5-1-2022

Evaluating Repetitive Transcranial Magnetic Stimulation to Reduce Opioid Cravings in Opioid Use Disorder

Cameron Duncan

EVALUATING REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION TO REDUCE OPIOID CRAVINGS IN OPIOID USE DISORDER

By

Cameron Duncan

Bachelor of Arts- Nursing
University of Nevada, Reno
2010

Master of Science- Nursing
Grand Canyon University
2012

Doctor of Nursing Practice
University of Arizona
2014

A dissertation submitted in partial fulfillment
of the requirements for the

Doctor of Philosophy-Nursing

School of Nursing
The Graduate College

University of Nevada, Las Vegas
May 2022

UNLV | GRADUATE COLLEGE

Dissertation Approval

The Graduate College
The University of Nevada, Las Vegas

April 1, 2022

This dissertation prepared by

Cameron Duncan

entitled

Evaluating Repetitive Transcranial Magnetic Stimulation to Reduce Opioid Cravings in Opioid Use Disorder

is approved in partial fulfillment of the requirements for the degree of

Doctor of Philosophy-Nursing
School of Nursing

Hyunhwa Lee, Ph.D.
Examination Committee Chair

Rebecca Benfield, Ph.D.
Examination Committee Member

Jennifer Kawi, Ph.D.
Examination Committee Member

Brach Poston, Ph.D.
Graduate College Faculty Representative

Kathryn Hausbeck Korgan, Ph.D.
Vice Provost for Graduate Education & Dean of the Graduate College

Abstract

Opioid Use Disorder (OUD) is a multi-faceted, complex ailment affecting many individuals and their families across the globe. Currently, there are multiple interventions used in the treatment of OUD, many of which are designed to reduce cravings for opioids. Cravings for opioids are a strong predictor of relapse in the disorder. However, many of the interventions used in clinical practice have inherent risks including a potential for abuse and diversion. Repetitive Transcranial Magnetic Stimulation (rTMS) is an outpatient procedure that may be effective in reducing cravings for opioids, thereby reducing relapse.

Methods: This study employed a randomized, single-blind, experimental design with a control group. Ten rTMS or sham treatments were delivered. The intervention group received active rTMS treatment delivered at 10 Hz, 100% resting motor threshold, 2000 pulses delivered in five seconds per train with a 10-second intra-train pause, delivered once daily, five days per week, Monday through Friday for 10 days (10 total treatments). The control group received a sham treatment where the coil was turned 90 degrees counter-clockwise, and the side of the coil rested on the scalp over the area of the skull corresponding to the motor cortex, so the participant felt the coil making contact. Cravings for opioids were measured at various time points throughout the study, including at baseline, after a single treatment, at various increments throughout the delivery of 10 rTMS treatments, and again 30 days after the final treatment. The Desires for Drug Questionnaire (DDQ) was used to measure cravings for opioids. The DDQ contains 13 items to evaluate cravings in three domains: desire and intention, negative reinforcement, and control.

Results: Each of the intervention and control groups had 12 participants who were randomly assigned ($n = 24$). After a single rTMS treatment, the intervention group showed a

significant decrease in the desire domain score ($p < .001$) and negative reinforcement domain score ($p = .01$), and a significant increase in the control domain score ($p = .01$). 30 days after the last rTMS treatment, the intervention group had significant reductions in the desire domain score ($p = .042$) and negative reinforcement domain score ($p = .015$), compared to immediately after 10 rTMS treatments. Mixed effect regression revealed reduced cravings for opioids for the intervention group evidenced by a decreased desire domain score ($p < .001$) and negative reinforcement domain score ($p < .001$), and increased control domain scores ($p = 0.17$) over time. However, only the desire domain score revealed a statistically significant reduction in opioid cravings compared to the control group ($p < 0.001$).

Discussion: rTMS may be a useful intervention for clinicians to consider in the treatment of adults with OUD. These findings also contribute to the body of knowledge to help identify the most effective rTMS protocol to be used to reduce opioid cravings. There was a significant reduction in the desire domain of opioid cravings over time with rTMS treatment compared to the control group, but this reduction was not as prominent in the negative reinforcement and control domains of opioid cravings. This suggests that rTMS should be used with other treatment options to address the negative reinforcement and control domains of opioid cravings. This study also included female participants in the study design suggesting the effect of rTMS on opioid cravings in females may be similar to that demonstrated in males.

