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PILOT RCT OF MBRP IN OUTPATIENT METHADONE CLINIC: A NEUROPSYCHOLOGICALLY-INFORMED APPROACH

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**PILOT RCT OF MBRP IN OUTPATIENT METHADONE
CLINIC: A NEUROPSYCHOLOGICALLY-INFORMED
APPROACH**

BY

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B.S., Psychology, University of New Mexico, 2010
M.S., Psychology, University of New Mexico, 2015

DISSERTATION

Submitted in Partial Fulfillment of the
Requirements for the Degree of

**Doctor of Philosophy
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Albuquerque, New Mexico

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DEDICATION

For Janine Pommy-Vega

Prolific Writer, Poet and Activist

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ABSTRACT

Introduction: The primary study goal was to assess the feasibility of implementing a Randomized Clinical Trial (RCT) of Mindfulness-Based Relapse Prevention (MBRP) in a substance use and methadone clinic using a neuropsychological framework.

Methods: Participation interest, retention rates, and feasibility of study design were examined. 13 participants were randomized to waitlist (n = 6) or MBRP (n =7). Associations between baseline variables and retention were examined. Executive function (EF) performance and topological properties of fNIRS resting-state networks were assessed.

Results: Power was limited, but quantity of outside treatment was associated with retention. EF was variable, but within the average range. Network analyses revealed small world parameters in resting-state networks using fNIRS. Exploratory correlation analyses between EF and graph metrics were performed.

Conclusions: The feasibility of using neuropsychological measures of EF and fNIRS in the context of a RCT in an outpatient substance use clinic was demonstrated.

Keywords: Executive Function, fNIRS, Mindfulness, Opioid, Substance Use, Pilot Study,
Feasibility, Resting State

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INTRODUCTION

Each day roughly 130 people will die following an opioid overdose in the United States; and these rates continue to rise (NIDA, 2019b). Between 2016 and 2017 overdose deaths from fentanyl, for instance, increased by 45 percent (Scholl, Seth, Kariisa, Wilson, & Baldwin, 2018). The rate of overdose deaths associated with opioids in New Mexico remains well above the national average (NIDA, 2019a). Opioid Use Disorder (OUD) has been associated with increased psychiatric and comorbid substance use problems. In particular, previous use of other substances of abuse appears to be the norm rather than the exception. For instance, while a prior anxiety disorder diagnosis increased the odds of later developing an OUD by 50%, a prior substance use disorder (SUD) diagnosis increased the odds of developing an OUD by 300% (Blanco & Volkow, 2019). While medical interventions may be the first line of treatment for OUD, given the chronic and relapsing nature of OUD, behavioral interventions are needed particularly after patients are stabilized. Despite a significant need for more effective interventions, there remains a significant gap in the literature on the best psychosocial interventions (Dugosh et al., 2016).

There is clear need for additional treatment approaches for OUD. Advances in neuroimaging and clinical neuroscience have fueled interest in identifying new treatment targets for OUD via a neuropsychological approach (Jeong & Yuan, 2017; Stewart, May, Aupperle, & Bodurka, 2019). A neuropsychological framework to mental health can help identify new targets for treatment and assess changes in those markers over time through the use of neuropsychological assessments, neuroimaging methods and

self-reported symptoms. Following a brief overview of current treatments for OUD, a neuropsychological framework will be employed for the remainder of the paper.

Opioid Use Disorder: Treatment As Usual

Broadly, OUD treatments can be divided into three different approaches based on the treatment goal: crisis intervention (in context of overdose), medication-assisted/maintenance treatment, and abstinence-based intervention (Hser, Evans, Grella, Ling, & Anglin, 2015; Van den Brink & Haasen, 2006). While crisis intervention is beyond the scope of this paper, it is worth noting that this stage of treatment is when most individuals with an OUD seek treatment, with one in four individuals seeking additional treatment in the following month. Abstinence-oriented interventions occur in two phases: detoxification and relapse prevention. In general, treatment outcomes have been disappointing and appear effective for a relatively small subset of individuals with OUD with high social support, stable environments and high levels of motivation (Van den Brink & Haasen, 2006). Medication-assisted treatments (MAT) have greater success rates and emphasize a harm reduction approach to treatment. MAT involves one of three FDA-approved medications: methadone, buprenorphine, and naltrexone (Connery, 2015). All three medications target the mu-receptor: methadone is a full agonist, buprenorphine is a partial agonist, and naltrexone is an antagonist. In a recent review of RCTs of methadone, buprenorphine and naltrexone, the efficacy of these medications for prevention of opioid relapse and continuation in treatment has been demonstrated (Connery, 2015). Of the three, Methadone remains the gold standard for OUD treatment.

Methadone Maintenance Therapy (MMT), a type of opiate replacement therapy (ORT), has been associated with decreased likelihood of overdose, reduced contraction of HIV/Hepatitis C among intravenous drug users, and has been shown to enable individuals to have more functional lives through reduction of criminal risks and increased ability to gain employment (WHO, 2009). Despite this success, mortality rates in long-term cohort studies of individuals receiving methadone, nonetheless, were 6 to 20 times greater than that of the general population, and 25-50% of the cohorts were deceased 20 years after baseline (Hser et al., 2015). The authors suggest mortality rates were impacted by AIDS among areas with high HIV prevalence, and impacted by suicide and trauma in countries with lower rates of HIV/AIDS (Hser et al., 2015).

A number of behavioral interventions have been used in conjunction with MMT and include: contingency management, 12-step recovery, cognitive behavioral therapy, motivational interviewing, risk reduction counseling, Acceptance and Commitment Therapy (ACT), general therapy, and supportive counseling (Dugosh et al., 2016). However, most research has focused on contingency management and cognitive behavioral therapy in conjunction with methadone maintenance (Dugosh et al., 2016). While research has supported the incremental value of using behavioral interventions in conjunction with ORT, success varies based on treatment outcomes and comparison groups.

A significant majority of individuals reporting symptoms of OUD report no treatment (L. T. Wu, Zhu, & Swartz, 2016). Given the risks associated with OUD this is concerning. Further, even among individuals that eventually seek treatment, most individuals reported use of opioids 6 to 10 years before initiating treatment (Hser et al.,

2015). In addition to the limited access to treatment and delays in treatment seeking, among patients that initiate treatment, there are high drop-out rates that are concerning. Research has shown that patients that remain in MMT for longer periods of time have better treatment outcomes. The first year of treatment appears to be especially critical (Hser et al., 2015). However, there is a vast literature suggesting the majority of patients drop out of treatment in the first year. Furthermore, in outpatient settings, drop-out rates are even higher than in randomized controlled trials (Roberts, 2018). Efforts to identify and ameliorate barriers to treatment are of great interest. In particular, individuals using prescription opioids and individuals who are adolescent or from ethnic minority backgrounds are less likely to receive care (F. Wu, Fu, & Hser, 2015). There is a significant need to target prevention and treatment efforts towards these populations.

Concerns with Treatment As Usual

While ORTs have undoubtedly reduced rates of overdose deaths and contraction of HIV/Aids and Hepatitis C, the high rates of drop and low treatment engagement suggest more can be done to improve treatment. The MMT phase of treatment may last for years or for the patients' life. There remains among providers, a debate as to whether efforts should be made to facilitate discontinuation of methadone treatment or whether it should remain a lifelong option (Schuckit, 2016). On the one hand, some individuals seeking ORT may perceive it as an alternative to criminalization (Frank, 2018), alternatively, for individuals seeking to eventually discontinue methadone, this may not be perceived as a good fit either.

ORT is generally provided at outpatient substance use clinics, methadone clinics, or inpatient substance use settings. Access to specialty clinics may be an additional

barrier, particularly among individuals with limited transportation or those that live in rural communities (Amiri et al., 2018; Sigmon, 2014). Alternative models of care including, primary-care-based models have been explored, with the hope of increasing access to care (Korthuis et al., 2017). Even among individuals receiving treatment at outpatient substance use clinics, there has been concern that individuals are not always prescribed the most effective medication or are prescribed doses that were below the effective dose. In 2011, for instance, in a nationwide sample of patients on MMT, 41 percent of the sample received doses that were too low to be optimally effective (D'Aunno, Park, & Pollack, 2019).

Historically, under-dosing of methadone had been a clinical concern. Notably while this pattern has improved within the general population, among ethnic minorities this remains a significant clinical concern (D'Aunno et al., 2019). Further, treatments may not adequately serve all individuals. Research assessing gaps in access to care has found that individuals from different cultural backgrounds may find the MMT approach inadequate. For instance, a recent qualitative study interviewed 53 Latino and African American individuals that were using intravenous drugs but had declined to continue receiving treatment at a methadone clinic (Zaller, Bazazi, Velazquez, & Rich, 2009). The authors identified specific beliefs related to discontinuing treatment, including belief that methadone was harmful to one's health, perception that methadone should be discontinued, and belief that one cannot be abstinent from substances of abuse if on MMT. Additionally, financial burden and the time requirements for treatment were barriers noted.

Opioid Use Disorder Complexity

ORT may not sufficiently address the range of complexity observed within this population. While substance use disorders are diagnosed for the individual substance of abuse, instances of comorbid substance use disorders remain a clinical issue. A recent publication using the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) data examined prevalence of multiple substance use disorder diagnoses at two time points (McCabe & West, 2017). The authors found individuals diagnosed with multiple SUDs at time point one were more likely to exhibit a SUD at time point two, relative to individuals diagnosed with one SUDs at time point one. Further, the authors found individuals with multiple SUDs were less likely to receive any SUD treatment relative to individuals with a single SUD (McCabe & West, 2017). Among OUD samples, research from the 2015-2017 National Survey on Drug Use and Health data found significant rates of co-occurring drug and alcohol use among adults diagnosed with an OUD (Jones & McCance-Katz, 2019). More specifically, the rate for co-occurring SUDs ranged from 26.4% for alcohol to 10.6% for methamphetamine (Jones & McCance-Katz, 2019). Among individuals with OUD, 57.3% met criteria for polydrug use disorder, with alcohol as the most frequently reported substance used in addition to opioids (Hassan & Le Foll, 2019). Further, polydrug use among individuals with an OUD may be associated with greater psychopathology, including PTSD (Hassan & Le Foll, 2019). While polysubstance use disorder was not included in the latest iteration of the Diagnostic and Statistical Manual of Mental Disorders (DSM), use of multiple substances, particularly among OUD clients remains an important clinical concern.

Adults with an OUD exhibit elevated rates of psychopathology. More specifically, 64.3% of adults with an OUD experienced mental illness in the past year and 26.9% experienced serious mental illness within the past year (Jones & McCance-Katz, 2019). Among those individuals with OUD that experienced mental illness in the past year, 24.5% reported receiving treatment for both substance and mental health concerns, while 29.6% of individuals with OUD and serious mental illness reported receiving treatment for both conditions. Among a sample of treatment seeking individuals with a SUD, 32% reported a past suicide attempt and of those, 59% reported a serious attempt (Icick et al., 2017). Clearly, more comprehensive interventions that address the complexity of OUD are needed.

While ORTs have the potential to greatly improve the lives of individuals with an OUD, they are unfortunately underutilized. In part, perhaps, because ORTs do not address the prevalent comorbid substance use and mental health concerns in this population. Interventions are needed that can simultaneously address substance abuse and comorbid mental health issues. Mindfulness-Based Interventions (MBIs) show great promise in this respect.

Mindfulness-Based Interventions (MBIs)

MBIs are being increasingly used in the treatment of a wide range of psychiatric conditions (Alfonso, Caracuel, Delgado-Pastor, & Verdejo-Garcia, 2011; Hofmann, Sawyer, Witt, & Oh, 2010; Witkiewitz & Bowen, 2010). The vast majority of MBIs are based on Mindfulness-Based Stress Reduction (MBSR) during which individuals learn ways to practice techniques to increase mindfulness, defined broadly as "...paying

attention in a particular way: on purpose, in the present moment, and nonjudgmentally” (Bowen, Chawla, & Marlatt, 2011).

MBIs have shown efficacy for individuals with SUDs and have been shown to reduce both substance use behavior and self-reported craving across a variety of substance-using samples (Bowen et al., 2014; Chiesa & Serretti, 2014; Witkiewitz & Bowen, 2010; Witkiewitz et al., 2014). One prominent approach, Mindfulness-Based Relapse Prevention (MBRP) has been shown to reduce craving and prevent relapse in individuals with an SUD via improved mood (Witkiewitz & Bowen, 2010) and acceptance of thoughts (Witkiewitz et al., 2014).

Implementing MBRP within an outpatient methadone clinic is relatively novel. Recently, Bowen and colleagues (2017) conducted a pilot study of clients receiving treatment at a MMT clinic (Bowen, Somohano, Rutkie, Manuel, & Rehder, 2017). In that study, 15 individuals completed the baseline visit, and seven completed the follow up visit. Participants in the study were recruited from a community-based methadone clinic. Average age of the sample was 43.8 years (ages 27 to 65 years old), the majority of the sample were white (93%) and employed full-time (87%). Regarding clinical variables, over half had a history of inpatient substance use treatment and the majority of the sample was concurrently participating in a 12-step program. Preliminary results based on direction and magnitude of mean change suggested improvements in outcome associated with MBRP. The largest effect size was for change in craving ($g = 0.98$, $p = .032$). Medium effect size for change in mood and a smaller effect size for change in trauma-related symptoms was also found ($g = 0.63$, $p = .03$; $g = 0.09$, $p = .025$). A second study examined the impact of MBRP on relapse and self-report ratings of impulsivity among

patients receiving MMT (Yaghubi, Zargar, & Akbari, 2017). Seventy patients referred to MMT centers in Iran were randomized to receive either, treatment as usual (TAU) or an 8-week MBRP group. Lower rates of relapse were observed in the MBRP group immediately following the intervention ($p = 0.012$) and at a two month follow up visit ($p = .010$). Relative to the TAU group, the MBRP group scored significantly lower on a self-report measure of impulsivity, the Barrett Impulsivity Scale (BIS-11) ($p < .001$), immediately following the intervention. The drop in self-reported impulsivity remained two months following the completion of the intervention. While potential mechanisms of action associated with MBRP are still being explored, executive function (EF), which includes impulsivity, has shown great promise as a possible treatment target for SUDs and as a possible mechanism by which MBIs work.

Definitions and Measures of Executive Function

Broadly, executive function (EF) refers to a set of interrelated cognitive processes that enables one to carry out goal-directed behavior and inhibit prepotent (automatic) responses (Kramer et al., 2014; Lezak, Howieson, & Loring, 2004; Miyake et al., 2000). Various models of EF have been proposed. One distinction that has particular application to SUD is that of “cool” EFs and “hot” EFs. Namely, while “cool” EF refers to abilities in a context-free environment, “hot” EF refers to those abilities in affective contexts (involving emotion, motivation, reward). Typically, the EF tasks used in lab and clinic settings are “decontextualized”, meaning they do not have an “affective or motivational component” (Prencipe et al., 2011).

Miyake and Friedman’s model of EF (Miyake et al., 2000), a well validated, developmentally relevant model of EF captures the cool EFs, including: updating,

shifting, and inhibitory control. While this model was originally tested within typically developing adults, a longitudinal study examining individuals performance on measures of EF during late adolescence and young adulthood, found the unity/diversity model of EF was supported (Friedman et al., 2016).

Cool EF can be measured with neuropsychological tasks that measure: updating and monitoring working memory; shifting between tasks or mental sets; and inhibiting dominant or prepotent responses (Miyake et al., 2000). Given the multifactorial nature of EF, a single score on a test does not sufficiently capture the construct of interest, which, in part motivated the creation of The Delis-Kaplan Executive Function System (D-KEFS), a widely used battery of EF tests.

In more recent years, efforts to develop computerized tasks of EF have been made. The National Institute of Health (NIH) Toolbox for the Assessment of Neurological and Behavioral Function (NIH-TB) Cognitive Battery measures EF across the lifespan at multiple time points. The Toolbox contains multiple measures of EF that map well onto Miyake and Friedman's model of EF, including: Dot Counting and N-back (updating), Set Shifting (shifting) and Flanker (Kramer et al., 2014; Macleod, 1992).

Hot EFs continue to develop during late adolescence into young adulthood and involve: affect intensity and reactivity (having to do with the initial affective response) and affective modulation, cognitive modulation and behavioral control (domains more related to top-down control of emotion) (Wilcox, Pommy, & Adinoff, 2016). Hot EF can be measured with self-report and tasks that measure: negative affect, reactivity, and coping with emotions. Examples of tasks and self-report measures of hot EF include: Difficulties in Emotion Regulation Scale (DERS) and White Bear Suppression Index

have been tied to hot EF in substance use disorders (H. C. Fox, Axelrod, Paliwal, Sleeper, & Sinha, 2007; H. C. Fox, Hong, & Sinha, 2008; Garland, Carter, Ropes, & Howard, 2012; Toll, Sobell, Wagner, & Sobell, 2001).

The neuroanatomical correlates of EFs have been examined using both structural and functional neuroimaging studies (Friedman & Miyake, 2016). While EF typically involves multiple brain regions, they are often associated with the prefrontal cortex (PFC) (Otero & Barker, 2014; Stuss & Alexander, 2007). Based on lesion studies, cool EFs are frequently localized to dorsolateral PFC and the anterior cingulate cortex, hot EFs are typically localized to ventromedial PFC (Robinson, Calamia, Glascher, Bruss, & Tranel, 2014). There is some evidence to suggest specific properties of neural networks may be correlated with specific EFs, as well (Reineberg, Gustavson, Benca, Banich, & Friedman, 2018).

