychopathy (callous, manipulative, and selfish use of others) and secondary psychopathy (impulsivity and poor behavioral controls; Levenson et al, 1995).
Phenotyping Assessment Battery (PhAB) Measures.

Measures will be administered in non-fixed order. After NIDA Phenotyping Battery Measures administration subjects will complete Debriefing/Satisfaction survey. After Interim Data Analysis (see Section 8.4) the order of measures administration can be changed and the order may become fixed.

Attentional Network Test (ANT; available in the Millisecond Test Library): Cue-target test using reaction time to measure Alerting, Orienting, Executive Control. Our focus is on Executive Control. Single testing session, 1 block test 9 min, connects with neuronal networks. (Fan, McCandliss, Sommer, Raz & Posner, 2002).

Stop Signal Reaction Task ((SST) available in the Millisecond Test Library) A measure of response inhibition in which subjects perform a "go task" in response to a stimulus, and occasionally the go stimulus is followed by a "stop signal", which requires subjects to withhold the go response (Verbruggen et al, 2008). .

Hypothetical Purchase Task. A time- and cost-efficient simulation procedure to assess reinforcement efficacy in humans. Respondents answer questionnaires asking how much of a particular substance (e.g., bags of heroin) they would purchase across a range of prices within a fixed period of time. (Jacobs & Bickel, 1993).

Visual Digit Span (backward recall; available in the Millisecond Test Library): Brief (approximately 5 minutes) commonly used test of working memory, in which subjects are tasked to recall (in reverse order) a sequence of numerical digits presented to them via computer. Increasingly longer sequences are added in each subsequent trial. (Wechsler, 1997).

5-Trial Adjusting Delay Discounting task (available in the Millisecond Test Library; Koffarnus & Bickel, 2014). A brief task designed to obtain a subject's discount rate in less than one minute. Based on the premise that individuals tend to value rewards less as the amount of time increases until those rewards would be received.

Emotional Go/Nogo Task (Tottenham, Hare & Casey, 2011; will be available in the Millisecond Test Library). Task designed to assess cognitive control in the context of emotional information as a measure of emotion regulation. Mix of behavioral inhibition with embedded probe of attentional capture by emotional/social cues.

SUPPS-P (available in the Millisecond Test Library). A 20-item version of the original UPPS-P questionnaire, used to assess self-reported personality traits associated with impulsive behavior across five dimensions: urgency, premeditation, perseverance, sensation seeking, and positive urgency (Whiteside & Lynam, 2001)

Cue Interference Task- Attentional Bias Line Counting Task (will be made available in the Millisecond Test Library). A modified version of a previously developed attentional bias task (Passamonti, Luijten, Ziauddeen, et al, 2017), which measures the degree by which people are distracted by drug cues, will be used in the present study.

Distress Tolerance Scale (DTS) (available in the Millisecond Test Library). A 15-item self report measure of emotional distress tolerance. Items are loaded across 4 factors: tolerance, absorption, appraisal, regulation (Simons & Gaher, 2005)

PROMIS- Depression scale. A brief (4-item) self-report measure which assesses four domains of depression: negative mood, views of self, social cognition, and decreased positive affect and engagement. With regard to psychometric characteristics, Choi and colleagues (2010), found that the short form scores were highly correlated with the longer PROMIS measures.

PROMIS- Anxiety. A brief (4-item) self-report measure which assesses anxiety symptoms (e.g., hyperarousal), experienced in the past 7 days.. Subjects rate the frequency of experiencing each symptom, on a 5-point Likert-type scale, from 1 (never) to 5 (always).

Buss Perry Aggression Questionnaire- 29 item self measure of aggression. Participants rank statements along a 7-point Likert-type scale, ranging from 1 (extremely uncharacteristic of me) to 7 (extremely characteristic of me). The measure includes four subscales: physical aggression, verbal aggression, anger, and hostility (Buss & Perry, 1992).

Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al, 1995). Available in the Millisecond Test Library. A 14-item scale which measures anhedonia. Previous research has found the SHAPS has adequate construct validity and test-retest reliability (ICC=0.70) as well as high internal consistency (Cronbach's alpha of 0.94) among both clinical and nonclinical populations (Franken et al, 2007).

Metacognitions Questionnaire-30 (MCQ-30; available in the Millisecond Test Library). A brief (approximately 5 minutes) self-report measure of metacognitive beliefs associated with the five-factor metacognitive model of psychological disorders, including: cognitive confidence, positive beliefs about worry, cognitive self-consciousness, negative beliefs about uncontrollability of thoughts and danger, and beliefs about the need to control thoughts. The MCQ-30 has demonstrated good internal consistency, convergent validity, and test-retest reliability (Wells and Cartwright-Hatton 2004).

