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Cognitive Impairments and Reversibility Among Opioid Users

by

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of the Degree of Bachelor of Arts

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Abstract

Extensive studies have shown that acute and chronic use of opioids is related to cognitive impairments in different aspects. This study aims to explore impairments in executive functions among opioid users, focusing on cognitive impulsivity, cognitive flexibility, spatial working memory, and verbal working memory, as well as investigating the potential reversibility of these impairments under conditions of methadone maintenance treatment. In a sample including active opioid users, methadone maintenance patients, and healthy controls from downtown Los Angeles who do not meet exclusion criteria, the research will employ four tasks and scales to evaluate and compare executive functioning among these groups. Also, a longitudinal aspect will track changes in executive functioning performance among methadone patients over a 90-day period. It is expected that active opioid users and methadone maintenance patients will exhibit worse performance in executive functioning compared to healthy controls, with methadone patients outperforming active users, even when considering the history of head injuries. Additionally, it is expected that within the user groups, there will be a negative correlation between the frequency of overdoses, length of opioid use, and executive functioning. The study also anticipates an improvement of executive functioning in methadone maintenance patients over a 90-day period. This research hopes to increase awareness about the cognitive risks associated with opioid use and inform more effective treatment strategies for opioid addiction by emphasizing cognitive rehabilitation as a component of recovery.
Cognitive Impairments and Reversibility Among Opioid Users

A critical aspect of opioid addiction is that many studies have shown that acute and chronic use is related to cognitive processing and impairments in different aspects, such as a higher tendency to behave impulsively (Lee et al., 2005), impairment of cognitive flexibility (Darke et al., 2000a), and working memory (Ornstein et al., 2000; Wang et al., 2008). However, the reversibility of these cognitive deficits remains largely unexplored. After an overview of opioid use disorder and its related impacts on people and society, the characteristics of opioid addiction and executive functions will be discussed as a background for the relationship between them. A detailed review of the empirical evidence on the impairments of different executive functions among opioid users will then be conducted. The purpose of this research is to further investigate on the impacts of opioid use on executive functions and conduct longitudinal study to examine the reversibility of these deficits.

Overview

Substance Use Disorder (SUD) is a chronically relapsing disorder with compulsion in drug-seeking and drug-taking, failure to limit intake, and rise of negative emotions (Koob & Volkow, 2016). Addiction to drugs, including opioids like heroin, is characterized by significant disruptions in motivational circuits across three stages: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation. These stages involve neurobiological changes in the basal ganglia, extended amygdala, and prefrontal cortex, with key neurotransmitters playing crucial roles (Koob & Volkow, 2016; Wilcox et al., 2016).

Various genetic and environmental factors have been shown to make individuals more susceptible to drugs' influences and therefore easier to get addicted (Torregrossa et al., 2011).
Chronic use of drugs may change the learning and memory mechanisms that under normal circumstances serve to pursue reward and cues related to reward, which further contributes to the development of addiction (Hyman, 2005; Torregrossa et al., 2011). Moreover, individuals with opioid use disorder (OUD) frequently show co-occurring substance use and mental disorders, highlighting an urgent need for the development of services that address both substance use and mental health comorbidities (Jones & McCance-Katz, 2019). The addiction wave of heroin in the US started around the 1960s in urban areas among minority populations (DuPont & Greene, 1973) and spread to whites in suburban and rural areas (Bowser et al., 2017). The number of overdose deaths due to the misuse of heroin has significantly increased in past years (Skolnick, 2018), and the overdose death for 2020 is 13,165 (Centers for Disease Control and Prevention [CDC], 2021).

Brain changes associate with opioid dependence are well documented. Amygdala is identified as a critical structure in the foundation of opioid addiction, with subpopulations in it being involved in both the creation and retrieval of withdrawal memories (Frenois et al., 2005). Furthermore, opioid drugs bind to multiple receptors with differences in affinity and efficacy (Volkow & Blanco, 2021). Drugs like heroin and fentanyl, which rapidly enter the blood brain barrier and act as full agonists at mu-opioid receptor (MOR), offer heightened rewards, which further leads to the desensitization of MOR in amygdala (Maher et al., 2005). Beyond MOR activity, there is modulations of gamma-aminobutyric acid receptor function and alterations in the targeting of glutamate receptors in the amygdala (Glass et al., 2005; Zarrindast et al., 2004). Similar changes are also found in prescriptive opioid use. Functional connectivity decreases observed in patients were mediated by both the volume of the amygdala and the structural
integrity of its connecting pathways (Upadhyay et al., 2010). Extending these findings, another study revealed that thirteen brain regions showed significant changes in volume, with the degree of these changes being correlated with the dosage of morphine administered (Younger et al., 2011).