Neurodevelopmental Correlates of Executive Function

Many of the neurodevelopmental changes that occur in the PFC during adolescence and young adulthood have been linked to the protracted development of EF (Asato, Terwilliger, Woo, & Luna, 2010; Barnea-Goraly et al., 2005; Squeglia, Jacobus, Sorg, Jernigan, & Tapert, 2013). Substance use during adolescence and young adulthood has the potential to disrupt these developmental processes in clinically significant ways.

In particular, EF development during adolescence has been associated with increased within-PFC connectivity, increased PFC activation at rest and during EF tasks, as well as changes in the topological features of connectivity (Fair et al., 2007). Developmental changes in within-PFC connectivity can be observed in both structural connectivity and functional connectivity. For instance, during adolescence increasing age

is positively correlated with increasing structural integrity of white matter within the prefrontal cortex (Barnea-Goraly et al., 2005). Further, white matter connectivity in tracts connecting PFC to PFC (e.g., genu of the corpus callosum) continue to develop during adolescence (Asato et al., 2010). Functional connectivity analyses provide further support. For instance, decreased short-range connectivity and increased long-range connectivity and reduced white matter integrity of the genu of corpus callosum has been associated with higher scores on a self-report measure of EF behaviors (Clark, Chung, Thatcher, Pajtek, & Long, 2012).

SUDs have been associated with aberrant development of these neurobiological pathways. Further, given the increase in substance use during adolescence, the use of drugs and alcohol also directly impact the development of the neural circuits underlying EF. While additional deficits have been associated with SUD, broadly, EF in particular is tied to neurodevelopmental changes that occur during adolescence and have significant correlates. Functional neuroimaging methods are able to detect the functional connectivity between brain regions. Functional Near-Infrared Spectroscopy (fNIRS) is an approach that has great promise.

Functional Near-Infrared Spectroscopy (fNIRS)

fNIRS is a non-invasive, functional neuroimaging technique that infers changes in neural activation via changes in oxygenation levels and blood flow in the brain. When neural activity increases in response to a task there is an increase in the cerebral blood flow (CBF) to the brain region involved. When there is an increase in CBF to an area of the brain fNIRS detects an increase in the ratio of oxygenated hemoglobin relative to deoxygenated hemoglobin in that region of the brain (i.e., the hemodynamic response)

(Tachtsidis & Scholkmann, 2016). More specifically, the fNIRS device emits light of varying wavelengths that penetrates approximately one to two centimeters into the cerebral cortex. Oxygenated blood (HbO₂) and deoxygenated blood (Hb) absorb different light wavelengths of electromagnetic radiation. Based upon the properties of the tissue the light is then scattered at different rates. The scattered light is then detected by the fNIRS device and based upon how much light was absorbed one can infer differences in hemoglobin concentration. More specifically, greater light absorption suggests increased blood flow to that brain region (i.e. greater deoxygenation) which is thought to reflect an increase in neural activity in cortical regions of the brain.

Relative to alternative neuroimaging methods, fNIRS has a number of advantages (Cui, Bray, Bryant, Glover, & Reiss, 2011). First, compared to fMRI, fNIRS is relatively inexpensive and simple to use, making it ideal for longitudinal studies that assess treatment effects. Further, motion artifacts are less of a concern with fNIRS making it a useful alternative to fMRI among adolescents. Finally, fNIRS is portable and can be used within an office or hospital setting making it a convenient and ecologically valid approach for clinical populations (Noah et al., 2015).

A variety of different analytical methods have been applied to fNIRS data. In addition to detecting changes in activation in a given region of the brain, recent studies have used fNIRS to explore properties of neural networks in the brain using Complex Network Analyses (Fekete, Beacher, Cha, Rubin, & Mujica-Parodi, 2014). Efforts to apply functional connectivity analytic methods have been particularly promising. In particular, the properties of resting state networks may provide insights into potential biomarkers of substance use disorders as well as associations with EF. Resting state

networks have frequently been studied as potential endophenotypes associated with different psychiatric issues. Resting state networks can be studied using a variety of different statistical methods. For this study, a graph analytic approach was utilized to characterize various topological properties of the fNIRS resting state networks. Graph theory is a branch in mathematics concerned with the study of networks. Recent work has applied graph theory techniques to structural and functional neural networks (Bullmore & Sporns, 2009). Briefly, graphs can be used to describe a complex network by characterizing it as a set of nodes or vertices, connected to one another by a subset of edges (Bullmore & Sporns, 2009). Specific topological properties of the graph can then be calculated at a global level (the entire network), at a nodal level (properties of a given node in the network), and at a modular level (clusters of densely connected nodes within the network).

Relative to random graphs, graph of brain networks have higher clustering and more variable degree centrality at each node (i.e., more variability in the number of connections between a given node and the rest of the regions in the network). Brain networks have been found to have high clustering and shorter path lengths, a phenomenon referred to as “small worldness”. Path length and global efficiency are measures believed to capture the integrative nature of a network (Papo, Buldu, Boccaletti, & Bullmore, 2014).

Graph theory analyses have been shown to predict meaningful properties of how the brain networks across a range of populations and has been utilized in efforts to identify potential endophenotypes that may serve as future treatment targets. In sum, fNIRS has the potential to assess changes in the BOLD signal in a given region, as well

as, changes in FC between regions of a neural network (M D. Fox & Raichle, 2007; M. D. Fox et al., 2005).

fNIRS and Executive Function

fNIRS has been used to explore neurobiological correlates associated with EF. In healthy controls, increased oxyhemoglobin was observed in bilateral DLPFC during interference trials of the Stroop task (Schroeter, Zysset, Kruggel, & von Cramon, 2003). In a different sample, the switching condition of the Stroop was associated with greater activation in bilateral anterior DLPFC and bilateral anterior VLPFC activation (Lague-Beauvais, Brunet, Gagnon, Lesage, & Bherer, 2013). Further, variability in EF performance has been associated with variability in oxyhemoglobin changes during an EF task in children, providing further support that changes in EF can be detected with fNIRS (Schroeter, Zysset, Wahl, & von Cramon, 2004). fNIRS has also been used to explore EF impairments in clinical samples. For example, compared to healthy controls, adults with EF impairment (diagnosed with ADHD), exhibit less oxy-hemoglobin increases in the ventrolateral PFC during a working memory task (Ehlis, Bahne, Jacob, Herrmann, & Fallgatter, 2008). Finally, fNIRS has been used to improved diagnostic accuracy rates (Monden et al., 2015). More specifically, using pattern classification methods, neural activation during an inhibitory control task improved diagnostic accuracy rates in a sample of children with ADHD and typically developing controls.

The clinical applications of fNIRS have only recently being explored. However, fNIRS has been shown to be informative in predicting treatment outcomes for EF. For instance, fNIRS was used to assess changes in oxyhemoglobin in the PFC following an exercise intervention for EFs. Results showed the changes in PFC function explained a

significant proportion of the variance associated with EF improvement (Lambrick, Stoner, Grigg, & Faulkner, 2016). Lastly, fNIRS has been used to assess the impact of a pharmacological intervention on EF. In a sample of individuals with ADHD, improvements in performance on a task of inhibitory control (go/no-go task) following methylphenidate administration was associated with increased right lateral PFC activation (Monden et al., 2012). EFs and PFC function have been examined in SUD samples using fNIRS, as well (Monden et al., 2015).

Prefrontal Cortex and Substance Use

fNIRS has been used to detect clinically meaningful differences among individuals with SUD. In particular, differences in PFC activation patterns in individuals with SUD have been linked to reward processing. For instance, when exposed to drug cues, individuals with SUD often exhibit greater PFC activation suggesting increased effort needed to respond to cues. For instance, individuals with alcohol dependence demonstrated increased activation in the left anterior lateral orbitofrontal (OFC) and middle OFC when responding to alcohol cues (Ernst et al., 2014). Craving, an indicator of SUD severity, was found to be associated with different PFC activation patterns when viewing drug cues. More specifically, in adult smokers increased self-reported craving at baseline was correlated with increased activation in the OFC and less activation in the left DLPFC during smoking cue exposure (Kroczek, Haeussinger, Fallgatter, Batra, & Ehlis, 2015). When viewing non-drug related reward cues, however, individuals with SUD exhibit a different pattern of activation. For instance, individuals receiving treatment for opioid dependence exhibited decreased left ventrolateral prefrontal cortex (VLPFC) activation to images of positive social interactions and decreased activation in left rostral

PFC/VLPFC, right VLPFC, and left medial rostral PFC in response to appetitive food cues (Huhn et al., 2016). Overall, this suggests within individuals with SUD, different PFC activation patterns are observed when viewing of reward cues relative to controls.

Changes in PFC function while viewing reward cues has been associated with markers of treatment success. For instance, greater right DLPFC activation to a drug cue was observed in recently detoxified individuals with opioid use disorder compared to individuals that underwent opioid detoxification several months earlier (Bunce et al., 2015). Similarly, within individuals with a history of alcohol dependence, when viewing an alcohol cue, decreased activation in DLPFC and dmPFC was associated with increased days of abstinence (Dempsey et al., 2015). Lastly, length of recovery was positively correlated with increased oxygenated hemoglobin concentration in the PFC among the abstinent group during a fluency task (Dresler et al., 2012). In summary, PFC activation during reward processing may be an important marker of SUD and a potential biomarker of treatment success.

Executive Function: Treatment Target for Substance Use Disorder

Among adults with a SUD, however, EF is one of the best predictors of relapse. Impairments in cognitive inhibition of prepotent responses, and other related executive deficits, can lead to lack of control over drug or alcohol use, heightened severity of dependence, and poor treatment response (Goudriaan, Grekin, & Sher, 2011; Miller, 1991; Poling, Kosten, & Sofuoglu, 2007). Among adults with a SUD, those with evidence of impaired hot EF, such as increased negative affect (Miller, 1991) and affective instability (Nace, Saxon, & Shore, 1986) have increased craving, increased SUD severity, and poorer treatment outcomes (H. C. Fox, Bergquist, Hong, & Sinha,

2007; Sinha, 2007). Among adolescents, hot EF deficits predict escalated drinking patterns and binge drinking, suggesting substances may be used in an attempt to modulate negative emotions (Colder, Campbell, Ruel, Richardson, & Flay, 2002). Likewise, adolescents are at increased risk for developing a SUD if they exhibit impaired EF (Dom, De Wilde, Hulstijn, van den Brink, & Sabbe, 2006; Perry et al., 2011; Squeglia, Jacobus, & Tapert, 2009; Wilcox, Dekonenko, Mayer, Bogenschutz, & Turner, 2014) with earlier onset of substance use linked to greater EF impairments (Sagar et al., 2015).

A recent meta-analysis examined the neuropsychological impairments associated with OUD across 14 different cognitive domains (Wollman et al., 2019). The authors reported the largest effect size difference (Hedges' $g = 0.970$) across studies was for complex psychomotor ability, which included Digit Symbol Substitution Test and Symbol Digit Modality Test. Further, length of time abstinent was correlated with a reduction in the effect size for complex psychomotor ability. However, the authors reported the average raw score for individuals with an OUD were within the normal range. Additionally, in follow up meta-regression analysis, attention (Trails A time) statistically predicted effect sizes for executive function (verbal fluency, inhibition, working memory), and verbal memory. Among individuals with OUD, differences in delay-discounting were observed among individuals that use heroin relative to individuals that use prescription opioids (Karakula et al., 2016).

EF task performance has been linked to changes in PFC activation among individuals with SUD. For instance, compared to healthy controls, individuals with alcohol dependence exhibited impaired performance on a fluency task and smaller functional activation (oxygenated hemoglobin concentration) in regions of the PFC

during the task (Dresler et al., 2012). In a different SUD sample, while performance on a fluency task was comparable between an Alcohol Use Disorder (AUD) group and healthy control (HC) group, the AUD group exhibited less of an increase in oxygenated hemoglobin in the PFC relative to the control group (Schecklmann et al., 2007). Differences in neural activation on tasks of hot EF have been observed in SUD as well. For example, on the Iowa Gambling task, individuals with polysubstance use exhibited decreased bilateral DLPFC activation compared to healthy controls (Hammers & Suhr, 2010). A few studies have reported increased PFC activity in the absence of performance differences in individuals with SUD compared to HC. This effect, may, in part, be related to the substance of abuse. Specifically, in studies that included ecstasy use increased oxygenated hemoglobin in PFC areas was observed during inhibitory control and fluency (Roberts & Montgomery, 2015). In sum, while several fNIRS studies have shown SUD is associated with reduced PFC activation during EF tasks, this may be moderated by substance of abuse.

Reduced PFC activation during EF has also been shown to predict future substance use using a correlated methodology, fMRI. For instance, adolescents that later went on to use substances exhibited less activation in the ventromedial prefrontal cortex (vmPFC) during an inhibitory control task compared to adolescents that did not initiate substance use (Mahmood et al., 2013). Likewise, reduced activation in the prefrontal cortex during inhibitory control was also associated with later substance use initiation among adolescents (Norman et al., 2011). Further, severity of future substance use (positive history of black outs associated with drinking) was positively associated with reduced activation in prefrontal regions during inhibitory control trials as well (Wetherill,

Castro, Squeglia, & Tapert, 2013). Finally, improvements in emotional reactivity following a period of abstinence have been observed among adolescents with a SUD, suggesting hot EF improvements are associated with recovery as well (Winward, Bekman, Hanson, Lejuez, & Brown, 2014). Reduced PFC activation during EF is observed in adults with SUD, in adolescents that later develop SUD, and is associated with SUD severity among adolescents, suggesting it may be an appropriate target.

Brain Function During Resting State and Substance Use Disorder

Resting state fMRI data provide support to suggest functional connectivity is altered in individuals with SUD. Graph theory analyses have been used to identify topological properties of networks associated with clinical variables. For instance, small world networks properties have been observed among individuals with SUD that are both less efficient and more connected compared to healthy controls (Wang et al., 2015). Another study found, relative to controls, individuals with SUD showed increased global efficiency and decreased local efficiency (Regner et al., 2016).

Resting state fMRI data also suggest reduced PFC function during resting state is associated with SUD, as well. Adolescents with a SUD exhibit less activation in prefrontal regions of the brain during resting state, including: superior frontal gyri, middle frontal gyri, and medial frontal gyri compared to typically developing controls (Dalwani et al., 2014). Adolescents that currently used alcohol and adolescents that would later go on to use alcohol both showed increased BOLD signal in the frontal cortex (among other regions), relative to adolescents that did not use alcohol (Ramage, Lin, Olvera, Fox, & Williamson, 2015). Finally, among adolescents with a SUD, abstinence from substance use was associated with greater activation in prefrontal regions at rest

(Dalwani et al., 2014). Overall, reduced PFC activation during rest is observed in adults with SUD, in adolescents that later develop SUD, and is associated with SUD abstinence among adolescents, suggesting it may be an appropriate target. While there are other cognitive deficits associated with OUD, the EF deficits are related to clinical issues directly and are the most appropriate target.

Reduced within-PFC connectivity during rest may also be an important treatment target. Reductions in within-PFC functional connectivity (N. Ma et al., 2010; Muller-Oehring, Jung, Pfefferbaum, Sullivan, & Schulte, 2015) and structural connectivity (Huang et al., 2013; W. C. Lin et al., 2012; X. Ma et al., 2015), are both associated with poorer EF, have been observed in adults with a SUD compared to healthy controls and are associated with higher addiction severity, indicating a possible treatment target.

Reduced white matter integrity in tracts connecting PFC regions with one another are observed in individuals with SUD compared to controls (De Bellis et al., 2008; Jacobus, Squeglia, Bava, & Tapert, 2013; McQueeney et al., 2009) (F. Lin et al., 2012) and increasing behavioral EF impairments was associated with decreasing within-PFC structural connectivity. Overall, reduced within-PFC connectivity during rest is observed in individuals with SUD and is associated with EF in SUD, suggesting it also may be an appropriate target.

MBIs and Improved Executive Function

Improvements in performance on neuropsychological tests of EF have been observed following a MBI across a range of populations. In healthy adult samples, improvements in cool EFs, including sustained attention, inhibitory control, working memory, and fluency have been observed after a MBI (Chambers, Lo, & Allen, 2008;

Deepeshwar, Vinchurkar, Visweswaraiyah, & Nagendra, 2014; Heeren, Van Broeck, & Philippot, 2009; Jha, Stanley, Kiyonaga, Wong, & Gelfand, 2010; Moore & Malinowski, 2009; Mrazek, Franklin, Phillips, Baird, & Schooler, 2013; Slagter et al., 2007; Tang et al., 2007; Vega et al., 2014; Zeidan, Johnson, Diamond, David, & Goolkasian, 2010). Improvements on tasks of hot EF have been observed in healthy adults following a MBI as well, including: affective Stroop, emotional attention network test, and Iowa Gambling Task (Ainsworth, Eddershaw, Meron, Baldwin, & Garner, 2013; Alfonso et al., 2011; Allen et al., 2012; Ortner, Kilner, & Zelazo, 2007). MBIs have been shown to improve performance on hot EF tasks in clinical samples as well (Alfonso et al., 2011; Allen et al., 2012). In clinical adolescent samples, improvements in cool EFs, including: sustained attention, inhibitory control, task switching, and self-reported EF behaviors (Bogels, Hoogstad, van Dun, de Schutter, & Restifo, 2008; Himmelstein, 2011; Le & Proulx, 2015; Leonard et al., 2013), and hot EFs have been observed (Leonard et al., 2013). The persistence of EF gains following MBIs are still being explored and longitudinal studies are needed. While there is evidence supporting a dose-response to mindfulness, it is unclear how long these changes persist in the absence of continued practice.