Multidimensional Assessment of of Interoceptive Awareness (MAIA; available in the Millisecond Test Library). A 32-item self-report measure that assesses awareness of body sensations, including the emotional/physiological state, physical discomfort and pain. Items are rated on a 6 point Likert-type scale, ranging from 0 (never) to 5 (always) (Mehling, Price et al. 2012).

Pittsburgh Sleep Quality Index-Revised ((PSQI) available in the Millisecond Test Library) A brief questionnaire assessing sleep habits, including disruptions in sleep and influence of sleep on daily functioning during the past week. (Buysse et al.,1989).

Concomitant Medication(s)
All concomitant medications taken during the trial must be recorded with indication, daily dose, and start and stop dates of administration. Medications taken within 28 days before the start of the trial will be documented as a prior medication. Medications taken after the start of the trial will be documented as concomitant medications.

7.5 MRI Scan Visit

Upon arrival to the clinic, participants will first complete biological measures, which includes vital signs (oral temperature, sitting blood pressure, pulse, respiratory rate, and weight), urine and breath samples. Immediately prior to MRI scanning, urine from each participant is screened for amphetamine, barbiturates, benzodiazepines, cocaine, methamphetamine, MDMA (ecstasy), opioids (methadone, buprenorphine, morphine, codeine, heroin, hydrocodone, hydromorphone, levorphanol, oxycodone, and oxymorphone), phencyclidine, propoxyphene, tricyclic antidepressants, and THC. Breath alcohol and carbon monoxide (for recent tobacco use) levels will also be obtained. Self report of recent drug use will also be collected. Participants will also complete the 24-hour Survey at both the mock MRI scan visit and the MRI scan visit, in order to document consumption of caffeinated beverages, alcohol and tobacco use in the past 24 hours. The appropriate Drug Intoxication Scale(s) (cocaine/opioid/marijuana) will also be completed with individuals who test positive for opioids, cocaine, and/or marijuana during the mock scan and/or MRI visit(s). The Opioid Craving Scale will also be administered to individuals with OUD at each visit. Finally, the Resting State Questionnaire will be administered following the MRI scan.

As an additional measure of phenotyping related to the neurobiology of drug addiction, a subset of participants (OUD primary (n=50), and HC (n=50)), will undergo an MRI scan consisting of a resting state fMRI and structural scans. Brain connectivity measures will be determined using functional and effective connectivity analyses.

The scan session will last approximately 80 minutes ~~from the time of successful position of~~ while the participant's head is in the scanner bore~~, including time for individual scan setups~~. The session consists of each of the following scans: 1) Localizer, 2) resting-state fMRI scan, during which the participant is asked simply to look at a crosshair, 3) T2 FLAIR scan for incidental pathology, 4) Structural T1-weighted MP-RAGE scan for calculation of brain volumes and co-localization of brain signal across different participants, 5) Drug-word Stroop task (see description below), 6) Two runs of the XY-GoNoGo task (see description below), 7) PRESS Spectroscopy sequence to assess concentrations of glutamate, choline, creatine, N-acetyleaspartate and other metabolites in the anterior cingulate cortex , 8) and Mega-PRESS spectroscopy sequence to assess concentrations of GABA in the anterior cingulate cortex. MR spectroscopy will be performed on the ACC region and will use Point-Resolved Spectroscopic Sequence (PRESS). The MRS scan is approximately 4.5 mins. MRS analysis for PRESS spectra will be performed by using the Java-based Magnetic Resonance User Interface (jMRUI). Specialized MRS of GABA and other metabolites will be performed using a Mescher-Garwood PRESS (MEGA-PRESS) sequence. The total time for this sequence is approximately 9 mins. MEGA-PRESS data will be analyzed with the MATLAB-based tool Gannet. In MR spectroscopy, the subject will experience nothing different compared to other MRI scans in the study.   Prior to each fMRI run, two EPI images with the same echo time and spacing as the main run are acquired with opposite phase-encode directions (less than 60 s duration). From this scan pair, susceptibility-induced off-resonance field correction is estimated using the method implemented in FSL "topup" software. In addition, peripheral pulse rate (using MRI compatible pulse oximeter) and respiratory rate (using standard MRI respiratory chest belt) will be recorded during the fMRI scans for removing artifactual physiological signals using ~~the~~ "retroicor" software.