Opioid dependence is also characterized by reinforcing effects that establish learned associations between drug use and associated experiences, potentially leading to conditioning (Volkow & Blanco, 2021). Repeated opioid use can result in the development of tolerance and physical dependence. The effect of tolerance increases the doses that are necessary to achieve the desired analgesia and hedonic effects, aggravating the risk of overdose (Dumas & Pollack, 2008; Volkow & Blanco, 2021). Physical dependence triggers withdrawal symptoms, which characterizes the negative reinforcement perspective of conditioning. The rate of opioid clearance from the brain affects physical dependence, with heroin causing more severe withdrawal than drugs like buprenorphine. Individuals with Opioid Use Disorder (OUD) face challenges like tolerance and physical dependence, and their symptoms of OUD correspond to changes in various brain circuits.

Executive functioning (EF) is a complex neuropsychological construct encompassing the abilities to establish goals, sustain focus towards achieving them, and adapt strategies in response to changing circumstances (Suchy, 2009). Additionally, it involves switching between tasks, using information for decision-making, and recognizing common elements across items (Banich, 2009). Several executive functions will be investigated in this study. Cognitive impulsivity examines the preference between immediate smaller rewards and larger, deferred ones, with impulsiveness and self-control exemplifying each choice respectively (Logue, 1988).
Cognitive flexibility measures an individual’s adaptability to new stimuli, crucial for considering multiple outcomes (Baldacchino et al., 2012). A diminished flexibility can lead to cognitive rigidity, manifested as perseveration, or reduced verbal fluency. Working memory is a system for short-term storage and manipulation of data that helps with cognitive tasks (Baddeley, 1992). Distinct processes are responsible for the temporary storage of verbal and visual information, and different brain regions and circuits are activated, with most of them in left hemisphere (Smith et al., 1996).

Frontal lobes are mainly in charge of executive functioning (Alvarez & Emory, 2006). Specifically, cognitive impulsivity, working memory, and verbal fluency have been shown to correlate with the activities in prefrontal cortex (Baldo et al., 2001; Miller, 2000; Thompson-Schill et al., 2002). Therefore, the changes of these executive functions are associated with the relapsing nature of opioid addiction as frontal regions were particularly affected among opioid addicts (Büttner et al., 2000; Koob & Volkow, 2016). Possible impairments include the impaired signal transduction systems, reduction of certain receptors (Büttner et al., 2000), and abnormal blood flow (Pezawas et al., 2002). Aligning with the theory, previous studies observed executive functions’ impairments in different aspects among acute and chronic opioid addicts.

**Cognitive Impairment**

Many studies characterized poor impulse control as well as the tendency to behave hostilely related to acute and chronic use of heroin. Pau et al. (2002) investigated the relationship between heroin addiction and impulse control by comparing 30 subjects who were heroin addicts but are currently abstinent and 25 normal controls. The impulsivity of participants was evaluated by Porteus Maze Test (PMQS). The score of PMQS demonstrated
significant differences between the two groups, which indicated that previous chronic use of heroin serves as a strong predictor for a lower degree of impulse control. Similarly, Clark et al. (2006) examined this relationship by comparing 40 current opioid users, 24 current amphetamine users, 24 previous opioid or amphetamine users, and 26 healthy controls, using the Barratt Impulsiveness Scale Version-11 (BIS-11). It is shown that compared to healthy controls, the opiate group had significantly higher scores in nonplanning subscale, and the ex-users group scored higher in both attentional and nonplanning subscales.

Besides psychological measures, it is crucial to notice that neuroimaging approaches like functional magnetic resonance imaging technology also demonstrated similar results in heroin users who were newly admitted to rehabilitation centers in China (Lee et al., 2005). The disparities in cognitive control of behavior and its related neural activity between 21 heroin addicts and 11 normal controls were measured using a combination of cognitive tests and fMRI. Results indicated that heroin addicts took a significantly shorter time to complete the more demanding reverse condition in the task than normal controls. This phenomenon can be described as disinhibited and impulsive behavior, which is consistent with the results of previous research.

Although findings consistently suggested that acute and chronic opioid abuse is associated with poor impulse control to some extent (Clark et al., 2006; Lee et al., 2005; Pau et al., 2002), limited studies aimed to test whether such impairment is entirely permanent, so it remains unclear. Baldacchino et al. (2015) aimed to examine if a period of abstinence will improve different aspects of impulse control in former heroin addicts by comparing impulsivity in 24 current heroin addicts and 29 former heroin addicts who are currently treated with
methadone in Fife and Tayside, Scotland, and UK. Furthermore, it used 28 normal controls to compare with the current heroin users and the group on methadone respectively. Results suggested that current heroin addicts exhibited more serious impulse control impairments than the group on methadone, and both groups have poorer impulse control than normal controls. Summarily, it can be suggested that partial changes in impulsivity are due to the currently active use of opioid, and a period of abstinence may reverse this part (Baldacchino et al., 2015). However, some impairments will remain after a period of abstinence. Nevertheless, it remains unclear if changes in impulsivity that ex-opioid users share are permanent or because of further use of opiates like methadone for treatments.