Further, preliminary results suggest MBI may be helpful for adolescents and adults with ADHD (a neuropsychological disorder partly characterized by EF deficits) as evidenced by improved measures of EF (Zylowska et al., 2008) and behavior (Haydicky, Wiener, Badali, Milligan, & Ducharme, 2012). Improvements in symptoms of inattention and hyperactivity have been observed among individuals with ADHD following MBI (Bogels et al., 2008; Bueno et al., 2015; van de Weijer-Bergsma, Formsma, de Bruin, & Bogels, 2012; Zylowska et al., 2008). Among adolescents with ADHD, improvements in

both self-reported and parent-reported symptoms of ADHD (including EF) were observed (van de Weijer-Bergsma et al., 2012; Zylowska et al., 2008). Among adults with ADHD, improvements in self-reported clinical symptoms of ADHD and EF were found (Zylowska et al., 2008). In summary, MBI show promise in the treatment of a disorder of EF in both adult and adolescent samples.

MBIs and Changes in Prefrontal Cortex Activity

There is preliminary evidence to suggest MBIs may change the pattern of neural activation during EF tasks. The improvements in cognitive control associated with a MBI have been associated with changes in neural processing in the right prefrontal cortex (Deepeshwar et al., 2014). Within a sample of older healthy adults, improvements in EF were observed that were associated changes in activation patterns using a different neuroimaging technique, EEG. More specifically, greater right frontal alpha activation was observed (Moynihan et al., 2013). Specific to Hot EFs, increased activation of the DLPFC was observed during a task of Hot EF (affective Stroop task) (Allen et al., 2012). Further, amount of meditation was positively correlated with activation in regions including the DLPFC and medial PFC during a Hot EF task (Allen et al., 2012). Lastly, within a clinical sample, following a MBI individuals exhibited greater activation in the ventrolateral PFC when processing emotions (Holzel et al., 2013). However, among healthy individuals reduced reactivity to sadness following a MBI was associated with *increased* activation in regions of the ACC, vmPFC, and right superior frontal gyrus (Farb et al., 2010). During resting state, greater activation in the left PFC were observed in healthy adults following a MBI (Tang et al., 2009). Though preliminary, these results provide support for the idea that MBIs alter the way the brain processes emotional states.

More specifically, reductions in emotional reactivity may be related to changes in PFC recruitment during processing of emotions. As mentioned earlier, while there is support for a dose response to mindfulness, the persistence of changes in the absence of continued mindfulness practice is unknown.

MBIs and Changes in Prefrontal Cortex Structure

MBIs have been shown to impact the structure and function of the prefrontal cortex, a region of the brain associated with EFs (Funahashi & Andreau, 2013). For instance, in a sample of healthy adults, increased cortical thickness in a cluster that included the right inferior frontal gyrus was observed following an eight-week Mindfulness-Based Stress Reduction intervention (MBSR) (Santarnecchi et al., 2014). Further, increased white matter integrity was observed in the anterior cingulate cortex (ACC) (Tang et al., 2010). Specific to functional changes, two studies found increased activity in the prefrontal cortex (Davidson et al., 2003; Tang et al., 2009), while a third study reported decreased activity following a MBI in bilateral frontal pole of the brain (Chen et al., 2015). Each of these studies utilized a different imaging/analysis technique and a different MBI. Consequently, while it is difficult to make a precise hypothesis based on these findings, these results do suggest effects in the prefrontal cortex across studies.

MBIs have been associated with increased recruitment of regions of the prefrontal cortex based on functional and structural connectivity. Improved efficiency within the anterior cingulate cortex (ACC) during resting state was observed following a MBI (Xue, Tang, & Posner, 2011). Following a MBI, healthy adults experiencing unemployment demonstrated increased functional connectivity between the left DLPFC and a seed

within the DMN, the posterior cingulate cortex(Creswell et al., 2016). Increased rsFC between the between the DLPFC and the dACC was observed following a MBI(Chen et al., 2015). Similarly, within a clinical sample, increased functional connectivity between the PCC and bilateral medial PFC was observed following a MBI(Wells et al., 2013). Interestingly, greater within PFC functional connectivity (increased fc between right dorsomedial PFC to left lateral OFC) was observed in the clinical group but not the healthy sample of individuals receiving a MBI, suggesting MBIs may impact functional connectivity differently in clinical samples(Chen et al., 2015).

Changes within PFC functional connectivity are supported by changes in white matter within the PFC observed following a MBI. More specifically, increased white matter integrity was observed in in white matter tracts that connect different regions of the PFC and within white matter tracts that connect the PFC inter-hemispherically (Tang, Lu, Fan, Yang, & Posner, 2012; Tang et al., 2010). In sum, MBIs have been associated with increased recruitment of PFC at rest based on connectivity measures and increased PFC activation during EF. Overall, MBI may improve EF in substance users by improving measures of EF and via neurobiological changes within the PFC.

MBIs and Culture

Despite the profound benefits of mindfulness practices on various facets of health, including SUD it is important to consider the applicability of a MBI for individuals from marginalized populations. The use of mindfulness-based interventions in marginalized populations has become a focus in recent years. A recent study examined self-reported engagement in mindfulness related practices and identified potential socio-demographic barriers that are worthy of further consideration (Olano et al., 2015). Having more than a

high school diploma was associated with increased use of mindfulness practices. Further, non-Hispanic whites were more likely to engage in mindfulness practices compared to Hispanic and non-Hispanic Black respondents. Further, men were less likely to utilize mindfulness practices relative to women.

Similarly, there is research that suggests among the more common mindfulness interventions, MBSR and MBCT, the vast majority of randomized clinical trials have samples that are predominantly white (Waldron, Hong, Moskowitz, & Burnett-Zeigler, 2018). The authors found only one study specifically targeting a MBI among ethnic/racial minority or lower SES samples and that study did not report findings. When examining research studies that reported findings for other ethnic groups, 76% of the participants reported on were white. Further, across studies, individuals had a higher education than the normal population and more than 50% of samples reporting employment status and mean income of \$40,000 or greater. Notably, this review did not include MBRP, which has more support for use in underserved communities.

Preliminary research supports the use of MBRP in ethnic minority populations. In a sample of women receiving court referred residential treatment for substance use, MBRP was found to be more efficacious than relapse prevention (Witkiewitz, Greenfield & Bowen, 2013). Further, the role of racial/ethnic composition may moderate impact of MBRP on specific treatment outcome variables. In particular, MBRP may be more effective than RP for preventing heavy drinking days among whites, while among racial/ethnic minorities, MBRP may be more effective than RP in preventing drug use days (Greenfield et al., 2018).

Specific Aims and Hypotheses

The primary aim of the study was to assess the feasibility of implementing a MBRP within an outpatient substance use and methadone clinic from a neuropsychological framework. As mentioned earlier, a neuropsychological framework to mental health can help identify new treatment targets and assess changes in those markers over time through the use of neuropsychological assessments, neuroimaging methods and self-reported symptoms. Clinical neuropsychology consistently addresses cognitive problems and in conjunction with psychological problems. SUD, and OUD in particular, can be conceptualized as disorders of EF. Given the rates of substance use and mental health problems during adolescence in individuals that later go on to develop SUDs behavioral interventions that are able to simultaneously treat substance use, comorbid psychopathology and EF are needed. MBRP is a MBI with the potential to target each of these clinical concerns.

Overarching Aim. The current study was a pilot randomized control trial to assess the feasibility of implementing a MBRP in an outpatient substance use clinic, serving predominantly individuals receiving ORT. Treatment targets and study design utilized a neuropsychologically-informed framework. The study aimed to recruit both adolescent and young adult participants.

Specific Aim 1. Assess the feasibility of implementing a MBRP intervention study at an outpatient substance abuse treatment clinic providing opioid replacement therapy for adolescents and young adults. Examine participation interest and retention rates across study and feasibility of study design, including data collection procedures and outcome measures. Exploratory Aim: No hypothesis.

Specific Aim 2. Examine clinical characteristics of resulting sample at baseline and identify potential relationship between baseline factors and retention. *Hypothesis 1a:* Individuals enrolled in the study will demonstrate elevated levels of psychopathology and substance use. *Hypothesis 1b:* Individuals retained will demonstrate less psychopathology at baseline relative to individuals that were lost to follow up.

Specific Aim 3. Assess EF at baseline and the relationship among specific EF measures. *Hypothesis 2a:* Individuals will demonstrate impaired EF at baseline compared to the population mean. *Hypothesis 2b:* EF measures will be correlated, with higher correlations among neuropsychological measures of EF relative to self-reported measures of EF.

Specific Aim 4. Assess topological properties of fNIRS resting state networks and relationship to baseline measures of EF. *Hypothesis 3a:* Resting state networks will exhibit small world properties. *Hypothesis 3b:* Performance on neuropsychological measures of EF will be associated with small world network parameters.

METHODS

Experimental Design

The study used a single-site, randomized waitlist control study to assess the effectiveness of Mindfulness Based Relapse Prevention (MBRP) in adolescents and young adults diagnosed with a SUD. Potential participants were recruited from the adolescent and young adult clinic at the Addiction and Substance Abuse Program (ASAP) at the University of New Mexico.

All existing clients expected to continue in treatment for at least another 8 weeks, and newly enrolled clients thereafter (ages 14-34) were informed about the study. Interested participants were given a copy of the study consent form and a study flyer with contact information. Adolescents were encouraged to take the consent form home and talk to family members before signing it. All young adult participants (age 18-34) were randomized to receive: 1) MBRP, or 2) Waitlist Control and were not blinded to group assignment. Participants in the MBRP group received a 4-week MBRP treatment. Participants in the WC received treatment as usual during that time. Both groups completed one follow up visit following completion of treatment phase. The WC group was offered the MBI after all assessments had been completed.

Recruitment Procedures

Potential participants were recruited from the adolescent and young adult clinic at the Addiction and Substance Abuse Program (ASAP) at the University of New Mexico. The adolescent clinic at ASAP opened in October 2015 and at the time of our initial submission had 30 clients enrolled, ages 14-22 years, meeting criteria for opioid use disorder, alcohol use disorder, cocaine use disorder, cannabis use disorder, and

polysubstance use disorder. 2-4 clients per week are screened. The clinic reports 85% of the patients in the adolescent clinic have been retained in their program for 8 weeks or longer. At the time of our submission, the clinic reported 70% of the treatment population is receiving Opioid Replacement Therapy (ORT) with the 30% on additional psychotropic medications. Per director's report, adolescents are excluded if a residential or higher level of care is warranted based on screening visit at the clinic (i.e., active severe suicidal/homicidal ideation, active severe behavioral/aggression issues). Typical co-occurring disorders observed at this clinic include: posttraumatic stress disorder, major depressive disorder, pervasive developmental disorder, generalized anxiety disorder, and panic disorder.

In May 2018 the study team was made aware of changes to the clinic that impacted recruitment. The clinical director of ASAP, Larissa Maley, Ph.D., provided the study team an update on recent structural changes within ASAP. Per director report, adolescents ages 14 to 17 years of age receive treatment within the adolescent clinic at ASAP, while young adults, ages 18 years and older receive treatment in the adult clinic at ASAP. This decision was made based upon the clinical needs of the population served within ASAP. Additionally, per clinic director's report, the clinic has received an influx of individuals under 18 years of age with severe psychopathology that would likely result in them being excluded from this study. Consequently, based on these updates to the clinic, the clinical recommendations of providers at ASAP, and a reduction in the size of the recruitment pool within this age range, adolescents between the ages of 14 and 17 years interested in participation will be consented and enrolled in an Under 18 MBRP

group. They will not be randomized to the waitlist control condition, because it was deemed unlikely there would be sufficient sample size to achieve this.

Additional inclusion criteria include: current diagnosis of SUD based on the Structured Clinical Interview for DSM-V (SCID). Additional exclusion criteria include: 1) significant impairment of cognition or judgment (as observed by study staff or indicated by chart review) rendering the person incapable of informed consent, 2) brain injury with loss of consciousness greater than 30 minutes based on Center for Disease Control's definition of moderate to severe TBI, 3) diagnosis of epilepsy (based on chart review), 4) active psychosis (determined by both chart review and SCID). Participants currently taking prescribed psychoactive medications were not excluded, however, participants were stabilized on psychiatric medication, including ORT, prior to enrollment in the study.

Study Intervention and Assessment Procedures

The assessment battery (EF, ER, and substance use assessments) were completed at baseline and at a follow up visit (following completion of treatment) by trained research assistants in quiet rooms designed for testing. The assessment battery took approximately 3 hours. Transportation was provided to transport participants between ASAP and Center for Psychiatry Research/MRN as needed. As mentioned earlier, participants underwent a 30-minute fNIRS scan visit at baseline and at follow up. The participant was seated at a desk and the cap of the fNIRS acquisition device was placed on the participant's head. After 2-3 minutes for equipment checks, the experimenter administered a seven-minute resting state task.

MBRP. Participants received a condensed version of Mindfulness-Based Relapse Prevention an intervention that integrates cognitive-behavioral relapse prevention and mindfulness practices (Bowen et al., 2011; Roos, 2019). The study intervention was provided over the course of eight bi-weekly sessions (60 minutes each) and followed the procedures outlined in the treatment manual(Bowen et al., 2011; Roos, 2019). In each session participants were instructed on specific mindfulness practices (e.g. body scan, mindful movements) and ways to use these practices during high-risk situations (i.e. situations that trigger substance use). Participants were assigned to practice mindfulness activities at home between group therapy sessions. All MBRP sessions were provided at ASAP in rooms designed for group therapy.

Therapist Qualifications, Training, and Supervision. Therapists had at least a master's degree in a related field with clinical experience working with pediatric and adult samples. Consistent with prior MBRP studies, therapists were required to read the entire therapy manual, attend a basic training in MBRP, and commit to a personal daily mindfulness practice (Bowen et al., 2011). Cases were discussed in weekly group supervision.

Assessments

Neuropsychological Measures of EF. Subtests were selected from two different assessment batteries: the Delis-Kaplan Executive Function System (D-KEFS) and the National Institute of Health (NIH) Toolbox for the Assessment of Neurological and Behavioral Function (NIH-TB).

The Delis-Kaplan Executive Function System (D-KEFS) is a widely used battery of EF tests (Delis, Kaplan, & Kramer, 2001). The D-KEFS was normed on a sample of

1,700 children and adults (age 8-89 years) with demographic characteristics consistent with the United States population according to the 2000 US census. In particular, the trail making test (TMT), Color word Interference and Verbal Fluency tasks are frequently used. The TMT was designed to measure different cognitive skills that contribute to performance on the more widely known Trail Making Testing with two conditions. TMT consists of five conditions that measure, visual scanning, number sequencing, number-letter switching, and motor speed, respectively. Verbal Fluency measures fluent productivity in the verbal domain across three conditions. On the first condition, the individual is asked to say names beginning with a specific letter (Letter Fluency), on the second condition the individual is asked to name words from a specific category (Category Fluency), and on the third condition the individual is asked to switch between saying words from two different categories (Category Switching). Two scores are produced from this condition: total number of words and accuracy in switching. Color-Word Interference is similar to the Stroop test. The individual is asked to name color patches in condition 1, read the color names printed in black ink on the second condition, and then on condition 3, the participant must name the color of the ink that color words are printed in (e.g., the individual must say "red" when reading the word "blue" which is printed in red ink). The fourth condition adds a switching condition, where the individual is instructed to shift back and forth between naming the ink colors and reading the color words. Internal consistency across the select subtests varies. Internal consistency from TMT for combined number and letter sequencing composite ranges from .60 to .81. Verbal fluency internal consistencies by condition: Letter Fluency .68-.90, Category Fluency .53 to .76, Switching Total Correct .37 to .68, and Switching Accuracy .51 to

.76. Internal consistency for Color Word Interference for combined color naming and word reading composite score ranges from .62 to .86. Correlations between tasks on the D-KEFS are relatively low, while correlations among measures from the same task are higher.

The National Institute of Health (NIH) Toolbox for the Assessment of Neurological and Behavioral Function (NIH-TB) was developed to measure four domains: cognition, motor function, sensation and emotion (Weintraub et al., 2013; Weintraub et al., 2014). Specific to the Cognition Domain, the toolbox includes several tests of EF that can be used to measure the construct across the lifespan at multiple time points. The Cognition Battery covers seven cognitive subdomains, defined by the creators as: Executive Function, Episodic Memory, Language, Processing Speed, Working Memory and Attention. The tasks were normed on a sample of 476 individuals ages 3 to 85 years. Three levels of education and 3 racial/ethnic categories were included. The Toolbox contains four measures of EF that map well onto Miyake and Friedman's model of EF.