Acknowledgments

I am deeply grateful to my Committee Chair, Dr. Hyunhwa Lee, for her guidance and persistence in encouraging me during my journey to complete the requirements for the Doctor of Philosophy in Nursing. I also want to recognize Dr. Rebecca Benfield for her motivation, Dr. Jennifer Kawi for pushing me to think outside the box, and Dr. Brach Poston for his expertise in transcranial magnetic stimulation. I could not have finished this dissertation without each one of you.

Dedication

To my caring, supportive and silly partner, Andy. Thank you for encouraging me every day, for making sure I take time for myself and make time for us, and for picking up my slack over the past few years. I could not have accomplished this without you.

To my friends and colleagues, I appreciate everything you have done to support me along the way. I am especially grateful to my friend, Dr. Pauline Stoltzner, for her encouragement and support along this journey. I am also thankful to Dr. Debera Thomas for encouraging me to enroll in a Ph.D. program and for fostering my growth as a nurse educator and leader

Table of Contents

List of Tables

Chapter 1: Introduction

Introduction

Opioid use disorder (OUD) is a public health concern in the U.S. and around the globe. New, innovative, and comprehensive strategies are needed to combat this disorder. Currently, there are evidence-based options to treat OUD, but there remains a significant prevalence of the disorder in the U.S. Repetitive Transcranial Magnetic Stimulation (rTMS) may be an effective treatment for OUD. rTMS is a noninvasive, magnetic neuromodulation therapy believed to modulate neural circuitry in the brain (McClintock et al., 2018). This chapter will describe the background and significance, state the problem that is OUD, explain the purpose of the study, present the research question, and provide definitions specific to this research study.

Background and Significance

Between 1999 and 2017, almost 400,000 people died from an opioid overdose in the U.S. (Center for Disease Control Prevention, 2018). Eighty-seven thousand adults aged 18 to 25 years and 658,000 adults aged 26 years or more admitted to the use of heroin, an illegal type of opioid, within the past year (Substance Abuse and Mental Health Services Administration [SAMHSA], 2020). Opioid misuse has become an economic burden costing Americans approximately $78.5 billion per year for healthcare, addiction treatment, and criminal justice costs (Florence et al., 2016). Understanding the clinical criteria and treatment options of the disorder is key to identifying potential solutions to this public health crisis.

When an individual uses any type of opioid, OUD may develop. Given the current epidemic and the national as well as global push for curbing OUD as a disease, there is plenty of literature defining OUD and its clinical criteria. The Diagnostic and Statistical Manual-5 (DSM-5) defines OUD as a “problematic pattern of opioid use leading to clinically significant

impairment or distress… within a 12-month period" (American Psychiatric Association [APA], 2013, p. 541). During those 12 months, there must be a combination of at least two symptoms or behaviors present to meet clinical criteria. The full clinical criteria are presented in Appendix A.

Medication-assisted therapy (MAT) is the gold standard for the treatment of OUD (Bell & Strang, 2020; SAMHSA, 2019). However, MAT poses serious risks, including diversion, respiratory depression, overdose, and death (Chilcoat et al., 2019; Faul et al., 2017). There is also a significant lack of access across the nation to this type of treatment (Jones et al., 2015). A less invasive alternative treatment, rTMS, may be an effective option to treat OUD, eliminate the risk of diversion, increase patient safety and access to OUD treatment, and decrease stigma surrounding addiction (Bell & Strang, 2020).

rTMS is a form of brain stimulation that administers electromagnetic currents into the skull to modulate neuronal excitability (Kluger & Triggs, 2007). Depending on the frequency rTMS is delivered, measured in Hertz (Hz), these currents could increase (high frequency) or decrease (low frequency) cortical excitability (Kluger & Triggs, 2007). Different areas of the brain may be targeted by rTMS to disrupt the processes contributing to illness. Specific to addiction, rTMS can be applied to the brain's dorsolateral prefrontal cortex (DLPFC) to alter the biological mechanism contributing to cravings, impulsivity, and other behaviors or thoughts related to addiction (Bellamoli et al., 2014). Dopamine and other neurotransmitter levels can be normalized by rTMS treatment. The electromagnetic coil in which rTMS is delivered depolarizes neurons in the prefrontal cortex and other specific areas of the brain, which may inhibit the release of dopamine and other neurotransmitters (Bellamoli et al., 2014). Furthermore, rTMS therapy has been effective in treating many substance use disorders (SUDs), including cocaine,

methamphetamine, nicotine, and alcohol use by regulating these neurotransmitters (Bolloni et al., 2016; Mishra et al., 2010; Su et al., 2017; Terraneo et al., 2016).