The effects of heroin on the verbal fluency aspect of cognitive flexibility are also well documented in research. Darke et al. (2000) investigated the impacts of heroin use on cognitive functions by employing matched control study, comparing 30 patients on methadone maintenance patients and 30 healthy controls from southwestern Sydney. The verbal fluency was evaluated by Controlled Oral Word Association Test (COWAT). The analysis of the COWAT score demonstrated that former heroin users undergoing methadone maintenance treatment performed below the level of healthy controls. However, the methadone maintenance group displayed an increased prevalence of risk factors that may contribute to this relationship, with 73% having overdosed, 63% meeting lifetime alcohol dependence criteria, and 67% reporting at least one head injury. Notably, the number of DSM-IV alcohol dependence symptoms and the frequency of heroin overdoses were identified as significant predictors of reduced cognitive performance. Therefore, for more robust implications, future studies should aim to control for
or take into account factors like the number of overdoses and the use of other drugs such as alcohol to mitigate potential confounding variables.

Ornstein et al. (2000) conducted another study comparing 22 individuals with exclusive opiate dependence to 23 individuals with only amphetamine dependence and a control group of 48 healthy subjects, matching the age and verbal IQ of healthy controls with the other two groups. All participants were recruited in Cambridge. Both letter and semantic verbal fluency tests were conducted, and the findings underscored a discernible impairment in verbal fluency in both tests among opioid addicts. Furthermore, Soyka et al. (2008) utilized Regensburger Word Fluency Test (RWT). 59 opiate-dependent patients on methadone or buprenorphine and 24 healthy controls were recruited, and the reversibility of cognitive impairment was assessed in a longitudinal form in this study. Opiate dependents showed a significant improvement in verbal fluency after another 8-10 weeks of stable methadone and buprenorphine treatment, but healthy controls performed better overall. While there is a general consensus on verbal fluency outcomes, it is important to consider the limited inclusion of active opioid users in previous studies, which predominantly focused on former opioid dependents undergoing treatment. Actively recruiting more current opioid users could offer more insights into verbal fluency impairments, facilitating direct comparisons among active users, former dependents, and healthy controls.

Expectedly, studies have also reported general impairments in both spatial and verbal working memory correlated with acute opioid use. Ornstein et al. (2000) conducted a study involving three groups: 22 individuals solely dependent on opiates, 23 individuals solely dependent on amphetamines, and a control group of 48 healthy subjects. The participants for
this study were all recruited from Cambridge. This study suggested that acute and chronic use of heroin significantly impairs cognitive functions, including spatial working memory. There was a significant difference in the Cambridge Neuropsychological Test Automated Battery scores between abstinent heroin-dependent individuals under treatment and normal controls. However, the lower education level in the heroin addict group explained part of this result. Moreover, Ersche et al. (2006) extended the findings by comparing 4 groups of participants: individuals currently using amphetamines, current opiate users, former opiate users and/or amphetamine users, and healthy controls who had no history of using illegal substances. This study utilized the Pattern Recognition Memory (PRM) and the Paired Associate Learning (PAL) in the same CANTAB task, which further showed the impairments of spatial working memory among current opioid users as current users made more errors, took longer to learn paired associations, and recognized less patterns. 

In terms of verbal working memory, Mintzer & Stitzer (2002) aimed to investigate the relationship between methadone maintenance patients and their cognitive impairments, including verbal working memory. This study included 18 opioid-dependent methadone maintenance patients and 21 matched controls from Baltimore. 50% of the patients in the methadone maintenance group reported previous heroin dependence. Scores of a classic measure of verbal working memory, the Two-back task, are significantly different between methadone maintenance patients and the control group, which suggested impaired verbal working memory. After 3 years, Mintzer et al. (2005) extended this finding by recruiting another 20 abstinent opioid users and comparing their cognitive performances with the two groups in Mintzer & Stitzer (2002) using same cognitive tests. Results indicated that individuals who are
now abstinent exhibit cognitive performance levels that are between those of individuals currently undergoing methadone maintenance treatment and healthy controls. This finding suggested that methadone maintenance might be associated with additional cognitive impairments beyond those caused by long-term substance abuse.