The NIH-TB Flanker Inhibitory Control and Attention Task is a variant of the Eriksen flanker task used on the Attention Network Test. On each trial, the individual is presented with an arrow in the center of the screen, flanked by similar arrows on either side of it. On congruent trials, the center arrow and the flankers are pointing in the same direction. On incongruent trials, the flankers are pointing in the opposite direction as the center arrow. The participant must respond to indicate the direction of the center arrow as quickly as possible. This task measures one's ability to inhibit attention to visual distractors. This task takes approximately 4 minutes to complete and consists of 40 trials.

The NIH-TB Dimensional Card Sort Test measures shifting ability. Individuals are presented with a target image and then asked to match it to one of two stimuli based on either shape or color. The word “color” or “shape” appears on the screen to indicate which category to use. This task takes approximately 4 minutes to complete and consists of 40 trials.

The NIH-TB List Sorting Working Memory Test was adapted from the Mungas’ List Sorting task. Participants are presented with a series of stimuli visually and orally, one at a time. In the first condition, participants must then repeat back the items in order of smallest to largest. While all the stimuli are from the same category in the first condition, in the second condition, participants are given stimuli from two different categories. They are then asked to repeat back the items from smallest to biggest for the first category and then the second category. The number of stimuli presented increases across trials. The test is discontinued when an individual fails two trials of the same length. This test takes approximately 7 minutes to administer. The NIH-TB Pattern Comparison Processing Speed Test is based on the Salthouse’ Pattern Comparison Task. On this task, participants are asked to pick if two images or patterns are the same or different. This task takes approximately 3 minutes to administer and the score is the total number of correct items (up to 130) finished in 90 seconds.

Self-Report Measures of EF. Barrett Impulsiveness Scale (BIS-11) is a 30-item self-report measure of impulsivity. Internal consistency coefficients range from .79 in a sample of patients receiving treatment for substance use to .82 for undergraduates and .83 for psychiatric samples (Patton, Stanford & Barratt, 1995). White Bear Suppression Inventory (Wegner & Zanakos, 1994) is a 15-item questionnaire measure of thought

suppression. Internal consistency coefficients ranged from .87 to .89 and reliability ranged from .92 to .69. The Difficulties in Emotion Regulation (DERS) is a 36-item self-report measure of self-reported emotion regulation problems (Gratz & Roemer, 2004). Internal consistency ranged from .82 to .94 (Hallion, Steinman, Tolin, & Diefenbach, 2018).

Mood and Anxiety Measures. Perceived Stress Scale (PSS) is a 10-item scale that measures the extent to which events in one's life are perceived as stressful. Internal consistency ranged from .84 to .86 and test-retest reliability ranged from .55 to .85 (Cohen, Kamarck, & Mermelstein, 1983). The Penn State Worry Questionnaire (PSWQ) is a 16-item measure of frequency and intensity of worry (Meyer, Miller, Metzger, & Borkovec, 1990). It has good internal consistency (.88 to .95) and good test-retest reliability (.92). The Beck Depression Index-Two (BDI-2) is a 21-item self-report measure of presence and severity of symptoms of depression. It takes approximately 10 minutes to complete. Internal consistency coefficients range from .73 to .92 and internal consistency (alpha coefficients from .86 to .81) (Beck, 1988). State Trait Anxiety Index (STAI) is a 40-item questionnaire that assess both state anxiety and trait anxiety symptoms (Spielberger, 1983). Internal consistency coefficients range from .86 to .95, with test-retest reliability coefficients from .65 to .75 (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983).

Substance Use Measures. The Form 90 is a semi-structured interview that captures substance use and treatment use in the past 90 days. The Alcohol & Drug Consequences Questionnaire is a 28-item questionnaire created to capture motivations to make changes in substance use behaviors and motivations to stay the same. A Visual

Analogue Scale for craving was administered where individuals mark on a 100-millimeter line the extent of craving they feel at that moment for the drug of abuse, ranging from 0 to 100.

Mindfulness Measures. Mindful Attention Awareness Scale (MAAS) is a 15-item questionnaire created to measure receptive a core component of trait mindfulness: the awareness and attention to present moment experience. Internal consistency was .89 (MacKillop & Anderson, 2007). The Kentucky Inventory of Mindfulness Skills (KIMS) is a 39-item questionnaire that assesses four mindfulness skills: observing, describing, acting with awareness, and accepting without judgment (Baer, Smith, & Allen, 2004). Internal consistency coefficients range from .76 to .91 and test-retest reliability ranges from .65 to .86.

Additional Measures. Substance Use and Psychotic and Associated Symptoms sections of the Structured Clinical Interview for DSM-V (SCID), CASAA Demographic Questionnaire, and an experimental hot EF task, an emotional go-no-go task were administered. Specific to the hot EF task, on each trial participants' were presented with one of two shapes (circle or square) and instructed to only respond (i.e., hit the space bar on a laptop) when they saw one of the two shapes. Participants were presented with neutral or distressing images in between each trial.

Neuroimaging Acquisition and Analyses

NIRS data was collected using the NIRScoutX 64x32 imager system produced by NIRX Medical Technologies, LLC. A sampling rate of 2.60 was utilized based upon the number of channels. A NIRX cap was utilized and a user-defined montage was designed based on previous studies examining whole-head resting state scans using NIRS (Geng,

Liu, Biswal, & Niu, 2017; Novi, Rodrigues, & Mesquita, 2016). The montage was comprised of 46 optodes: 22 source optodes and 23 detector optodes, for a total of 80 identified potential channels out of 552 possible channels. The montage created was intended to capture cortical activity in frontal, occipital, temporal and parietal cortices. 24 channels covered the frontal lobes. The EEG 10-20 coordination system was used to support accurate placement of optodes. Per NIRX instructions, all caps placed on participants' heads were aligned with the CZ point as measured on each individual (measure inium to nasium).

Raw data was converted to nirs format using a modified version of the NIRx2nirs script running in matlab that utilizes functions from Homer2 toolbox for nirs analysis preprocessing. Data preprocessing involved 3 steps to reduce the “noise” in the data: truncate the time series to select appropriate time intervals, removal of data artifacts, i.e., “steps” and “spikes”, and filter frequency bands that are irrelevant to the data. Several different frequency bands are available for use. A low pass frequency filter removes all data above a predefined threshold or time scale, and is often used to de-noise the data. A high pass frequency filter is used to de-trend the data. For the present analyses, a band pass filter was selected as it serves to filter out both high and low frequency data and is a combination of the high and low pass filters. Parameters for Hb-concentration calculations were selected and used to compute the hemodynamic states making use of the Beer-Lambert Law.

Preprocessing was completed using the FC-NIRS toolbox. All raw data went through the following processes: Intensity2OD, OD_bandpassFilter, OD2Con, Detrend, MotionCorrect_Spline, and MotionCorrect_CBSI. Cut time was the only step removed

from the default setting and the two motion correction methods were added: a spline interpolation method and a correlation-based signal improvement (CBSI) approach.

Resting-State Task. Prior to initiation of the task, participant were told they would be asked to sit quietly for eight minutes with their eyes closed. They were instructed to do their best not to move during the task. Following a 30 second baseline, participants were then instructed to “close your eyes, think about nothing in particular”.

Functional Connectivity Analysis. Functional connectivity was calculated first using the whole-brain correlation approach. Relative to a seed-based approach, the whole brain approach to connectivity calculates the strength of the correlation between brain regions. Pearson correlations between channels were generated. Graph metrics were generated using FC-NIRS toolbox, which utilizes the Gretna toolbox. The Gretna toolbox uses scripts and functions from the Brain Connectivity Toolbox (BCT). BCT is a matlab toolbox that analyzes complex brain connectivity networks using graph theory. The methods in BCT have been applied to both structural and functional connectivity analyses across a range of different imaging methods including fMRI, DTI, and EEG. When applying graph metrics to fnirs data, each channel is a vertice and the connectivity between two channels is an edge(Xu et al., 2015). The FC-NIRS toolbox performs graph analyses on the HbO, HbR and HbT maps separately.

Global and nodal topological features of the network are calculated via the FC-NIRS toolbox and compared to random networks (Wang et al., 2015). Gretna uses the Markov-chain algorithm to generate random networks. Using this approach, random networks were generated (1000) with the same number of nodes, edges, and degree distribution. Binary networks were examined using a sparsity threshold (0.1 to 0.5 with

0.01 intervals). Five small world properties were calculated (clustering coefficient, path length, gamma, lambda, and sigma), two measures of efficiency (global and local efficiency), and one nodal measure (degree centrality) were calculated. The Area under the curve (AUC) was for network measures as well.

Small worldness was measured using five different, but related variables. The clustering coefficient of the network (C_p) and the shortest path length of the network (L_p) were generated for each participant and at the group level. Gamma was calculated, which is the ratio of C_p and the mean value of C_p from the random network. Lambda is the ratio of L_p and the mean value of L_p from the randomized network. Sigma is the ratio of Gamma and Lambda. The Area Under the Curve (AUC) was generated for C_p and L_p to get a scalar variable for these variables that is not impacted by threshold selection.

Statistical Analysis

Data analyses for specific aims 1 through 3 were conducted using IBM SPSS Version 26. For specific Aim 4 the following programs were used: FC-NIRS toolbox and Gretna toolbox that use scripts and functions from the Brain Connectivity Toolbox (BCT) run in Mathworks (MATLAB 2019a).

Specific Aim 1. Retention rates and frequency analyses were performed.

Descriptive statistics were performed on baseline characteristics.

Specific Aim 2. Descriptive statistics were performed on symptom measures.

Mann-Whitney U Tests were performed to examine differences between individuals that completed follow up relative to those that did not on 11 baseline variables. Fisher's Exact Tests were performed to assess differences in 7 categorical baseline variables among individuals that completed follow up and those that did not.

Specific Aim 3. Spearman correlation coefficients were calculated to examine relationships between EF tests (4 scores from the NIH toolbox, 13 scores from D-KEFS, and 3 scores from self-report measures) at baseline. Single sample T-tests were performed to examine differences between population mean and study sample mean for the EF scores (4 scores from the NIH toolbox, 13 scores from D-KEF).

Specific Aim 4. Functional connectivity matrices were generated for resting-state fNIRS networks using Pearson correlation coefficient. Topological properties of resting state networks were generated across multiple sparsity thresholds and using Area Under the Curve scalar values. Spearman correlation coefficients were calculated to examine relationship between 20 EF variables (17 neuropsychological scores and 3 self-report scores) and 7 network measures.

RESULTS

Specific Aim 1: Feasibility Assessment

Recruitment Phase. The treatment protocol was presented at staff meetings for treatment providers in the general clinic and within the STAR program team. Based upon recommendations from treatment staff members, participants were recruited from the clinic on a variety of days and times. Clients at the clinic receive medication on different schedules based upon treatment phase. Thus, while some clients present to the clinic daily to receive medication, others are able to take home several doses at a time. With extended compliance of treatment demands, clients may earn up to a 30-day supply of medication to take home. Thus, recruitment efforts were coordinated to ensure the widest net was cast within the adult clinic (age 18 and older). Based upon staff recommendations, additional recruitment efforts were conducted in early morning hours (6:00 am to 11:00am).

Efforts to recruit from the STAR program were similarly coordinated based upon client flow in the clinic. Treatment staff recommended efforts to recruit from the adolescent clinic be scheduled in afternoons. The flow of adolescent patients to the ASAP clinic during the recruitment phase of the study (May 2018 through July 2018) were significantly fewer than originally predicted (0 to 3 adolescents presenting to the clinic on any given day). As previously mentioned, the psychopathology among the adolescents was more severe than had been previously expected during initial meetings with the staff. Flyers were also placed throughout the clinic with the study contact number. Additionally, on recruitment days, potential participants were offered flyers and later a

recruitment table was set up. Overall, 78 participants indicated interest in participating in the group. Of those, at least 45 were within the targeted age range for the young adult group. One potential participant under 18 years of age indicated interest but was unable to attend due to transportation. Four individuals age 18 to 20 years of age indicated interest, of those two were disqualified by ASAP staff, one declined to participate due to scheduling conflicts and one declined to participate for personal reasons.

Qualitatively, it was noted interested participants verbally expressed interest in the neuroimaging component of the study. Compensation was very limited and participants interested in the treatment verbally expressed motivation based on the treatment opportunity and research experience. Per staff and patient report, group interventions were relatively new to the clinic, which likely impacted recruitment. Over the course of the study increased referral from staff and referral among patients were helpful.

Retention. Throughout the course of the study, retention was a significant challenge. At each phase of the study participants were lost to follow up. 20 Participants, six men and fourteen women, were consented to the study. Nine participants were Hispanic, one participant was Native American/Alaska Native, and ten participants were white. Participants averaged 28.90 years of age ($SD = 3.26$, range 23-34). Of those, 16 participants completed screening visits. One participant consented to treatment but was excluded prior to screening visit based on ASAP staff personnel suggestion. Two participants that consented to treatment declined scheduling a screening visit due to schedule changes and/or personal reasons, and one participant was lost to follow-up after the consent visit.

During the screening process, two participants were excluded due to active and uncontrolled psychosis, and one participant was excluded due to psychosis, severe depression, severe suicidal ideation, and a history of aggressive behaviors associated with psychotic episodes. 13 participants completed baseline assessment visit and were randomized to treatment.

Treatment Exposure and Follow-Up. Six participants were randomized to waitlist and seven participants were randomized to the intervention condition. Among individuals randomized to receive treatment (intent to treat), 6 of the 7 attended two or more sessions. One participant declined to participate in treatment following randomization and received 0 sessions. Of those that attended treatment, they received an average of 4.5 sessions of treatment. Six of the thirteen participants (3 per group) completed the follow up visit. Please see Figure 1 for recruitment and retention outline.

There were no adverse events reported. Several participants underwent changes to psychiatric medications during the study. Of the 13 individuals randomized to treatment, two participants received an administrative discharge from the ASAP treatment program, one participant discontinued services at the treatment program, and one participant was lost to follow up by all treatment staff following a relapse. Additional issues impacting retention: included lack of transportation to ASAP clinic, lack of stable means of communication with study team, and scheduling conflicts associated with school/work. This is a significant limitation of the study that will be explored further in the discussion section.

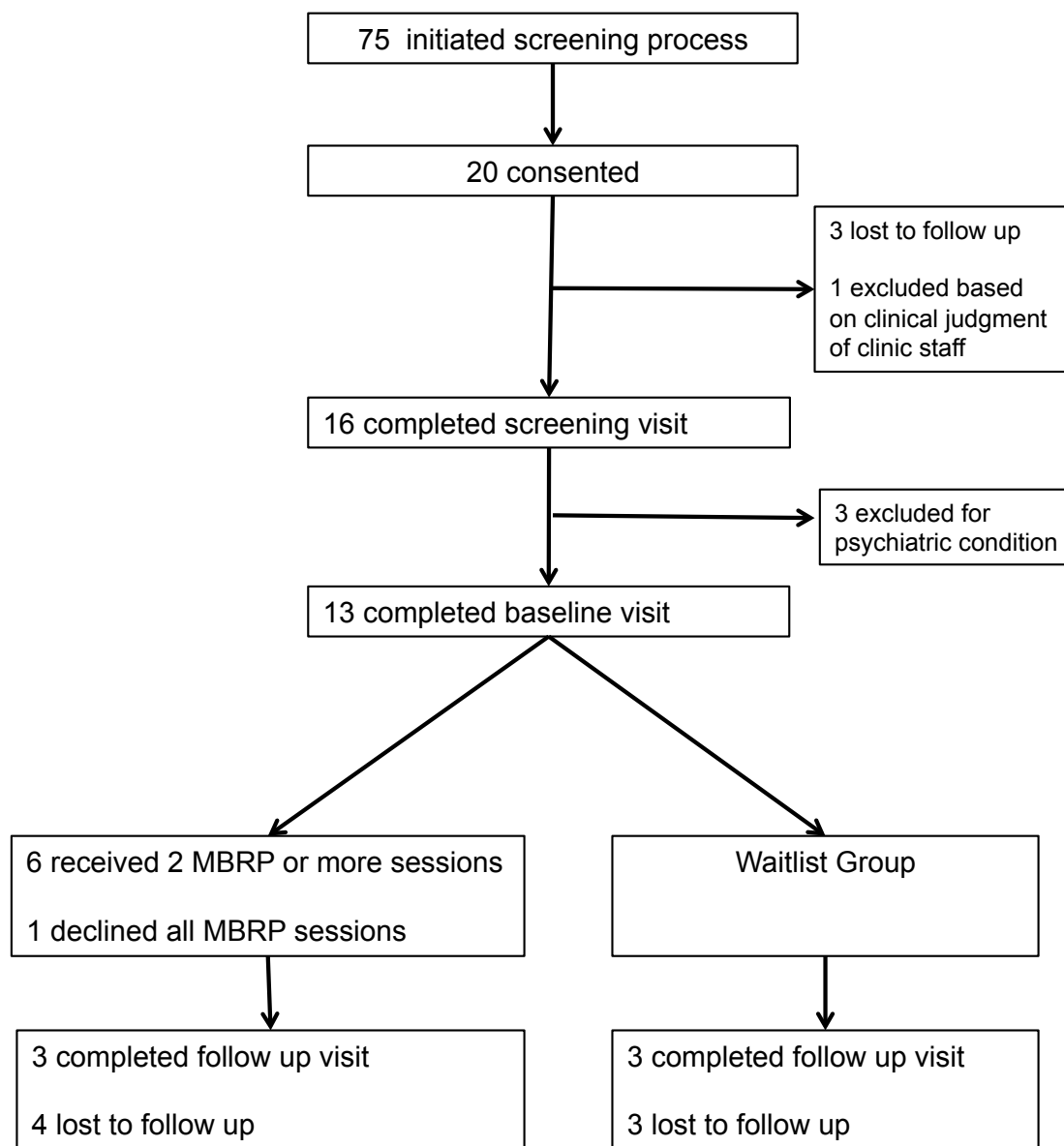


Figure 1. Flowchart for study recruitment and retention. MBRP, Mindfulness-Based Relapse Prevention.