Specific to OUD, Shen and colleagues (2016) demonstrated effectiveness in reducing opioid cravings in males with OUD after one day (one treatment) and five days (five treatments), delivering one rTMS treatment per day. Later, Liu and colleagues (2020) administered 20 treatments to males with OUD, delivering one rTMS treatment per day on a Monday – Friday schedule. This treatment demonstrated a significant reduction in opioid cravings immediately after treatment, at 30 days, and at 60 days after completion of rTMS treatment (Liu et al., 2020). However, the efficacy of rTMS at reducing opioid cravings with more than five, but less than 20 treatments, is unknown. A reduced number of rTMS treatments may elicit the same response as demonstrated by Liu and colleagues (2020) meanwhile decreasing costs and time burdens, and improving adherence to the complete treatment regimen. Based on these findings, it is unknown whether rTMS is effective in females with OUD. It is also unclear whether there is a incremental effect of each treatment on reducing opioid cravings since neither Shen et al. (2016) nor Liu et al. (2020) measured cravings during the rTMS treatment delivery. Instead, Shen et al. (2016) measured cravings at baseline and after the first and last treatments, and Liu et al. (2020) measured at baseline, after last treatment, and 30 and 60 days after the last treatment.

Notably, given that the relapse rate for heroin users is approximately 54% within the first month, it is essential to understand the extended effect of rTMS on OUD after treatment ceases (Rong et al., 2016). It is also important to note that Shen et al. (2016) and Liu et al. (2020) used a single-item measurement tool to assess opioid cravings in these two studies. While the Visual Analog Scale (VAS) is valid and reliable (Kleykamp et al., 2019), it fails to provide data on the

various domains of opioid cravings that may help clinicians develop treatment plans for these individuals in clinical practice.

Statement of the Problem

OUD is a prevalent ailment in the U.S. and around the globe. Currently, there are treatment options for this disorder including the gold-standard MAT. However, this treatment option has inherent risks including diversion and potential misuse or abuse, and also is limited in its availability to the general public. Therefore, this public health concern requires additional, effective treatment options to improve access and reduce the incidence of OUD. rTMS has been demonstrated in the literature to be a potential treatment option, but the specific treatment protocol, longitudinal effect of the treatment, and the durability of the effectiveness at reducing cravings for opioids remain unclear.

Purpose of the Study

According to the American Academy of Colleges of Nursing (AACN), one of the primary roles of a PhD-prepared nurse is to "develop the science" (AACN, 2010, p. 2). This study adds to the scientific knowledge base by filling multiple OUD literature gaps. Furthermore, the results of this study provide new knowledge to guide clinicians and nurses in the treatment of OUD. OUD is a significant public health concern that has economic, social, and physical implications affecting individuals and communities around the globe. It is within the scope and mission of nurses to be part of the solution for this disorder. Based on available evidence, rTMS may be a possible solution for individuals with OUD. More research is needed to fully understand the effect that rTMS treatment has on opioid cravings. Therefore, the purpose of this research study was to test the effect of rTMS on opioid cravings among adult patients with OUD.

Research Question

To further explore the effect of rTMS in OUD beyond what has already been demonstrated in the literature, this research was designed to answer the following research question: Is there a significant change in opioid cravings between intervention and control groups among patients with OUD due to treatment with rTMS?

Definitions

In order to develop a clear understanding of the terminology used to identify the multiple variables in the study, each variable has been given a conceptual definition. Below are the conceptual definitions used in this study:

Opioid Use Disorder is defined conceptually as a disorder described in the DSM-5 evidenced by a "problematic pattern of opioid use leading to clinically significant impairment or distress… within a 12-month period" presenting with an additional set of specific symptoms (APA, 2013, p. 541). The exact definition as presented in the DSM-5 will be used as the definition of OUD in this study.

Opioid cravings are conceptually defined as a desire to use an opioid that can be described along a continuum (Abrams, 2000).

Repetitive Transcranial Magnetic Stimulation is defined conceptually as a noninvasive, magnetic, neuromodulation therapy applied over the DLPFC to elicit the depolarization of neurons and the modulation of neural circuitry (McClintock et al., 2018). rTMS is most often delivered in a series of intermittent pulses, or trains, which represent depolarization of neurons, at a high-frequency (>5Hz) for treatment of SUDs (Gorelick et al., 2014). The pulses are delivered in sets with intra-train pauses until the total number of pulses is delivered. Each pulse is delivered at a specific percentage motor threshold (% MT).