However, impairments differ in aspects of verbal working memory. Wang et al. (2008) assessed the verbal working memory using the n-back task. The differences in scores between abstinent heroin-dependent individuals and normal controls suggested impaired verbal working memory for the 1-back and 2-back level, but not for the 0-back level. A potential explanation might be the higher complexity associated with the 1-back and 2-back tasks, which require more active update of information in working memory, as opposed to the simpler 0-back level that primarily involves immediate recognition. Moreover, it can be inferred that at least part of the impairments will persist even after abstinence. Nevertheless, similar to other domains, the fact that active opioid users are not recruited makes it difficult to quantify the reversibility.

**Study Overview and Aims**

The reviewed literature briefly provided the background of SUD and executive functioning, and summarized the cognitive changes and impairments related to heroin addiction. Although previous research has shown that opiate addiction can cause a broad range of cognitive impairments, including poor impulse control, deficits in verbal fluency, and the impairment of working memory, little research has attempted to determine if those impairments are reversible. Additionally, most previous studies have overlooked active opioid users in their recruitment, and potential confounding variables have not been adequately controlled or addressed.
To address the identified research gap, the proposed study aims to understand the cognitive impairments of executive functioning among opioid users and their potential reversibility, employing a battery of cognitive tests to evaluate domains including cognitive impulsivity, cognitive flexibility, specifically verbal fluency, and working memory (both spatial and verbal). Based on a quasi-experimental framework, the cognitive performance of healthy controls, active opioid users, and methadone maintenance patients (MMP) will be compared. Furthermore, a longitudinal assessment will be carried out on MMP to discern the potential reversibility of these cognitive deficits. The research considers a set of possible confounding variables—ranging from age, IQ level, education level, other drug use, head injuries, mental illness history, the length of abstinence, and the number of previous overdoses—to ensure a detailed and robust analysis.

It is hypothesized active heroin users and people on methadone maintenance treatment will have significantly worse performance on cognitive impulsivity, cognitive flexibility, spatial working memory, and verbal working memory measurements than healthy controls but participants on methadone maintenance treatment will perform significantly better than those currently on heroin. These relationships will still hold after controlling for the history of head injury. Additionally, it is hypothesized that active users and methadone maintenance patients with higher number of overdoses and longer length of opioid use will have significantly worse performance on cognitive impulsivity, cognitive flexibility, spatial working memory, and verbal working memory measurements. Lastly, it is hypothesized that the length of abstinence has a positive impact on the reversibility of executive functioning, with methadone maintenance
patients performing better on the above executive function tests at the end of a 90-day period than at the beginning of the 90 days.

Method

Participants

The study will involve populations from downtown LA, comprising healthy individuals, active opiate users meeting the DSM-V criteria for Opioid Use Disorder, and individuals in methadone maintenance treatment for 15 to 30 days. The target sample size is 540 participants: aiming for a minimum of 180 healthy controls, and 180 participants for each of the other two groups to meet the sample size requirements determined by G*Power analysis for a study utilizing MANCOVA, MANOVA, and multiple linear regression. This analysis seeks to detect a medium effect size with a power of 0.8 and an alpha level of 0.05. The aim will be to recruit for 636 participants 212 participants in each group to account for an approximately 15 percent attrition rate.

In terms of exclusion criteria, all participants need to be above 18 years old. Active heroin users must meet the DSM-V criteria for Opioid Use Disorder and demonstrate a history of at least three years of opioid use to meet the study criteria. Similarly, methadone maintenance patients must have had a minimum of three years of opioid use prior to their current treatment. At the time of recruitment, methadone maintenance patients must be within the specified 15-30 day range of treatment to ensure a consistent level of treatment exposure across participants. For active users and methadone maintenance patients, the use of stimulant that meets the DSM-V criteria for stimulant use disorder, will result in exclusion. This is to maintain clarity on the impact of opioid use and recovery without the confounding
influence of other substances. Moreover, active users and methadone maintenance patients with comorbid psychiatric conditions other than opioid use disorder will not be included. Healthy controls are required to have no history of any drug use and psychiatric disorder, ensuring the validity of this group as a comparison for the other two cohorts.

To engage these distinct groups, tailored recruitment strategies will be implemented. Active heroin users will be approached at local needle exchanges between 1pm to 5pm, where we will collaborate with staff to identify potential participants. Researchers will provide the overview of the study and inform them the compensation amount they will receive at the end. People who are willing to participant will provide their contact information and the date they would like to do it. For methadone maintenance patients, we will randomly choose local rehabilitation centers and partner with them to identify individuals within the targeted range of treatment days and have previously been diagnosed with Opioid Use Disorder. Then researchers will go there to ask if they would like to participate on dates rehabilitation centers provide. These participants will also be offered compensation upon agreeing to take part in the study. Finally, healthy controls will be recruited through advertisements on research platforms, detailing the study's overview, compensation, and location, along with a sign-up link. These strategies will be pursued rigorously to achieve the desired sample size, maintaining a strong adherence to the outlined exclusion criteria to ensure the integrity of the data collected.