XY Go-NoGo task This task probes brain responsiveness to sporadic requirements to inhibit prepotent motor behavior. The subject must periodically interrupt a general stream of cue-elicited motor responses that are elicited once per second. The subject sees a sequence of either the letter X or the letter Y presented in the middle of the screen once per second (i.e. 1 s trial; stimulus duration = 400 to 600 ms). The remaining time of each one-second trial is composed of blank screen). The subject is instructed to respond to each letter if it is different than (i.e. alternates with) the previous letter. Periodically, the subject will see a second X or a second Y presented in a row, and must withhold his or her response. The scan task will be performed in two fMRI runs (5 minutes each). During task performance, an indicator LED light flashes in the scanner control room with each button press, thereby alerting the research staff of subject engagement in the task in real-time.

 Drug Word Stroop Task Participants see opioid words (OWs) and neutral words (NWs) within four alternated 30-s OW blocks and NW blocks. Each presented word is randomly printed in blue, green, or red. The participant is instructed to ignore the meaning of the word and to press a button to denote the word color. For each participant, the mean reaction times (RTs) during the OW blocks and during the NW blocks are computed. The effect of opioid cues on the reaction time (ΔRT) are measured by the mean RT during all the correct-response trials in the OW blocks minus the mean RT during all the correct-response trials in the NW blocks, i.e., ΔRT = RT (OW) minus RT (NW). ΔRT is treated as the behavioral measure of attentional bias.

L	Resting	T2	Struct	Stroop	XYGNG	XYGNG	PRESS	mPRESS	DTI

| 0 | 3 min | | 18 | 23 | 30 | 37 | 44 | 50 | 57 | 69 min |

7.6 Participant Reimbursement

All participants will receive $40 for completing the screening visit and $75 for completing the assessment visit, for a total of up to $115 for completing the assessment battery portion of the study.

Additionally, individuals who are eligible to screen for the MRI portion of the study (Healthy Controls and individuals with OUD) will receive up to an additional $75 for screening ($25 for the additional screening measures- the physical exam and blood draw, and $50 for the mock MRI), and $100 for the MRI (for up to $290 for completing both the assessment battery portion and MRI portion of the study). Payment will be in the form of cash. Participants who are returning only to complete the MRI screening/scanning portion of the study will receive up to $75 for the MRI screening ($25 for physical exam and blood draw, and $50 for mock MRI), and $100 for the scan visit.

The pro-rated compensation schedule for individuals who do not complete a given study visit is as follows:
Participants will receive $10 per hour for a study visit (with the maximum available $40 for individuals in marijuana and cocaine groups and up to $115 for individuals in the healthy control and opioid use disorder groups for screening, maximum of $75 for assessment visit (regardless of group status), and a maximum of $100 for the MRI visit) if they do not complete a given study visit.
All participant payment will be in the form of cash.

8. DATA MANAGEMENT PROCEDURES

8.1 Data Collection

Individual subject data will be obtained via structured interview evaluations, self-report measures, and computerized behavioral tasks. This information will be collected at specified time points during the study. The biological specimens obtained from all subjects will include urine, and breath samples for alcohol detection. All materials will be obtained for the specific purposes of this research. Trained research personnel will collect study data according to written protocol.

8.2. Data Entry and Validation

In an effort to enhance efficiency and accuracy of the data, hard copy self-report measures will be converted into electronic data capture forms (using REDcap electronic data capture system) for direct computer-based entry by study participants. Remaining self-report and interview data will be entered by research assistants into an existing, secure database (i.e. REDcap). Data integrity will be maintained by restricting allowable input values on a standardized entry forms. Double entry of a random subset of 10% of the observations will be used to identify problematic data entry issues.

8.3. Interim Analysis & Full Data Analysis

The primary data analyses will focus on final modifications to the PhAB and Platform battery. Data will be evaluated over all enrolled subjects. Number and percentage of dropouts, non- completers of the PhAB Battery and Platform Instrument measures will be assessed. Time to complete the assessment batteries will also be recorded for each task and each participant. Findings with regard to average time to complete each measure, redundancy between assessments, and sensitivity and specificity of measures will guide decisions on the refinement of the battery and the selection of instruments to be included in the final version of both the Platform instrument and PhAB assessment batteries. Additional analyses will focus on examining relationships between task performance, assessment response patterns, and SUD diagnoses, and how these relationships vary according to various other psychosocial influences (e.g., trauma, gender, depression, etc).