Feasibility of Study Design and Procedures. Three research assistants were trained to assist in recruitment to enable recruitment to target both the STAR clinic and adult clinic simultaneously. Consistent research study staff presence helped address frequent no shows. For instance, on days multiple research team members were present, it was possible to schedule multiple potential participants or meet with “walk in” participants. Given the culture of “walk-in” health care available at the clinic, when possible, it was beneficial for study staff to be available to meet with walk-in study participants or participants that wished to reschedule. Qualitatively, it was noted potential participants at the clinic often engaged with study staff on multiple occasions before requesting additional information about the study.

Flexibility around timing of study procedures also appeared important. For instance, on several occasions staff members met with interested participants for the consent visit over multiple sessions. Since there was no permanent or semi-permanent office space consistently available within the clinic, it was important to have all materials needed on hand for the different stages of recruitment. Notably, the baseline procedure involved neuroimaging and neuropsychological testing equipment and was completed at a different location. Likely, if baseline and follow up visits could have been completed at the clinic in semi-permanent space, this might have increased follow up rates. Finally, the intervention was successfully implemented to participants in the treatment group. Thus it was feasible to implement an empirically supported intervention within a methadone clinic.

Feasibility of Study Measures. Regarding measures of EF, both the neuropsychological measures and self-report measures were successfully administered.

The experimental hot EF task was administered to a subset of the participants. Qualitatively, the task was time consuming (approximately, 15 minute minimum). It was the last EF task administered to prevent a carry over effect to cool EF tasks. While it was tolerable for most participants, based on clinical judgment it was not administered to several participants. Again, the presence of multiple study staff members significantly expedited the set-up time need for NIRS. Similarly, on occasions when multiple participants arrived at the clinic together, when multiple staff members were present, the process was faster. Qualitatively, it was noted that participants expressed interest in NIRS and all participants requested pictures or video of their brain scans. FNIRS does enable immediate display of activation on a glass brain, which makes it a more reinforcing experience for participants. Several analysis toolboxes have been created for fNIRS, with varying complexity. FC-NIRS is relatively, user-friendly program with relatively fast computation time. While some tasks could be batched during the analyses, future efforts to batch preprocessing steps would likely speed up the analyses further. While the GUI interface was user friendly, many of the preprocessing steps (e.g., calculation of Hb-concentrations, application of frequency filters, truncation of time series) were performed for each participant separately. Thus, for each participant, the user must manually select the input and output file locations, select the desired frequency filters, and enter the time series to be selected. While this was quite feasible with a small sample size, it would be more taxing with larger sample sizes. Automating this process through scripts or via a GUI designed to run batch jobs would be helpful.

Regarding measures of mood, there was some redundancy across measures. Elimination of some measures would likely shorten the process. Likely, one of the two

mindfulness measures would likely be sufficient. While a heterogeneous sample in terms of substances of abuse may reflect more “real world” clinics, often measures of substance use and measures of SUD outcome, are designed for a single substance of abuse.

Assessment measures designed to capture multiple substance uses would likely be helpful. Finally, measures specific to ORT would perhaps be useful. The Drug Use Consequences form likely was not appropriate for participants at all stages of treatment as it captures consequences and benefits for quitting rather than maintaining the current behavior change. Measures of motivation and readiness to change might be particularly useful for this sample. Finally, measures of functional outcome would likely be useful to capture meaningful change in the context of ORT.

Specific Aim 2a: Clinical Characteristics of Sample

Demographics. Participants were nine women and four men with DSM-5 substance use disorder. Three participants were Hispanic, one participant was Native American/Alaska Native, and nine participants were white Non-Hispanic. Mean age was 28.28 (SD 2.6, range 25-33). Participants averaged 12.4 years of education (SD 2.2, range 8-16). One participant reported English as a second language and three participants reported speaking a second or third language. Three participants reported part-time employment, nine participants were unemployed, and one participant was receiving disability. One participant was living in his/her own apartment, one participant was living in a transitional substance use treatment facility, and eleven participants were living with relatives. None of the participants reported experiencing homelessness and none of the participants reported being court-ordered to treatment.

Baseline Characteristics. Of the 13 participants that completed the baseline visit, nine participants presented with opioid use disorder, one participant with alcohol use disorder, one participant with inhalant use disorder, one participant with cannabis use disorder, and one participant with methamphetamine use disorder. All but one of the participants was being treated with MAT. Of the 12 individuals prescribed MAT, seven participants were prescribed methadone, three were prescribed buprenorphine, and two were prescribed naltrexone. In total, 12 of the 13 participants reported use of two or more substances when using their drug of choice. Nine of the 13 participants reported concurrent abuse of opioid and stimulants.

Psychiatric History and Present Level of Care and Substance Use Treatment. Mean number of inpatient psychiatric hospitalizations was 1.38 (range 0-6) and seven of the 13 participants had attempted suicide one or more times (range 0-6). A significant proportion of the sample (92%) reported one or more co-morbid psychiatric diagnoses and nearly three quarters of the sample (76.9%) were taking one or more psychiatric medications (range 0-5 psychiatric medications). In the 90 days prior to baseline assessment, mean number of outpatient therapy sessions was 11.61 (range 3-28; SD = 6.55). Lastly, mean age of first psychiatric problems was 15.15 (range 10-26, SD = 5.28), mean age of first alcohol use was 15.83 years (SD = 3.29) and mean age of first substance use was 14.84 years (SD = 2.54), while mean age of first substance use treatment was 22.76 years of age (SD = 3.91). Please see Table 1 for additional information on psychiatric and substance use history.

Table 1

Sample Demographics

Variable	RTF (n = 6)	LTF (n = 7)	Total (N = 13)	U	p-value
Age, years Mean (S.D.)	29.5 (2.95)	27.4 (2.25)	28.38 (2.69)	13	0.085
Sex (M, F)	1, 5	3, 4	4, 9	-	0.559
Ethnicity Hispanic	2	1	3	-	0.559
Native American	0	1	1		
Non-Hispanic White	4	5	9		
Ethnic Minority Status	2	2	4	-	1.0
MBRP Group	3	4	7	-	1.00
Total Study Visits	7.5 (3.99)	4 (1.29)	5.6 (3.28)	9	.08
Employment Status (Number Unemployed)	4	5	9	-	1.0
Education	11.5 (2.81)	13.14 (1.07)	12.38 (2.14)	10	0.198
Living with Relatives	5	5	10		
Transitional Living	1	0	1	-	0.462
Living Independently	0	2	2		
Age of First Mental Health	14.83 (3.66)	15.43 (6.68)	15.15 (3.3)	18.5	.720
Age at First Drug use Mean (SD)	15.83 (2.32)	14 (2.58)	14.85 (2.54)	11	.15
Age Substance use treatment	23.17 (4.36)	22.43 (3.82)	22.77 (3.92)	20	.886

Number of Suicide Attempts	2.6 (2.3)	1.17 (1.94)	1.81 (2.14)	8.5	.219
Inpatient Hospitalizations	2 (2.76)	0.43 (0.53)	1.15 (1.99)	16.5	.477
Outpatient Therapy Days	11.5 (4.51)	11.71 (8.3)	11.62 (6.55)	18.5	.720
Drug of Abuse Days	0.33 (0.82)	23.71 (30.48)	12.92 (24.74)	11.5	.122
Other Drug Days	19 (35.05)	64.42 (43.67)	43.46 (44.95)	11.5	.151
Number of Psych Medications	3.5 (1.52)	1 (1.15)	2.15 (1.82)	4	.013
Discontinued at Clinic	0	5	5	-	.021

Note: RTF, Return To Follow Up; LTF, Lost to Follow Up; M, male; F, female; S.D., standard deviation. Significance levels were determined by Mann-Whitney U test and Fisher's Exact Test.

Measurements of Substance Use. Participants reported a high level of perceived benefit associated with changing/maintaining reduction in substance use ($M = 4.47$, $SD = 0.58$), and a relatively lower level of perceived cost associated with this change ($M = 2.36$, $SD = 0.73$). Perception of current level of craving was also measured using a visual analogue scale ($M = 21.75$, $SD = 21.88$). In the past 90 days, roughly one third of participants (38%) reported use of substance of abuse (days of use: $M = 12.90$), and about three quarters of the sample (76.9%) reported use of another substance of abuse (days of use: $M = 43.4$). Abuse of prescription medication was reported by at least two participants. Over half the sample (61%) reported use of marijuana at baseline. Finally, all but one participant reported some tobacco use in the past 90 days. Please see Tables 1 and 2 for additional information on substance use reported at baseline.

Table 2

Baseline Self-Report Measures

Measure	TOTAL M (SD)	RTF M (SD)	LFT M (SD)	U	P
BDI-2	19.69 (13.07)	27 (15.06)	13.43 (7.3)	9	.086
PSS	21.92 (6.92)	22.83 (8.04)	21.14 (6.36)	14	.313
PSWQ	57.15 (11.25)	61.5 (8.76)	53.43 (12.42)	13	.252
STAI-S	37.67 (9.72)	42.8 (13.10)	34 (4.58)	12.5	.414
STAI-T	46.33 (12.07)	54 (13.27)	40.86 (8.11)	7	.088
KIMS-Total	120.38 (15.06)	114.17 (17.06)	125.71 (11.8)	12.5	.221
MAAS	3.78 (0.88)	33.50 (6.12)	45.14 (9.77)	6	.031
VAS Craving	21.75 (21.88)	24.00 (24.31)	19.5 (21.22)	15.5	.688
ADCQ benefits	4.47 (0.58)	4.34 (0.72)	4.58 (0.46)	16.5	.517
ADCQ costs	2.36 (0.74)	2.40 (0.48)	2.33 (0.94)	16.5	.52
BIS-11	67.92 (8.89)	69.5 (10.13)	66.57 (8.24)	16.5	.52
WBSI	53.54 (7.62)	53 (9.44)	54 (6.43)	20.5	.943
DERS	94.31 (23.0)	106 (23.55)	84.29 (18.50)	10	.116

Note: BDI, Beck Depression Inventory; PSS, Perceived Stress Scale; PSWQ, Penn State Worry Questionnaire; State Trait Anxiety Inventory-State, STAI-S; STAI-T, State Trait Anxiety Inventory-Trait; KIMS-T, Kentucky Inventory of Mindfulness Skills- Total; MAAS, Mindful Attention Awareness Scale; VAS, Visual Analogue Scale; ADCQ, Alcohol and Drug Consequences Questionnaire; BIS, Barrett Impulsivity Scale; WBSI, White Bear Suppression Inventory, WBSI; DERS, Difficulties in Emotion Regulation Scale; RTF, Return To Follow Up; LTF, Lost to Follow Up; M, mean; S.D., standard deviation. Significance levels were determined by Mann-Whitney U tests and Fisher's Exact Test.

Measurements of Mood, Anxiety and Mindfulness. At a group level,

participants reported elevated levels of depressed mood on the BDI-2 (M = 19.69, SD = 13), with six reporting moderate or greater depressed mood and seven reporting minimal to mild depressed mood. Regarding anxiety, participants reported high levels of trait worry (PSWQ: M = 57.15, SD 11.25), and elevated levels of state and trait anxiety (STAI-T: M = 46.8, SD 12.5; STAI-S: M = 37.6, SD 9.7). Participants also reported experiencing an elevated number of events perceived to be stressful over the past month (PSS: M = 21.9, SD = 6.9). Regarding self-reported mindfulness, on the Mindful

Attention Awareness Scale (MAAS) scores were comparable to that reported by a college student sample ($M = 3.78$; $SD = 0.87$). On the KIMS Total Mindfulness score was 120.38 ($SD = 15.05$). Please see Table 2 for additional information on symptoms reported at baseline.

Specific Aim 2B: Examine Correlates Between Retention and Baseline Correlates

Using Fisher's Exact Test, follow up attendance did not differ by gender, ($p = .559$); Hispanic ethnicity ($p = .559$); ethnic minority status ($p = 1.0$); employment status, ($p = 1.0$). No differences in age at baseline ($U = 13$; $p = 0.245$), age at first substance use treatment encounter ($U = 20$; $p = 0.886$), suicide attempts ($U = 8.5$; $p = 0.219$), age at first mental health encounter ($U = 18.5$; $p = 0.720$), number of inpatient hospitalizations ($U = 16.5$; $p = 0.477$), age first drug use ($U = 11$; $p = 0.150$), number of outpatient therapy days at baseline ($U = 18.5$; $p = 0.720$), number of days substance of abuse was used ($U = 11.5$; $p = 0.122$), or number of days other substances used ($U = 11.5$; $p = 0.151$). Number of psychiatric medications ($U = 4$; $p = 0.013$) at baseline was significant, with greater psychiatric medications associated with greater likelihood of completing the follow up visit.

Consistent care within the treatment facility was an important factor. Four of the participants lost to follow up were no longer receiving care at the facility at the time of the follow up visit. Follow up attendance was related to continued care at the facility at the time of the follow up visit ($p = .021$, Fisher's Exact Test). Please see Table 1 and 2 for complete list of baseline variables examined and corresponding significance values.

Aim 3: Relationship Measures of EF

Neuropsychological and Self-Report Measures of EF at Baseline. At a group level, when compared to normative data, participants scored in the average range on all measures of EF, with the exception of PC ($M = 74.95$, $SD = 15.17$), which was below the general population, $t(12) = -5.95$, $p = 0.000$, 95%CIs [-34.21, -15.87]. More specifically, participants in the study scored between the 21st and 60th percentile on measures of executive function, with the exception of one measure of processing speed, which was at the 5th percentile. However, when the *number* of impaired EF scores was examined, all participants had one or more EF scores 1 or more standard deviations below the normative mean (16th percentile). Nine of the 13 participants had one or more EF scores 2 standard deviations below the mean or lower (2nd percentile). Regarding self-reported EF, participants reported elevated levels of emotion dysregulation (DERS: $M = 94.31$, $SD = 23$), impulsivity (BIS: $M = 67.92$, $SD = 8.89$), and an elevated tendency to suppress thoughts (WBSI: $M = 53.53$, $SD = 7.6$). EF performance of the sample is provided in Table 2 (self-report measures) and Table 3 (neuropsychological measures).

Table 3

Neuropsychological Measures of Executive Function

Score	M	SD	Comparison Value	Mean Difference	95% CI	t	df	P value
Trails 1	9.85	2.30	10	-0.24	[-1.55, 1.24]	-0.24	12	.814
Trails 2	9.00	3.24	10	-1.11	[-2.96, 0.96]	-1.11	12	.288
Trails 3	8.38	4.46	10	-1.31	[-4.31, 1.08]	-1.31	12	.216
Trails 4	8.92	3.35	10	-1.16	[-3.10, 0.95]	-1.16	12	.269
Trails 5	10.85	1.68	10	1.82	[-0.17, 1.86]	1.82	12	.094
Letter Fluency	9.08	3.69	10	-0.90	[-3.15, 1.30]	-0.90	12	.384
Category Fluency	9.69	3.12	10	-0.36	[-2.19, 1.58]	-0.36	12	.728
Switching Fluency	8.92	3.01	10	-1.3	[-2.90, 0.74]	-1.29	12	.222
Switching Accuracy	9.08	2.78	10	-1.2	[-2.60, 0.76]	-1.2	12	.255
Color Naming	8.23	3.27	10	-1.95	[-3.75, 0.21]	-1.95	12	.075
Color Word	9.15	2.64	10	-1.16	[-2.44, 0.75]	-1.16	12	.270
Inhibition	9.15	3.31	10	-0.92	[-2.85, 1.16]	-0.92	12	.375
Switching	8.77	2.28	10	-1.95	[-2.61, 0.15]	-0.24	12	.075
List Sorting	93.58	14.4	100	-6.42	[-15.13, 2.28]	-1.61	12	.134

Pattern Comparison	74.95	15.18	100	-25.05	[-34.22, -15.87]	-5.95	12	.000*
Flanker	88.62	21.03	100	-11.38	[-24.09, 1.33]	-1.95	12	.075
Card Sort	96.98	22.19	100	-3.02	[-16.43, 10.38]	-0.49	12	.632

Note: M, Mean; S.D. standard deviation; CI, Confidence Interval; df, degrees of freedom. Significance levels were determined by single sample t tests. Single asterisk (*) signifies a correlation is significant at the 0.05 level (2-tailed).

Correlations Between Measures of EF. Correlations between D-KEFS' scores was examined first. On the TMT, scores between TMT1, TMT2, TMT3 and TMT4 were all positive correlated (p values: .048 - .001). TMT5 was not significantly correlated within any other D-KEFS subtests examined ($p > .05$). On Verbal Fluency subtests, VF2 was positively correlated with VF1 and VF3 ($p = .035$ and $p = .005$); VF3 total correct and switching accuracy were correlated ($p = .002$). None of the CWI subtests were correlated ($p > .05$). Across measures on the DKEFS, VF1 was correlated with TMT4, CW1 and CW3 ($p = .020$, $p = .044$, $p = .011$, respectively). VF2 was positively correlated with TMT3, CW3 and CW4 ($p = .018$, $p = .020$, $p = .048$).