No available source has been found to document the racial and gender distribution among OUD patients. Therefore, demographics distribution for this study is expected to be align with the population of Los Angeles County (U.S. Census Bureau, n.d.). In terms of gender distribution, it is expected that there will be approximately 50.2% female participants and
49.8% male participants, with no specific data on non-binary/third gender people. In terms of racial distribution, it is expected that there will be approximately 44.9% White Alone, 8.6% Black or African American Alone, 0.9% American Indian or Alaska Native Alone, 11.9% Asian/Pacific Islander Alone, 9.8% Mixed/Multi Ethnic, and 48.4% Hispanic or Latino Origin.

**Materials**

**Demographics**

Basic demographics of the participants will be collected through a survey on Qualtrics. Age will be measured through an open-ended question. Ethnicity and gender will be measured using mixed questions that contained both open-ended and closed-ended choices, with free-response under open-ended choices. The question measuring gender will include “Male,” “Female,” “Non-binary/third gender,” “Prefer not to say,” and “Other”. The last one can be filled with a free response. The question measuring race will contain “White Alone,” “American Indian or Alaska Native Alone,” “Asian/Pacific Islander Alone,” “Black or African American Alone,” “Mixed/Multi Ethnic,” “Hispanic/Latino Origin”, and “Other”. Participants can choose the “Hispanic/Latino Origin” choice with another choice. The last two choices can be filled with free-response.

**Other Variables**

In addition to demographics, the study will examine several key variables pertinent to the participants' substance use profiles and relevant covariates and apply related exclusion criteria and following analysis based on them. This will also be part of the Qualtrics survey. The current (or previous) length of use will be asked in the unit of months among active opiate users and methadone maintenance patients. The length of abstinence will be measured among
methadone maintenance patients. As a free response question. The number of overdoses
experienced by active opiate users and methadone maintenance patients will also be recorded.
All the variables above will be recorded in number-only free response. A history of head injuries
was assessed in a multiple-choice form, with participants choosing either "yes" or "no". Healthy
controls will be asked in a multiple-choice form if they have any drug-taking history, including
opiates, stimulants, cannabis, and psychedelics, with participants choosing either "yes" or "no".
Healthy controls will be asked if they have any psychiatric illness history, and active opiate users
and methadone maintenance patients will be asked if they have any psychiatric illness history
except Opioid Use Disorder in a multiple-choice form, with participants choosing either "yes" or
"no".

**DSM-5 Opioid Use Disorder Diagnostic Criteria**

The diagnostic criteria for Opioid Use Disorder (OUD) that will be used in this study are
in the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM–5; American
Psychiatric Association, 2013). The criteria include eleven items, such as “Opioids are often
taken in larger amounts or over a longer period than was intended” and “Continued opioid use
despite having persistent or recurrent social or interpersonal problems caused or exacerbated
by the effects of opioids”. In order to diagnose OUD, at least two of the eleven items should be
presented within 12 months, with the presence of 2 to 3 symptoms being mild OUD, 4-5
symptoms being moderate OUD, and 6 or more symptoms being severe OUD. OUD must be
diagnosed by a clinician through the evaluation of symptoms and drug use history to identify
the impairments and distress caused by opioid use (Wakeman, 2020).
DSM-5 Stimulant Use Disorder Diagnostic Criteria

Stimulant Use Disorder is Substance Use Disorder involving any of the class of drugs that include cocaine, methamphetamine and prescription stimulants. The diagnostic criteria for Stimulant Use Disorder that will be used in this study are in the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM–5; American Psychiatric Association, 2013). The criteria include eleven items, such as “The stimulant is often taken in larger amounts or over a longer period than was intended” and “Continued stimulant use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the stimulant”. In order to diagnose Stimulant Use Disorder, at least two of the eleven items should be presented within 12 months, with the presence of 2 to 3 symptoms being mild Stimulant Use Disorder, 4-5 symptoms being moderate Stimulant Use Disorder, and 6 or more symptoms being severe Stimulant Use Disorder. Stimulant Use Disorder must be diagnosed by a clinician.

Barratt Impulsiveness Scale Version-11 (BIS-11)

The Barratt Impulsiveness Scale Version-11 (BIS-11) will be used in this study to assess cognitive impulsivity among participants (Clark et al., 2006). It will also be part of the Qualtrics survey. It is a scale used to assess the trait impulsivity on 3 factors across 30 items, developed by Patton et al. (1995). It has a Cronbach’s α ranging from .79 to .83 across four groups they tested on. The first factor, “Attentional Impulsiveness”, is characterized by items like “I am restless at the theater or lectures” and “I have ‘racing’ thoughts”. The second factor, “Motor Impulsiveness”, is characterized by items like “I buy things on impulse” and “I change jobs”. The third factor, “Non-planning Impulsiveness”, is characterized by items like “I say things without thinking” and “I’m more interested in the present than the future”. Each item is measured using
a four-point scale, with the options being 'Rarely/Never', 'Occasionally', 'Often', and 'Almost Always/Always'. The inter-item correlations for these factors range from .46 to .53 ($p < 0.0001$). The responses are assigned scores from 1 to 4, respectively, with a score of 4 reflecting the highest level of impulsivity. Total scores were calculated by summing up all scores, factoring in eleven reverse-keyed items. Higher scores reflected a higher impulsivity.