Effective connectivity analyses of resting state scans will be performed using dynamic causal modeling (DCM) in SPM. Effective brain connectivity will be compared between OUD, other relevant populations in the study and control participants and the relationship between effective brain connectivity and behavioral assessments from the PhAB will be assessed. Default mode and executive control networks will be the primary networks studied in this analysis. In addition, a effective connectivity brain analysis will be conducted in order to test the group difference in a large extent covering the whole brain. A preliminary functional connectivity analysis will be conducted in a large brain network to detect the brain regions showing largest group difference in functional connectivity. Nodes showing largest group difference in functional connectivity will be selected as DCM nodes for the large extent effective brain connectivity analysis.

9. SAFETY MONITORING AND REPORTING

The study PI is ultimately responsible for safety monitoring and adherence to the protocol, and will review all safety monitoring and study performance data and address any problems noted.

9.1 Subject protection

Subjects might experience psychological distress due to assessment procedures. It is not anticipated that serious psychiatric problems (including suicidality) will develop while participating in the study. If such an event occurs (whether or not it is thought to be study-related), the study team is experienced in handling these events and will follow clinic guidelines and immediately contact the appropriate study doctor and/or PI for evaluation. The participant will be referred for appropriate medical or psychiatric care as needed. It is more likely that during the clinic visits, participants may experience some degree of emotional discomfort or fatigue due to the screening and/or assessment procedures. However, the use of these procedures has not been shown to be harmful to psychiatric/substance abusing patients. In an effort to minimize the risk of distress and/or fatigue experienced by participants, breaks will be given at regular intervals and as needed, and participants will be informed that they have the right to refuse to answer questions that make them uncomfortable. Additionally, research personnel are trained to assess for level of distress and will be attentive to the participant's needs.

Confidentiality of patient records is maintained by assigning subject ID numbers and using these rather than subject names on all study records. Research data are kept in a locked filing cabinet; signed consent forms and subject ID keys are kept in a separate location in a locked cabinet.

9.2 Adverse event monitoring and reporting

An adverse event (AE) is defined as any untoward medical occurrence in a participant that may or may not have a causal relationship with study participation. Any mention of an untoward event will trigger an entry onto the AE log. All adverse events (AEs) occurring during the course of the study will be collected, documented, and reported to the PI. The occurrence of AEs will be assessed at baseline. Due to the nature of the current study, it is anticipated that a low number of study-related adverse events will occur. However, potential adverse events may include: psychological distress due to assessment procedures. Relapse to substances requiring hospitalization, drug overdose, and suicidality may also occur. A summary of AEs will be provided to the VCU IRB at the time of protocol continuing review, and will also be provided to NIDA Program Officer (Dr. Aidan Hampson) and Science Officer (Dr. Tanya Ramey).

9.3 Serious adverse event monitoring and reporting

A serious adverse event (SAE) is defined as any event that is fatal or life threatening, that is permanently disabling, requires or extends hospitalization of the subject, is a congenital anomaly, or requires intervention to prevent any of the above. This could include hospitalizations related to drug overdose or suicidality.

AE's deemed to be serious (SAEs), as defined by the FDA, will be systematically evaluated at each clinic visit. Study-related SAEs, will be reported to the VCU IRB, and the NIDA Program Officer within 24-48 hours. A full written report to all institutions will follow as soon as possible but in no more than three days. The written report will be in the format required by the local IRB and will contain information regarding the date of the SAE, description of the SAE, severity rating (Grade 1 to 4), assessment of cause, whether the SAE indicates an increased risk for current or future subjects, and whether changes to the informed consent form will be necessary.

9.4 Criteria for Participant Discontinuation from the Study

The reasons for discontinuation from the study may include: inability to comply with study procedures, change in study eligibility, or exhibiting potential harm to self or others. Participants must continue to meet inclusion criteria in order to remain in the protocol. If suicidal ideation is identified in any subjects while actively enrolled in the study, the subject will be withdrawn from the study. The study physician will be contacted immediately and meet with the subject. If the participant expresses having a plan, the subject will not be left alone until a study physician has met with him/her. A trained study staff will remain with the subject until a study physician meets with him/her or until the subject has been seen by a study psychiatrist for an emergency psychiatric consultation. A physician will be available at all times to assess the situation. If the study physician determines that the subject's suicidal risks are high, he/she will develop a plan for safety will the subject, including but not limited to: transferring the patient to the psychiatric unit of the VCU medical center.

In the event that a patient either withdraws from the study or the investigator decides to discontinue a patient due to SAE, the patient will have appropriate follow-up monitoring. Monitoring will continue until the problem requiring hospitalization has resolved or stabilized with no further change expected, is clearly unrelated to study, or results in death.

10. Institutional Review Board (IRB)/Independent Ethics Committee(IEC)

It is the responsibility of the investigator to have IRB approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, eg, advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to NIDA Science Officer (Dr Tanya Ramey).

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