Correlations among subtests of the Toolbox were examined next. List Sorting, Flanker, and Card Sort Scores were all positively correlated (p values = .009 - .001). Pattern Comparison was not correlated with any Toolbox measure ($p > .05$).

Correlations between DKEFS scores and NIH scores were examined next. Scores from the DCS, a measure of shifting, were significantly correlated with DKEFS VF: Switching Accuracy and VF1 ($p = .036$ and $p = .013$, respectively). Scores from the LS, a measure of working memory, were significantly correlated with DKEFS VF subtests: category fluency, switching total correct, and category switching accuracy ($p = .011$, $p = .035$, $p = .012$), as well as, DKEFS CW: shifting ($p = .003$). Flanker, a measure of attention and impulse control, was significantly correlated with DKEFS VF switching

accuracy ($p = .013$). Scores from the PC, a measure of processing speed, were positively correlated with DKEFS TMT: Motor Coordination ($p = .040$).

Lastly, correlations between self-report measures of EF and neuropsychological measures of EF (NIH Toolbox, D-KEFS: TMT4, VF, CW3 and CW4) were examined next. While BIS and DERS were elevated, they were not correlated with neuropsychological measures of EF (all p -values $> .05$). Follow up analyses examining correlations between simpler measures of attention and processing speed and self-report measures of EF. Please see for Table 4 for exact p -values and correlation coefficients.

Table 4. *Correlations Between Measures of Executive Function*

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1 trails1	-	.56*	.70**	.60*	-.16	.49	.52	.25	.17	.52	.14	.56*	.42	.30	-.22	.47	.41	0.03	0.52	0.34
2 trails2	.048	-	.81**	.58*	-.15	.19	.35	.39	.25	.19	-.13	.43	.13	-.04	-.13	.13	.23	-.039	0.04	0.21
3 trails3	.007	.001	-	.75**	.06	.48	.64*	.50	.23	.38	.01	.54	.36	.34	-.26	.29	.44	-.028	0.19	0.14
4 trails4	.031	.038	.003	-	.24	.63*	.42	.17	.16	.44	.35	.52	.39	.28	-.20	.43	.51	-.008	0.02	0.14
5 trails5	.600	.636	.856	.426	-	.34	.03	.32	.29	-.00	.54	.03	.15	.31	.58	.50	.37	-.005	-.024	-.012
6 vf1	.092	.545	.095	.020	.256	-	.59*	.18	.05	.57*	.35	.68*	.32	.41	-.13	.52	.59	-.012	0.10	0.37
7 vf2	.068	.240	.018	.158	.917	.035	-	.73**	.44	.45	-.02	.63*	.56*	.67	-.33	.33	.50	-.012	0.07	0.22
8 vf3	.416	.184	.079	.579	.284	.568	.005	-	.77**	.26	-.05	.43	.40	.59	.16	.39	.43	-.023	-.002	-.009
9 vf3	.581	.411	.445	.599	.343	.877	.132	.002	-	.26	.07	.24	.43	.67	.23	.67	.67	-.003	0.05	0.14
10 cwi1	.067	.542	.204	.132	.996	.044	.125	.388	.399	-	.36	.52	.32	.31	.15	.37	.31	-.029	0.35	-.008
11 cwi2	.657	.682	.971	.239	.059	.239	.956	.875	.825	.227	-	-.04	.40	.23	.36	.32	.22	-.020	-.031	-.002
12 cwi3	.047	.146	.055	.072	.929	.011	.020	.146	.434	.069	.890	-	.44	.36	-.25	.46	.50	0.07	0.28	0.06
13 cwi4	.152	.675	.229	.185	.631	.284	.048	.181	.146	.286	.180	.129	-	.76	-.10	.51	.54	0.37	0.18	0.16
14 LS	.330	.896	.255	.359	.299	.165	.011	.035	.012	.301	.460	.224	.003	-	-.14	.69**	.81**	0.23	0.18	0.25
15 PC	.461	.672	.386	.514	.040	.670	.276	.598	.443	.620	.227	.420	.737	.641	-	.48	.68	-.014	0.06	-.024
16 FL	.109	.672	.331	.140	.084	.068	.276	.185	.013	.221	.282	.117	.072	.009	.482	-	.90**	0.26	0.38	0.40
17 CS	.162	.459	.130	.073	.213	.036	.084	.139	.013	.305	.464	.087	.057	.001	.679	.000	-	0.13	0.20	0.49
18 DERS	.913	.194	.360	.801	.884	.690	.696	.442	.914	.336	.507	.828	.213	.453	.642	.384	.679	-	0.48	0.11
19 BIS-11	.071	.900	.538	.943	.436	.734	.827	.942	.885	.247	.308	.349	.554	.552	.858	.201	.520	.098	-	0.14
20 WBSI	.254	.497	.654	.641	.692	.209	.461	.775	.643	.801	.960	.849	.605	.410	.435	.176	.093	.733	.640	-

Note: M, Mean; S.D. standard deviation; CI, Confidence Interval; df, degrees of freedom; vf1, Verbal Fluency: Letter Fluency; vf2, Verbal Fluency: Category Fluency; vf3; Verbal Fluency: Switching Fluency; vf3a, Verbal Fluency: Switching Fluency Accuracy; cwi1, Color Word Inhibition: Word Reading; cwi2, Color Word Inhibition: Word Reading; cwi3: Color Word Inhibition: Inhibition; cwi3, Color Word Inhibition: Switching; LS, List Sorting; PC, Pattern Completion; FL, Flanker; CS, Card Sort; BIS, Barrett Impulsivity Scale; WBSI, White Bear Suppression Inventory; DERS, Difficulties in Emotion Regulation Scale. The upper values represent Spearman' rho and the lower corresponding p values. Significance levels were determined by Spearman's Rank Order correlations. Single asterisk (*) signifies a correlation is significant at the 0.05 level (2-tailed). Double asterisk (**) signifies a correlation is significant at the 0.01 level (2-tailed).

Exploratory Analysis: Correlations Between EF and Symptoms. Self-report measures of worry (PSWQ), perceived stress (PSS), and depressed mood (BDI) were generally not correlated with neuropsychological measures of EF. BDI was positively correlated with performance on color word inhibition switching ($r_s = .604$, $p = .049$) and Pattern Comparison was negatively correlated with State Anxiety ($r_s = -0.636$, $p = .026$). However, DERS total score was positively correlated with BDI ($r_s = 0.756$, $p = .007$), PSWQ ($r_s = 0.715$, $p = .006$), STAI-Trait ($r_s = 0.783$, $p = .003$), and PSS ($r_s = .742$, $p = .004$). WBSI was correlated with BDI ($r_s = .689$, $p = .019$). No significant correlations were observed between DERS total, WBSI, or BIS (all p values $< .05$) and or between BIS and measures of mood or anxiety.

Use of substance of abuse in the past 90 days was positively correlated with Trails 4 ($r_s = 0.599$, $p = .031$). Use of any substance was negatively correlated with card sorting ($r_s = -.611$, $p = .027$). No significant correlations between use and measures of mood or self-reported EF were found (all p -values $> .05$). Please see Table 5 for correlations between EF and self-report measures of mood, anxiety, mindfulness and substance use.

Table 5

Correlations between Executive Function and Symptom Measures

EF	BDI-2	PSS	PSWQ	STAI-S	STAI-T	KMIS	MAAS	VAS	ADCQ+	ADCQ-
1	0.15	-0.12	-0.29	-0.01	-0.19	0.06	0.1	-0.42	-0.39	0.23
	0.621	0.692	0.342	0.964	0.546	0.851	0.752	0.176	0.185	0.452
2	-0.09	-0.18	-0.34	0.05	-0.3	0.52	0.21	-0.28	-0.19	-0.04
	0.777	0.565	0.252	0.87	0.344	0.07	0.485	0.38	0.54	0.91
3	-0.03	-0.18	-0.4	-0.06	-0.19	0.21	0.26	-0.09	-0.32	-0.15
	0.936	0.556	0.17	0.862	0.555	0.499	0.399	0.785	0.29	0.619
4	0.08	0.01	-0.26	0.02	0.16	0.22	0.12	0.16	-0.23	0
	0.804	0.975	0.397	0.943	0.622	0.478	0.704	0.621	0.443	0.993
5	-0.29	-0.38	-0.02	-.61*	0.01	-0.05	-0.06	0.08	.64*	0.18
	0.345	0.207	0.95	0.034	0.981	0.868	0.845	0.814	0.019	0.553
6	0.01	-0.33	-0.24	-0.33	-0.04	-0.12	-0.37	0.27	-0.05	-0.03
	0.964	0.265	0.436	0.303	0.905	0.709	0.211	0.401	0.863	0.917

7	0.1 0.747	-0.15 0.62	-0.39 0.186	-0.11 0.744	-0.14 0.675	-0.15 0.617	0.02 0.949	0.18 0.578	-0.34 0.257	-0.31 0.297
8	-0.19 0.535	-0.27 0.374	-0.37 0.216	-0.51 0.091	-0.28 0.383	0.09 0.771	0.17 0.591	-0.21 0.522	0.06 0.838	0 0.993
9	0.08 0.807	0.01 0.986	-0.01 0.975	-0.36 0.245	0.14 0.668	-0.13 0.669	-0.16 0.61	-0.16 0.618	0.19 0.53	0.29 0.345
10	-0.16 0.594	-0.27 0.375	-0.47 0.107	-0.42 0.17	-0.27 0.401	0.17 0.589	0.02 0.961	-0.27 0.403	-0.11 0.72	0.34 0.257
11	-0.17 0.591	-0.5 0.082	-0.4 0.181	-0.2 0.544	-0.15 0.635	-0.02 0.96	0 0.989	0.08 0.817	.59* 0.034	0.36 0.227
12	0.15 0.624	-0.09 0.771	-0.3 0.327	-0.3 0.353	0.02 0.956	0.27 0.374	-0.27 0.381	-0.1 0.75	-0.39 0.193	0.21 0.499
13	.60* 0.031	0.12 0.728	-0.09 0.783	0.23 0.479	0.36 0.257	-0.25 0.415	-0.12 0.707	0.15 0.652	-0.15 0.62	0.07 0.823
14	0.42 0.159	0.06 0.847	0.02 0.947	-0.06 0.858	0.36 0.249	-.59* 0.035	-0.31 0.311	0.25 0.435	-0.04 0.889	0.01 0.964
15	-0.4 0.171	-0.36 0.223	0.04 0.901	-.64* 0.026	-0.29 0.354	0.24 0.423	0.12 0.686	-0.47 0.127	.67* 0.012	0.42 0.158
16	0.28 0.348	-0.04 0.907	0.2 0.523	-0.41 0.184	0.34 0.276	-0.31 0.307	-0.49 0.093	-0.17 0.594	0.17 0.587	0.48 0.094
17	0.35 0.243	0 1	0.12 0.705	-0.2 0.529	0.42 0.171	-0.42 0.156	-.56* 0.049	0.13 0.68	0.05 0.864	0.22 0.467
18	40 0.176	0.33 0.271	0.39 0.19	-0.04 0.901	0.23 0.47	-0.19 0.538	-0.12 0.689	-0.46 0.129	-0.48 0.1	0.28 0.36
19	.78** 0.002	.74** 0.004	.72** 0.006	0.41 0.184	.78** 0.003	-0.4 0.184	-0.23 0.446	0.15 0.64	-0.43 0.146	0.05 0.865
20	0.45 0.126	0.01 0.982	0.37 0.217	0.34 0.286	0.23 0.468	-0.53 0.063	-.59* 0.035	0.23 0.482	0 0.996	-0.21 0.497

Note: EF, Executive Function Variable; BDI-2, Beck Depression Inventory; PSS, Perceived Stress Scale; PSWQ, Penn State Worry Questionnaire; State Trait Anxiety Inventory-State, STAI-S; STAI-T, State Trait Anxiety Inventory-Trait; KIMS-T, Kentucky Inventory of Mindfulness Skills- Total; MAAS, Mindful Attention Awareness Scale; VAS, Visual Analogue Scale; ADCQ, Alcohol and Drug Consequences Questionnaire; 1, Trails 1; 2, Trails 2; 3, Trails 3; 4, Trails 4; 5, Trails 5; 6, Verbal Fluency: Letter Fluency; 7, Verbal Fluency: Category Fluency; 8, Verbal Fluency: Switching Fluency; 9, Verbal Fluency: Switching Fluency Accuracy; 10, Color Word Inhibition: Word Reading; 11, Color Word Inhibition: Word Reading; 12, Color Word Inhibition: Inhibition; 13, Color Word Inhibition: Switching; 14, List Sorting; 15, Pattern Completion; 16, Flanker; 17, Card Sort; 18, Barrett Impulsivity Scale; 19, White Bear Suppression Inventory; 20, Difficulties in Emotion Regulation Scale. Significance levels were determined by Spearman's Rank Order correlations. The upper values represent Spearman's rho and the lower values represent the corresponding p values. Single asterisk (*) signifies a correlation is significant at the 0.05 level (2-tailed). Double asterisk (**) signifies a correlation is significant at the 0.01 level (2-tailed).

Specific Aim 4: Examine Topological Properties of fNIRS Resting State Networks

Connectivity matrices were generated for HbO, HbR, and HbT maps for each participant and at the group level. A sparsity threshold (number of existing edges:

maximum number of edges possible) was applied to remove spurious correlations between channels. Each participants' connectivity matrices were empirically thresholded over a range of $0.1 < \text{sparsity} < 0.5$ (interval 0.01) to create sparse, positive binary networks. Please see Figure 2 for an example.

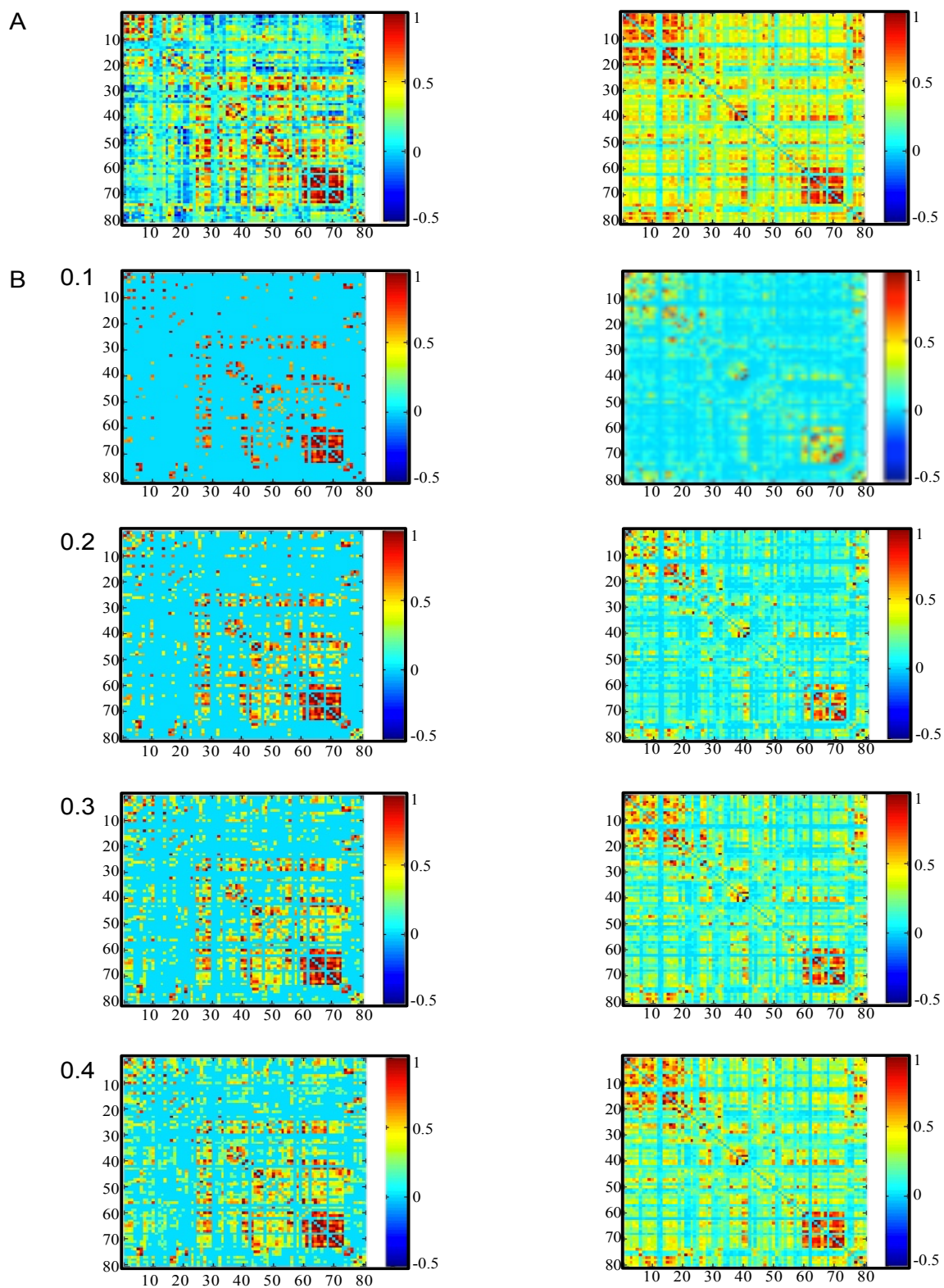


Figure 2. Example connectivity matrices across sparsity thresholds. Example fNIRS resting-state functional connectivity matrix at the individual level (right) and group level (left) calculated using Pearson Correlation Coefficients (A) and corresponding matrices at varying sparsity thresholds (B).