**Pattern Recognition Memory (PRM)**

The Pattern Recognition Memory (PRM) will be used in this study to assess spatial working memory capability (Ersche et al., 2006). It is taken from the Cambridge Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition Ltd), developed to measure short-term visual-pattern recognition memory. It will be conducted through a computer. During the task, participants will be shown a sequence of 12 visual patterns consecutively at the screen's center and asked to memorize them. These patterns are constructed in a way that makes them challenging for verbal identification. During the recognition portion of the test, individuals will be instructed to choose the previous one between the previously shown pattern and a new one. The patterns will be displayed in reverse sequence compared to their initial showing. This process will be conducted once more with 12 novel patterns. Following a 10 to 20 minutes delay, the second recognition session will take place. Upon completion, the participant is thanked without receiving feedback on their performance. The outcomes will consist of the number and percentage of correct responses, as well as the response time of the participant. Higher numbers of and higher percentage in corrected trials indicate better spatial working memory.
**Controlled Oral Word Association Test (COWAT)**

Controlled Oral Word Association Test (COWAT) will be used in this study to assess verbal fluency in cognitive flexibility (Darke et al., 2000b). COWAT is a subset of Multilingual Aphasia Examination, developed to measure verbal fluency (Benton et al., 1994). A researcher will carry out the process, ensuring that all responses are accurately documented. During the task, participants will be asked to verbally generate as many words as possible that begin with a particular letter of the alphabet, avoiding proper nouns and different forms of the same word. The test progresses through three letters, chosen for their varying levels of associative difficulty based on word frequency in the language. Participant will undergo three one-minute timed trials with the letters C, F, and L, with a stopwatch to track the duration. They are encouraged to persist until the time limit is reached. Responses for each letter trial are recorded by the researcher along with their correctness. Upon completion, the participant is thanked without receiving feedback on their performance. Higher total number of correctness indicates better verbal fluency.

**Two Back test**

A "two-back" task will be used to assess verbal working memory in this study (Mintzer et al., 2005). This task was first developed by Kirchner (1958) to study working memory, and this study will use the version modified by (Cohen et al., 1994). It will be conducted through computer. During the task, participants will view sequences of letters presented individually on the screen and will be asked to press a button when a specific condition was met. They will be required to do the tasks only using their heads without making any vocalization. For the control task, the condition is simply the appearance of the letter "X." However, in the working memory
task, the condition is more complex: participants need to press the button when they see a letter that is identical to the one presented two positions before in the sequence. The tasks differ only by the instructions and the presence of the letter "X" in the control task. Both tasks will have the letters presented for 500 milliseconds with a 1000 millisecond interval between them. Participants will complete ten 60-second blocks of each task, with the tasks switching and a 30-40 seconds rest period in between blocks. In this study, participants will be evaluated based on two measures: first, the ratio of correct button presses to total button presses made, and second, the ratio of correct button presses to the total number of instances where the button should be pressed.

**Procedure**

In order to conduct this study, our initial step involves establishing a collaborative effort with local rehabilitation centers to identify a partner center that will provide a space equipped with computers for our research. Once this partnership is established and participants are recruited, we will arrange transportation for active users from the needle exchange center to the designated study location on the date they chose. Participants currently in a methadone maintenance program will either remain at their center, if it is our chosen location, or be transported to our study site. Healthy participants will be directed to the study location at their chosen time, information which they will receive through a research study platform upon registration.

Upon arrival at the study location, participants will be briefed on the study's overview, the potential risks involved, and the benefits of the study. They will be presented with the survey on Qualtrics started with an informed consent form, which they will be required to read
thoroughly and sign to indicate that they understand that their participation is entirely voluntary and that they may withdraw at any point without any repercussions. Participants will also be informed that they will receive full compensation. For their participation, individuals will receive a compensation of 20 dollars, which they will receive whether they complete all tasks or choose to withdraw prematurely. Following the informed consent process, participants' demographic information and other variables mentioned previously in the materials section will be collected. A clinician will then assess active users for Opioid Use Disorder (OUD) and Stimulant Use Disorder, while methadone maintenance patients will be evaluated solely for Stimulant Use Disorder. After these steps, if they meet any exclusion criteria previously mentioned, they will be offered 20 dollars as compensation. Then, they will be directly taken to the last block of the Qualtrics survey, in which they will be thanked for their participation and provided with a debriefing form that offers detailed insight into the aims and purposes of the study.