Topological properties of the network were then calculated across sparsity thresholds. For the purposes of this study, the analyses were limited to eight metrics generated from the HbO maps: five measures reflecting small world properties; two measures of efficiency (network efficiency and local efficiency), and one measure at the nodal level (degree centrality). Area Under Curve (AUC) values were examined for small world metrics and efficiency metrics from the HbO, HbR, and HbT maps.

Across sparsity thresholds, small world network parameters were generally supported. Small Worldness is detected in networks where Gamma (γ) was greater than 1, Lambda (λ) at or slightly greater than 1, and was Sigma (σ) greater than 1. Clustering coefficient (C_p) varied across thresholds (M 0.43= at 0.1 to Mean = 0.71 at .4). The ratio of the clustering coefficient of the network to the clustering coefficient of the random network (gamma), at a given threshold, however was greater than 1 across thresholds (M = 1.97 at 0.1; M = 1.17 at 0.4). The shortest path length (L_p) varied across sparsity thresholds (M = 4.51 at 0.1; M = 1.47 at 0.4). The ratio of the shortest path length of the network to the shortest path length in randomly generated networks (lambda), was slightly above 1 across thresholds (M = 1.27 at 0.1; M =1.03 at 0.4). Finally, sigma (ratio of gamma to lambda) in the network was greater than 1 across thresholds (M = 1.59 at .01; 1.14 at 0.4), meaning the network has greater than random clustering and near random path length. Small world metrics across sparsity thresholds are displayed in Figure 3.

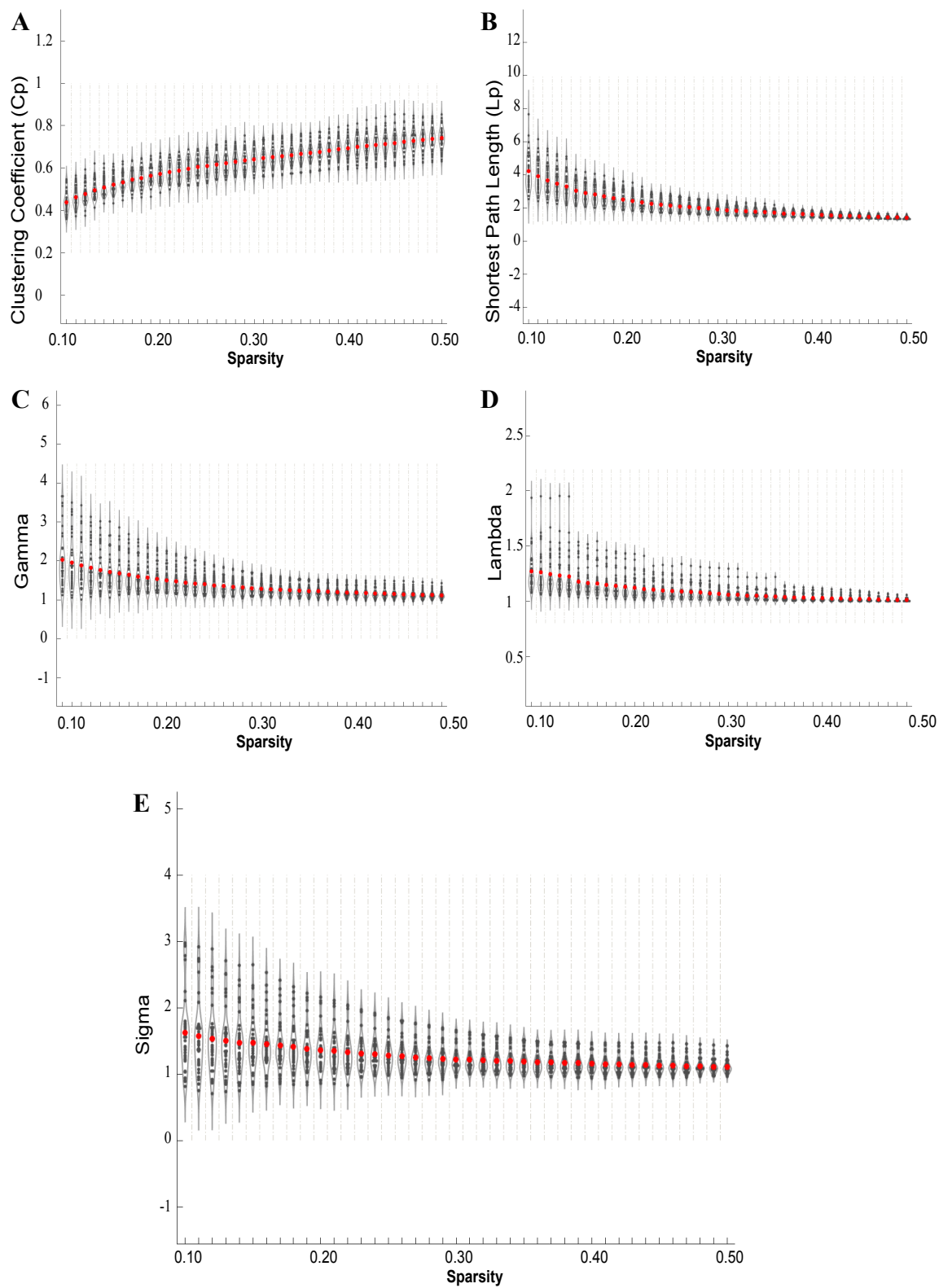


Figure 3. Small World Metrics. Results of clustering coefficient (A), shortest path length (B), Gamma (C), Lambda (D), and Sigma (E) areas as a function of sparsity threshold.

Global efficiency (e_g) varied across thresholds ($M = 0.24$ at $.1$; $M = 0.63$ at $.4$) as did local efficiency (E_{loc}) ($M = 0.51$ at $.1$; $M = 0.81$ at $.4$). Degree centrality was calculated for each node using AUC scalar value. Mean degree Centrality across all channels was 9.48 ($SD = 5.47$). Network Efficiency metrics across sparsity thresholds are displayed in Figure 4.

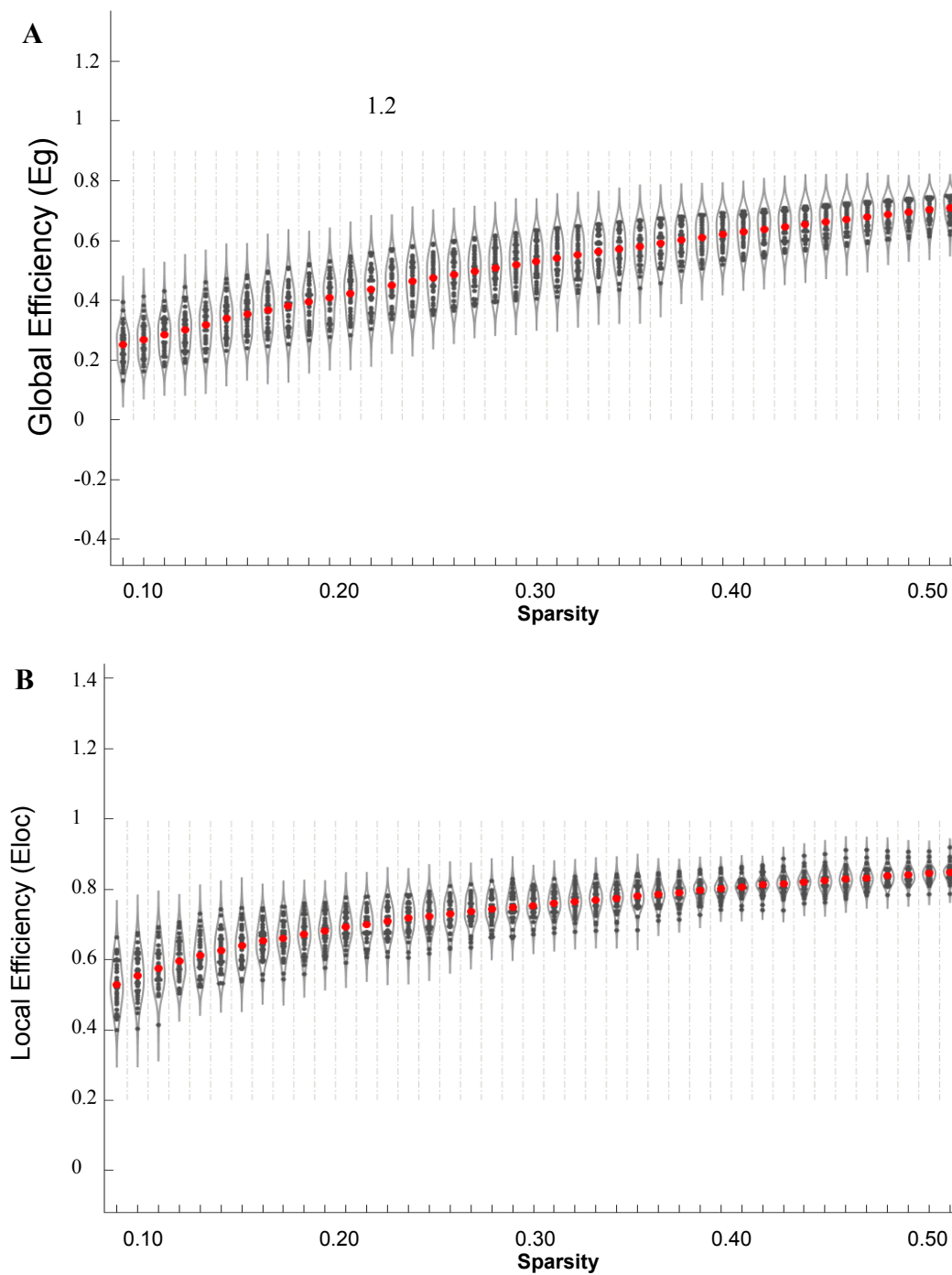


Figure 4. Network Efficiency Metrics. Results of global efficiency (A) and local efficiency (B) as a function of sparsity threshold.

Finally, the AUC for the five small world metrics and two efficiency metrics were examined in the HbO, HbR and HbT maps separately. AUC values for each of the seven metrics calculated for each map are displayed in Figure 5.

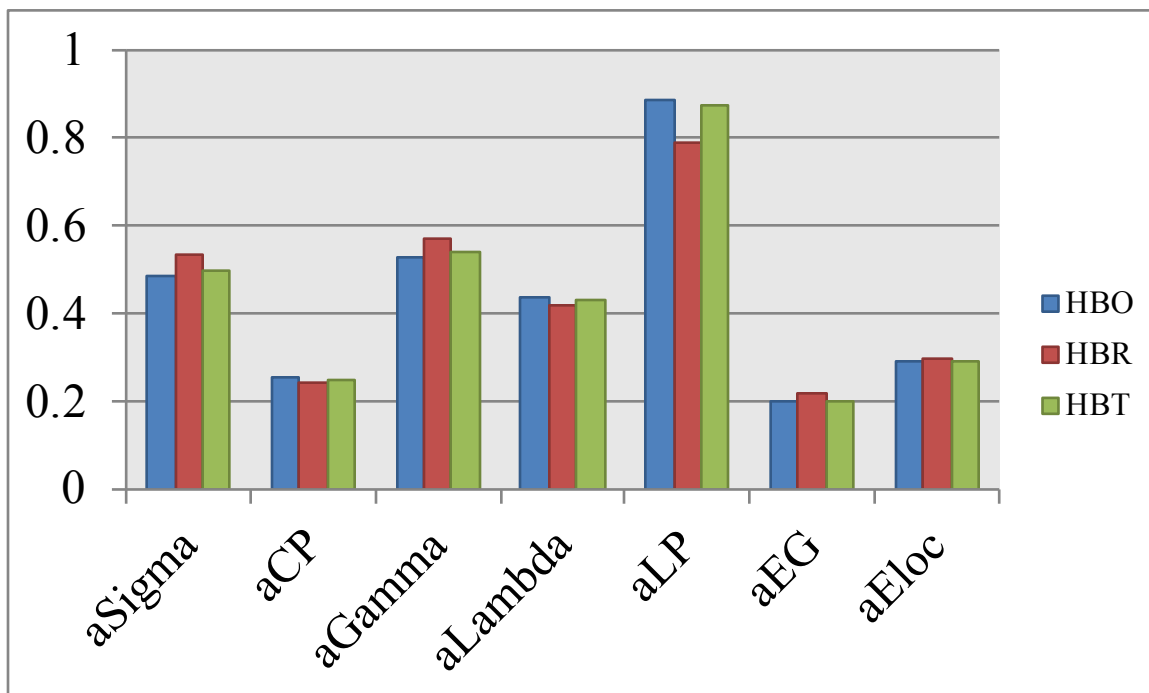


Figure 5. Area Under Curve (AUC) values for network measures: Sigma, clustering coefficient (Cp), Gamma, Lambda, shortest path length (Lp), global efficiency (Eg), and local efficiency (Eloc). Color bars represent: HbO, oxy-hemoglobin; HbR, deoxy-hemoglobin; and HbT, Total-hemoglobin.

Correlations between seven graph metric variables (AUC scalar variables for Gamma, Sigma, Lambda, Cp, Lp, Eg and Eloc) calculated from the HbO maps and EF measures were examined. Color word inhibition score was negatively correlated with aSigma ($r = -.590$, $p = .044$). Trails 1 scaled score was negatively correlated with aSigma and aGamma ($r = -.600$, $p = .038$; $r = -.725$, $p = .008$). No correlations were observed for the NIH toolbox tests. Total scores for self-report measures of EF were examined next.

BIS total score was negatively correlated with aSigma and aGamma ($r = -.708, p = .01$ and $r = -.636, p = .026$). Total score on the WBSI was negatively correlated with local efficiency (aEloc) ($r = -.597, p = .040$).

An exploratory follow up analysis examining correlations between BIS subscales and the seven graph metrics (Gamma, Sigma, Lambda, Cp, Lp, Eg and Eloc) was conducted. Of the second level factors (Attention, Motor, and Planning), the BIS Motor Scale was negatively correlated with aSigma and aGamma ($r = -.752, p = .005$; $r = -.689, p = .013$). Across subscales, the BIS perseverance subscale was negatively correlated with aSigma and aGamma ($r = -.814, p = .001$ and $r = -.788, p = .002$), and the BIS cognitive instability, a subscale of Planning, was positively correlated with shortest path length (aLp) $r = .601$ ($p = .039$). See Table 6 for exact correlations and p-values.

Table 6

Correlates between EF and Graph Metrics

Measure	Sigma	Cp	Gamma	Lambda	Lp	Eg	Eloc
Trails 1	-.60* .039	-.12 .705	-.73** .008	.28 .373	.31 .328	-.30 .342	-.41 .181
Trails 2	-.12 .709	-.14 .674	-.27 .399	-.14 .669	-.09 .785	.22 .493	-.08 .810
Trails 3	-.36 .257	.17 .590	-.32 .309	.27 .405	.03 .922	.06 .844	.02 .948
Trails 4	-.27 .397	-.21 .516	-.27 .395	.15 .643	-.11 .728	.14 .662	-.02 .944
Trails 5	.06 .857	-.07 .828	.37 .240	.49 .107	.05 .890	.00 .991	.24 .455
VF 1: Letter Fluency	-.29 .366	.12 .706	-.35 .260	.24 .444	.33 .291	-.43 .169	-.20 .540
VF 2: Category Fluency	-.22 .500	.37 .236	-.18 .572	.19 .563	.20 .534	-.35 .267	-.13 .690
VF 3: Switching Fluency	-.10 .754	.31 .331	.13 .692	.33 .293	.18 .581	-.17 .592	.03 .930

VF 3: Switching	-.10	-.13	.07	.22	.00	-.00	-.07
Accuracy	.759	.689	.827	.485	.991	.991	.826)
CWI 1: Color Naming	-.15	.27	-.20	.22	.000	-.11	.10
	.639	.395	.540	.499	1.000	.740	.756
CWI 2: Word Reading	.33	-.22	.26	.18	-.36	.27	.34
	.302	.503	.410	.576	.252	.400	.276
CWI 3: Inhibition	-.59*	.27	-.50	.44	.50	-.50	-.30
	.04	.40	.10	.16	.10	.10	.35
CWI 4: Switching	-.082	-.105	.000	.218	-.156	-.036	-.013
	.800	.746	1.000	.495	.628	.911	.969
List Sorting	-.19	.10	.01	.40	.01	-.14	.01
	.548	.759	.966	.193	.974	.656	.965
Pattern Comparison	.20	-.22	.32	.10	-.03	.03	.10
	.527	.500	.319	.770	.931	.940	.761
Flanker	-.48	-.34	-.36	.47	.31	-.32	-.34
	.111	.285	.255	.121	.331	.318	.279
Card Sort	-.32	-.15	-.23	.34	.12	-.14	-.16
	.309	.650	.467	.276	.711	.662	.622
DERS	-.47	-.38	-.32	.13	.30	-.38	-.50
	.124	.229	.319	.688	.354	.221	.099
BIS-11	-.71*	-.05	-.64*	.30	.46	-.46	-.47
	.010	.870	.026	.353	.131	.134	.120
WBSI	-.05	-.51	-.46	-.48	.12	-.27	-.60*
	.866	.088	.129	.119	.720	.401	.040

Note: VF, Verbal Fluency; CWI, Color Word Inhibition; BIS, Barrett Impulsivity Scale; WBSI, White Bear Suppression Inventory; DERS, Difficulties in Emotion Regulation Scale; Cp, clustering coefficient; Lp, shortest path length; Eg, global efficiency; Eloc, local efficiency. Significance levels were determined by Spearman's Rank Order correlations. In each cell, the top value represent Spearman' rho and the lower value represents the corresponding p value. Single asterisk (*) signifies a correlation is significant at the 0.05 level (2-tailed). Double asterisk (**) signifies a correlation is significant at the 0.01 level (2-tailed).

DISCUSSION

The primary aim of the study was to assess the feasibility of implementing a pilot RCT of MBRP within an outpatient substance use and methadone clinic from a neuropsychological framework. The continued increase in opioid overdose death rates in the United States is of grave concern and the need for additional treatments to better serve individuals with OUD cannot be understated. While recruitment efforts were targeted to adolescents and young adults, only young adult participants were successfully recruited. The feasibility of using both neuropsychological measures of EF and fNIRS, in addition to measures of substance use and mood, in the context of a RCT was demonstrated. The recruited sample demonstrated more variability in substance use history, more severe markers of psychopathology and greater unemployment rates than expected. However, none of the baseline variables measured was associated with attendance of the follow up session, with the exception of number of prescribed psychiatric medications. Overall, measures of executive function were within normal limits relative to the normative data, with the exception of one measure of processing speed. When EF performance variability was examined, however, a significant proportion of the sample had several scores in the impaired range, supporting the notion that EF is a multifactorial construct that may be best captured with multiple measures. This finding was supported by the limited number of significant correlations identified between the different measures of EF assessed in the study. Finally, resting state functional connectivity networks were successfully measured using fNIRS. Preliminary findings provided support for identifying small world networks using fNIRS.

The distinction between feasibility in a logistical sense and feasibility of the scientific methods employed in this study is worthy of consideration. Significant logistical constraints impacted the implementation of the study, including limitations in staff involved in study procedures, shifting between locations, and challenges related to retention. While these constraints impacted the overall sample size and power to detect changes, the scientific methods utilized were found to be feasible. EF was measured using several reliable and valid instruments; multiple clinical symptom measures were administered; fNIRS was successfully used to collect resting state network data; and topological properties of resting-state networks were identified with fNIRS data. Further, the treatment intervention was successfully implemented and randomization did not appear to impact follow-up rates.

Feasibility Issues: Recruitment and Retention

20 participants were consented, 13 participants were randomized to condition, and six participants completed through to the follow-up visit. While no specific baseline characteristics were found to be predictive of attendance of follow-up visit, with the exception of psychiatric medication use, continued care at the facility throughout the study was likely a contributing factor. While patients receiving care at a methadone clinic are in many ways a “treatment seeking” population, the level of motivation and interest for additional behavioral treatments within this population is unknown. Motivation and readiness to make behavioral changes, on any level, fluctuates throughout the course of a given day or stage in behavior change. This is natural and expected. While a significant number of individuals present to the clinic daily for ORT, appearing to the clinic for ORT may not be not be synonymous with seeking additional intervention.

Adolescents remain a population that underutilizes treatments for OUD. There is a significant need for treatments that target younger individuals. In this study, individuals under the age of 18 were not recruited despite significant efforts to target this subset of the treatment population, specifically. In part, the reduced flow of adolescent patients in the clinic and the increased severity of symptoms among those that were receiving care at the time of the study are likely contributing factors. However, there were some adolescents and families that did receive care at the clinic and were not interested in additional options. It is possible that at the time of study contact, a relapse-prevention framework was not an appropriate clinical fit. Clients experiencing withdrawal, currently being stabilized on an ORT, or still experiencing significant ambivalence about making changes in opioid use behaviors would not be a good fit for a relapse prevention program. Nonetheless, it would be helpful to better understand what factors impact treatment engagement among adolescents. One way to address this would be via qualitative methodology.

A qualitative approach may help to better identify barriers to treatment perceived by adolescents and their family members. Clearly, developing treatments that target adolescents are needed and understanding what factors impact engagement is a good first step. The majority of participants recruited in this study began using substances in their teens, yet on average there was nearly an 8-year lag between first use and first treatment encounter. A better understanding from their perspective would also help identify factors that may have motivated eventual engagement in services. Increased effort to gain support from family members would likely increase treatment engagement among adolescents, as well. Perhaps this could be accomplished via a brief presentation to

parents and family members at possible clinic orientation sessions. Since the vast majority of the recruited sample reported their first encounter with mental health providers occurred during adolescence, perhaps targeting substance use interventions to adolescents receiving mental health treatment might be a useful approach.

Approximately, half of the sample attended the final follow up session. With the exception of number of psychiatric medications prescribed, none of the baseline variables measured were found to be significantly associated with attendance at the follow up session. Given the small sample size, power to detect small to medium effect sizes was limited. Consistent care within the treatment facility, however, did appear to be an important factor for follow-up attendance.

Clinical Characteristics of the Recruited Sample

The recruited sample demonstrated variability in substance use history, severe markers of psychopathology, and significant unemployment rates. Most of the sample reported use of two or more substances when using their drug of choice, and over three quarters of the sample reported a history of concurrent abuse of opioid and stimulants. Substance use disorders are diagnosed by drug of abuse and consequently, treatment outcomes both clinically and in research contexts focus on the identified drug of abuse. This approach does not fully capture substance use patterns among all individuals with SUD. In particular, it fails to capture polydrug use, comorbid SUDs, and development of later SUDs during the course of care.

Approximately, one third of the sample reported using the substance of abuse in the past 90 days, however, nearly three-quarters of the sample reported use of a *different* substance of abuse. This finding highlights the complexity of assessing treatment

outcomes in this population. Methods for how to handle and detect the occurrence of new “addictions” during the course of treatment are needed. Abuse of prescription medications, alcohol or marijuana may emerge during the course of ORT treatment. A significant portion of the sample reported use of cannabis, as well as nicotine. Instances of using prescribed medications in ways that were not prescribed, was also reported.

Identifying the best treatment targets can be a dynamic process. Over the course of treatment, it may be necessary to reassess substance use patterns periodically. While a harm reduction approach makes sense at initiation of treatment, as clients become stabilized on an ORT, new substances of abuse may become increasingly problematic. As mentioned, many of the participants reported use of cannabis. Notably, there have been efforts to use cannabis as a treatment for OUD and it has been added to the list of conditions for which medical marijuana may be prescribed in New Mexico (Kunkel, 2019). While from a harm reduction perspective this may prevent overdose deaths, it also has the potential to foster additional substance use disorders. The latest research also suggests cannabis may not be associated with reduced overdose deaths in the long run (Shover, Davis, Gordon, & Humphreys, 2019) and may be associated with increased psychosis (Shover, Shoptaw, et al., 2019). Perhaps, effort to develop new behavioral treatments for OUD might be a better use of resources.

The prevalence of comorbid psychopathology was well documented in this sample. All participants reported being diagnosed with at least one additional psychiatric disorder and a significant proportion were on multiple psychotropic medications in addition to ORT or naltrexone. While there was a significant lag between initiation of substance use and first encounter with substance use treatment, participants had a history

of early mental health treatment. In fact, the average age for first drug use and first mental health encounter were within the same 12-month period. Continued difficulty with mental health symptoms was reported at the time of the study as well, with participants reporting symptoms of anxiety and low mood. This finding highlights the need for interventions that can address the complex comorbid mental health issues that often arise among individuals with OUD. Further, the self-report measures of EF included measures of emotion regulation and coping strategies. Participants reported reduced coping strategies and impaired ability to regulate emotions, providing additional support for the future use of MBRP in this population. As previously mentioned, MBRP, in particular, has been shown to be helpful with aspects of emotion regulation.

Executive Functioning at Start of Study

When compared to the normative sample, at a group level, participants in the study scored within between the 21st and 60th percentile on measures of executive function, with the exception of one measure of processing speed, which was at the 5th percentile. However, when the *number* of impaired EF scores was examined per participant, a significant proportion of the sample had one or more scores in the impaired range (below the 5th percentile). This finding supports the idea of EF as a multifactorial construct that is not easily measured by a single test or score. Non-significant correlations between measures of EF within this sample provide tentative further support for using multiple measures of EF to capture EF impairments. In future work, it would be helpful to generate a single measure of EF in addition to measures of specific EFs. In larger samples this could be done using a principal components analysis or by averaging standardized scores. The EF tests selected for this study captured a range of EFs,

however, in future work it may be useful to limit analyses to scores that capture the most demanding aspect of the task (e.g., Trails 4, but not Trails 1, 2, 3 and 5; color word inhibition and color word inhibition switching, but not color naming and word reading).

Interestingly, while self-reported EF problems were not correlated with performance on objective measures of EF, there were some correlations between self-report measures of EF and measures of mood and anxiety. The relationship between self-reported EF problems and other symptom measures has been examined in other populations, such as mild Traumatic Brain Injury (Rapoport, McCullagh, Shammi, & Feinstein, 2005; Schiehser et al., 2011). It may be useful to consider self-reported EF in the context of other mental health conditions in future research. In particular, in the treatment studies, it would be interesting to assess if treatment response to self-report measures of EF differs from treatment response to objective measures of EF.

Additional measures of EF, not used in the current study should be explored in future work. Specific to cool EFs, measures of planning, such as the Tower of London and measures of sustained attention would be informative. The variability in performance across measures of EF could, in part, be explained by a weakness in sustained attention. It is also possible that the variability in performance across tests could be explained by effort. In future studies, an objective measure of effort would be very informative.

Finally, hot EF tasks seem particularly relevant for this population. There were challenges associated with administering a hot EF task in this study. Hot EF tasks, including the one used in this study, can be time consuming. This can pose a real challenge for researchers administering a larger battery of cool EF tasks. In this study,

the hot EF task was administered last in the sequence of measures to prevent the hot EF task from influencing performance on the cool EF tasks. This could theoretically impact skew performance on the hot EF task if individuals are more fatigued when the hot EF task is administered. Among clinical samples it is important to consider when the task might be too distressing for a given participant, as well. It would be helpful to develop a standardized procedure for determining if a task is too distressing for participants.

Similarly, a set of standardized procedures for follow-up support for participants after the task would be worth further consideration. Additional hot EF tasks should be explored in this population as well. Tasks that capture decision-making and delayed discounting, for instance, would be particularly relevant for SUD treatment samples. Likewise, administering EF tasks with embedded drug-cues would further our understanding of EF in the context of triggers to use substances. While hot EF tasks are relatively new in the field of EF research, these tasks have the potential to capture the real-world impairments of EF that may not always be captured by cool EF measures.

In future research it would be helpful to tie specific EF impairments to functional outcomes. For instance, perhaps an individual with impaired fluency might exhibit greater difficulty generating new solutions to a problem. Alternatively, perhaps an individual with difficulty shifting on tasks of EF might demonstrate difficulties transitioning between home and work. It is important that one can connect impairments in EF in daily life with the EF impairments observed on study measures.

fNIRS is Both Feasible and Useful

Findings supported the presence of small world properties in the fNIRS resting state networks in this study. Exploratory analyses examining correlations between

network results and measures of EF, as well as, measures of mood, anxiety, substance use, and mindfulness were successfully performed. This provides support that fNIRS can be utilized in clinical research in very meaningful ways. fMRI research is very costly, yet provides important metrics for furthering our understanding of mental health problems. Resting state analyses, in particular have shown potential for meaningful clinical applications. While fMRI research is still needed to examine subcortical resting state networks, fNIRS proves to be an effective and relatively inexpensive alternative. As was demonstrated in this study, fNIRS can be used successfully to generate these more complex network analyses and can easily be used to examine clinical correlates.

The current montage was selected to capture resting-state activity across the entire cortex. While minor modifications could be explored (e.g., including additional channels in the prefrontal cortex and motor cortex) the general approach to montage creation was supported. Further, while not explicitly examined in these analyses, fNIRS can be used to examine specific neuroanatomical regions, as well. For instance, one could select specifically the nodes localized in the frontal regions for a ROI analysis. FC-NIRS toolbox can detect directed graphs and weighted graphs, as well. These analyses would be particularly relevant for measuring networks during tasks. Lastly, alternative analytic approaches could be applied to the fNIRS network as well, such as Independent Components Analysis.

Finally, while the power was limited, some findings were interesting and worthy of consideration in future research. First, small world network metrics were successfully detected using fNIRS. These parameters have been used to identify potential biomarkers of a variety of psychiatric conditions, including SUD. Changes in small world metrics

would be an excellent target for treatment that can be captured by fNIRS and could be emphasized in an ROI application. Additionally, some preliminary correlations between the graph metrics and self-reported EF were observed. Specifically, scores on a measure of impulsivity (BIS-2) was correlated with Gamma and Sigma, two metrics associated with small worldness. As mentioned earlier, a previous study of MBRP in OUD, found improvements on the BIS-2 in the MBRP group, but not the control group (Yaghubi, Zargar, & Akbari, 2017). Perhaps, one potential mechanism for a reduction in impulsivity following MBRP is via increased small worldness in the resting state network.

Limitations

The small sample size recruited and the drop-out rate were significant study limitations. The impact of the MBRP on substance use, executive functioning, and resting state connectivity could not be determined. Regarding measures, self-report measures of substance use are less reliable than objective measure of substance use, such as might be found from a urine analysis. Additionally, the study did not gather qualitative information from study participants, which could have guided future work. Finally, the participants recruited were heterogeneous in terms of comorbid psychiatric diagnoses, substance use history, and psychiatric medications. While homogenous, i.e., “clean”, samples are the gold standard during initial RCTs, often the clinical reality is one of greater complexity and heterogeneity.

Conclusions

Pilot studies can help inform larger studies. Understanding the steps needed to implement an empirically supported treatment into different outpatient clinics is a

necessary step in the dissemination of research. The protocol was already modified for a treatment setting, which increased the feasibility greatly (Roos, 2019). More specifically, sessions were briefer, offered multiple times a week, and a rolling group format was utilized. Frequently, providers express frustration or reluctance to adopt manualized protocols because there is a belief that clinical trials are not conducted in the “real world”. Fortunately, robust treatments, such as MBRP, can withstand more complex populations. Additional staff would be needed to successfully run this study at a larger scale. More specifically, it would be beneficial to have a least one part time staff member (i.e. study coordinator) on site at the clinic to facilitate continued contact with clinic staff and interested participants. Additionally, it would be helpful to have a second staff member present for active recruitment periods (i.e., during peak traffic times at the clinic). For baseline visits, two to three additional research assistants would enable participants to complete baseline measures more efficiently and would allow for multiple participants to be scheduled at once. Regarding therapy groups, ideally bi-weekly groups would be available at multiple time slots (i.e., four time slots) to capture both the morning wave and afternoon wave of participants. This would likely require three to four therapists. Lastly, for an RO1 application, a case manager or social worker on staff to help with patient care coordination would be helpful and a psychiatrist or psychiatric nurse (0.25 FTE) would be helpful to have on site in the event of any medical crises (e.g., overdose).

Prevention and early intervention efforts are paramount. The majority of individuals within this study began using substances in their teens, yet on average there was nearly an 8-year lag between first use and first treatment encounter. Clearly,

developing treatments that target adolescents are needed. The vast majority of the sample first experienced mental health issues in their teens as well. Specific targeted prevention efforts should be implemented within pediatric mental health clinics. Additionally, more in depth assessment of substance use should be included in every mental health intake conducted in pediatric health settings. Efforts to educate teachers and parents on substance use prevention should begin during elementary school given the early age of first substance use initiation. Finally, preventive interventions that boost EF, such as a modified MBRP, could be implanted in school systems and are worth future consideration.

A neuropsychologically-informed approach is feasible. At its core, neuropsychology is the study of brain-and-behavior relationships. The NIMH created the RDoC framework to further a dimensional approach to mental health, linking specific behavioral dysfunctions to specific neural circuits, reflecting a neuropsychological approach to mental health. Clinical Neuropsychology, as discipline, serves multiple roles including: development of treatment plans, formulation of accommodations needed to help an individual function, and in some contexts, prediction of treatment outcomes (Schoenberg, 2011). While perceived cognitive deficits motivate referrals to neuropsychology, psychological symptoms are a consistent part of the clinical presentation. Neuropsychology can make significant contributions in furthering our understanding of complex mental health conditions like SUD.

Advances in neuroimaging, in conjunction with a long history of clinical assessment, enables neuropsychology as a field to identify novel treatment targets for OUD. Further, neuropsychology is well suited to assess treatment-induced changes on

validated, specific treatment targets over time through the use of neuropsychological assessments and neuroimaging methods. An integration of neuropsychology with more traditional clinical trials research for mental health conditions like SUD is a worthy endeavor. While neuropsychological methods are often time consuming, the findings in this study demonstrate this approach is not only feasible, but has the potential to link behavioral symptoms with neural circuits via fNIRS.

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