If they do not meet any exclusion criteria, then they will engage the four cognitive tasks and measurements, which include the Barratt Impulsiveness Scale Version-11 for cognitive impulsivity, the Pattern Recognition Memory from CANTAB for spatial working memory, the Controlled Oral Word Association Test for verbal fluency, and the Two Back test for verbal working memory. They will first finish the BIS-11 on the Qualtrics survey, and the other three tasks will be carried out in a randomized sequence, with a five-minute intermission between each.

At the conclusion of the study session, individuals will receive a compensation of 20 dollars. Then, they will be taken to the last block of the Qualtrics survey, in which they will be
thanked for their participation and provided with a debriefing form that offers detailed insight into the aims and purposes of the study. Given the sensitive nature of the research, particularly for active users, we will also offer resources and contacts for support services to them following their involvement in the study.

After that, those in the methadone maintenance group will be invited to enroll in a follow-up session scheduled for 85-90 days later as part of a longitudinal component of the study. If a participant returns for this follow-up, they will undergo the same procedure as in the initial session.

**Ethical Considerations**

The level of risk associated with this study is above minimal risk. It includes potentially vulnerable population, which are methadone maintenance patients. Participants, especially active heroin users and methadone maintenance patients, may feel emotional distress when describing their drug use or mental illness history because of the sensitivity and common stigma around this issue. Furthermore, the cognitive tests may bring to light deficiencies that participants were previously unaware of, causing further distress. However, this elevated risk is necessary to address the research questions because in order to study the impacts of opiate on executive functioning, it is imperative to include individuals who are current or former drug users to gain more genuine insights. Moreover, querying about drug use and mental illness history helps control for variables that might affect cognitive test results. Moreover, the study involves the recruitment of active heroin users from needle exchange center, which poses safety concerns for researchers if users are mistrustful or under the influence. However, needle
exchange centers are one of the few places where active heroin users can be reliably found and approached in a somewhat structured environment.

The proposed study is completely voluntary, and no deception is involved in the process. To minimize these risks and ensure participants are truly voluntary, researchers will provide a detailed informed consent process outlining all potential risks and be clear that participants can withdraw at any time of the study. Also, a clear debrief will be offered to participants post-study to address any concerns. In addition, rehabilitation center service and therapy service will be provided to active users. The data collected will be anonymized. While participants’ specific responses might be recorded, they will be only corresponded to the participant id instead of their name or any personal information. This ensures that any data analyzed or shared cannot be traced back to an individual participant.

To minimize researchers’ safety concerns, a clear communication protocol will be established before the recruitment, including regular check-ins with other group members. They will contact staffs in the center beforehand to make sure they can work closely with them, and they will go the needle exchange center during daytime in pairs. Polite and respectful behaviors will be maintained during the recruitment to minimize the risks of resistance and aggressive behaviors from users.

The benefits of the study could potentially overweigh the risks. All participants in the study will receive a 20-dollar monetary compensation as the benefit. Moreover, the rehabilitation center and mental health service will be offered to participants who are active heroin users at the end of the study. The broader scholarly community would benefit from the study, contributing to the body of knowledge surrounding the cognitive effects of drug use.
Additionally, society at large would benefit by having a clearer understanding of the implications of drug use and become more capable of developing effective treatments.

**Anticipated Results**

**Data Analysis Strategy**

Several statistical tests will be employed in this study to analyze and evaluate the hypothetical data and test all hypotheses. The primary dependent variables are the results obtained from four executive function tests, which will be used to assess cognitive impulsivity, cognitive flexibility (verbal fluency), spatial working memory, and verbal working memory.

To evaluate the first hypothesis, a series of ANCOVA (MANCOVA) will be utilized to discern the differences in cognitive test scores between three groups: healthy controls, active heroin users, and methadone maintenance patients. The grouping variable, which is the participant's current drug use status, serves as the independent variable in this analysis. The history of head injury, coded as a dichotomous variable, with 1 for "yes" and 0 for "no", will be included as a covariate to control for its potential confounding effect on cognitive performance.

For the second set of hypotheses, multiple regression analyses will be performed to examine how the number of overdoses and the length of opioid use relate to cognitive functioning separately within the active heroin users and methadone maintenance groups. These analyses will allow us to determine if these factors are significant predictors of performance on the cognitive tests, after accounting for the variance explained by group membership.

Finally, to address the third hypothesis regarding changes and potential reversibility in cognitive functioning over time within the methadone maintenance group, we will conduct a
series of Repeated Measures ANOVA. This analysis will compare cognitive test scores at two
time points, namely, the beginning and the end of a 90-day period, thus providing insights into
the reversibility of cognitive impairments. The length of abstinence will be treated as a
categorical variable with two levels corresponding to the different time points.

**Anticipated Results**

It is hypothesized active heroin users and people on methadone maintenance treatment
will have significantly worse performance on cognitive impulsivity, cognitive flexibility, spatial
working memory, and verbal working memory measurements than healthy controls but
participants on methadone maintenance treatment will perform significantly better than those
currently on heroin. These relationships will still hold after controlling for the history of head
injury. These results are anticipated based on previous research. The relationship between
opioid use and impairments in executive functioning is indicated by numerous studies, which is
characterized by an increased likelihood of impulsive behavior (Lee et al., 2005; Pau et al.,
2002), diminished verbal fluency (Darke et al., 2000; Ornstein et al., 2000; Soyka et al., 2008),
and compromised spatial working memory (Ornstein et al., 2000; Ersche et al., 2006). Although
findings regarding verbal working memory deficits are inconsistent, with some studies showing
significant impairment (Mintzer et al., 2005) and others like Wang et al. (2008) reporting non-
significant difference, the hypothesis remains grounded due to the presence of suggestive, but
not definitive, evidence of impairment in verbal working memory among previous heroin
dependents. It is anticipated that these relationships will remain significant even when the
head injury history is controlled, as evidence suggests head injuries do not significantly
influence cognitive outcomes in these groups (Darke et al., 2000).
It is also hypothesized that active users and methadone maintenance patients with higher number of overdoses and longer length of opioid use will have significantly worse performance on cognitive impulsivity, cognitive flexibility, spatial working memory, and verbal working memory measurements. These results are anticipated based on previous research, which demonstrated a prevalent pattern of risk factors among methadone maintenance individuals (Darke et al., 2000a). These risk factors, such as a high incidence of overdoses and alcohol dependence, have been identified as predictors of diminished cognitive performance, indicating a potential dose-response relationship where increased substance-related adversities correlate with more severe cognitive deficits.

Lastly, it is hypothesized that the length of abstinence has a positive impact on the reversibility of executive functioning, with methadone maintenance patients performing better on the above executive function tests at the end of a 90-day period than at the beginning of the 90 days. These results are anticipated based on previous research. Specifically, Baldacchino et al. (2015) indicates that heroin users undergoing methadone treatment displayed less impairment in impulse control compared to those actively using heroin, pointing to the partial reversibility from the state of abstinence. Thus, the present study anticipates that a longer period of abstinence under methadone maintenance treatment will lead to better recovery in components of executive functioning.

**Scholarly Merit**

By rigorously assessing the impact of opioid addiction on cognitive impulsivity, cognitive flexibility, and different facets of working memory—and the possibility of recovery—the proposed study examines how prolonged substance abuse and subsequent abstinence can alter
cognitive performances. It stands to make a significant academic contribution by exploring the relationship between opioid use and executive function impairments, a domain that has garnered less attention in the broader context of substance use disorder research. This research is poised to clarify the mixed findings in the current literature regarding the cognitive impairments and its reversibility. By incorporating a longitudinal design, the study adds a dynamic perspective to the otherwise static cross-sectional analyses prevalent in current research. Moreover, the study's consideration of a comprehensive range of confounders, such as head injuries and overdose history, refines its methodological approach, allowing for more detailed and accurate interpretations and conclusions. In essence, this study shows the complexities of cognitive recovery in the context of opioid dependency through an effective methodology, ultimately contributing to a deeper understanding of SUD.

**Broader Impacts**

The broader impacts of this study extend beyond the academic perspective, offering vital insights for public health and rehabilitation strategies. By exploring the potential for cognitive recovery in opioid-dependent individuals, the findings could inform therapeutic practices, boosting intervention strategies that target specific cognitive domains affected by opioid use. Additionally, this study's focus on the reversibility of cognitive impairments could potentially inspire hope and motivate individuals in recovery. The possibility of cognitive restoration could encourage adherence to treatment plans, foster a more hopeful outlook among those battling the long-term effects of opioid use, and reduce the self-stigma associated with it, ultimately leading to improved mental health outcomes.
Finally, this study's findings aim to build public's perception of addiction as a condition with cognitive effects but can be improved through treatment, challenging the stigma that views substance dependency primarily as a moral weakness (Henderson & Dressler, 2017). By scientifically highlighting the reversible nature of cognitive impairments due to opioid abuse, the research advocates for compassionate, evidence-based approaches to addiction recovery. It underscores the necessity for policies that emphasize therapeutic interventions over criminalization, fostering a societal shift towards empathetic support and rehabilitation services for individuals struggling with substance use disorders. Such a perspective not only humanizes those affected by addiction but also advocates more health-oriented public policy decisions.
References