Chapter Summary

Affecting many individuals and families in the U.S. and around the globe, OUD is an illness that requires safe, effective, and accessible treatment options. Though there are evidence-based interventions available for the treatment of this disorder, OUD is both complex and prevalent and calls for additional, innovative treatment strategies. rTMS is a noninvasive treatment option that may be effective in the treatment of OUD. Further research is needed to fully understand the specific treatment protocol of rTMS therapy, the effect of rTMS on opioid cravings, and the durability of the effect in OUD.

Chapter 2: Review of the Literature

Introduction

Treatment for SUDs, including OUD, has been documented in the literature to be a global public health priority in need of innovative approaches to combat the disorder (Cochran et al., 2020). Specifically, rTMS has been studied as a potential treatment option for methamphetamine, cocaine, cannabis, alcohol, and opioid use disorders. However, there is only limited data on the effectiveness of rTMS at reducing opioid cravings in individuals with OUD. This chapter will present a summary of a literature review, describe the guiding theoretical and conceptual frameworks, and define the specific aims and hypotheses of the study.

Literature Review

To fully understand OUD and the use of rTMS as a potential treatment option, the two key variables, rTMS and cravings, were examined. Two separate literature review search methods were utilized for each of the variables. For this discussion, cravings for the various substances will be referred to as *cravings* since cravings for addictive substances are broadly defined in the literature (Sayette, 2016).

rTMS

To identify research specific to the use of rTMS on substance use disorders, a review of articles describing the use of rTMS on adults with SUDs was performed. Three electronic databases (PubMed, Scopus, and APA PsychInfo) were accessed to identify literature related to rTMS and SUD including search terms such as “repetitive transcranial magnetic stimulation AND:” “methamphetamine,” “opioid,” “cocaine,” “nicotine,” “heroin,” “alcohol,” “substance,” “addiction” or “dependence.” A total of 31 articles were extracted examining the effectiveness of rTMS at reducing opioid, methamphetamine, or cocaine cravings.

Key Findings

Three substances from the literature search were selected for inclusion in this review due to them being illicit substances: opioids, methamphetamine, and cocaine. Among the three substances, there is variation in the components of the treatment protocol. These inconsistencies must be reviewed to examine the specific effect they have on the reduction of opioid cravings. More specifically, the role of rTMS frequency, intensity, pulses, and the number of treatments will be examined.

Frequency. All of the studies evaluating the effect of rTMS on reducing cravings for substances utilized rTMS delivered at a high frequency of 10 Hz or more. The majority of studies utilized 10 Hz, with only a few exceptions (Pettorruso et al., 2018; Pettorruso et al., 2019; Terraneo et al., 2016; Liu et al., 2017). Despite the variance in results of the effectiveness of reducing cravings for methamphetamine and cocaine, both studies evaluating the effect of rTMS on opioid craving used a 10Hz frequency for treatment administration.

Intensity. All of the studies extracted in this review utilized the resting MT to determine treatment intensity. The intensity of treatment administration varied from 80% to 110% MT. However, the most common rTMS intensity used was 100% MT. It is important to note that in one study, it was initially planned to administer treatment at 100% MT but the intensity was reduced to increase patient comfort during treatment (Su et al., 2017). In another study, treatment was started at 90% MT and gradually increased over 3 days to 110% to improve patient tolerability (Martinez et al., 2018). Both studies evaluating rTMS on opioid cravings used 100% MT and no participants left the study because of intolerance to treatment (Shen et al., 2016; Liu et al., 2020).

Pulses. A wide range of pulses delivered during each rTMS treatment was found in the

literature ranging from 1000 to 2400 pulses. The studies that delivered 1000-1200 pulses did not result in a reduction of cravings for the substance (Bolloni et al., 2016; Martinez et al., 2018). Oppositely, the studies that administered 2400 pulses per rTMS treatment all resulted in the reduction of cravings, but were also administered at 15Hz and twice per day (Pettorruso et al., 2018; Pettorruso et al., 2019; Terraneo et al., 2016). Both studies evaluating opioid cravings administered 2000 pulses per day resulting in a reduction of craving scores (Shen et al., 2016; Liu et al., 2020).

Number of Treatments. Specific to the treatment of opioid cravings, Shen and colleagues (2016) administered five total rTMS treatments, while Liu and colleagues (2020) administered 20 total treatments using the same treatment protocol resulting in a significant reduction of opioid cravings. However, Shen and colleagues (2016) did not evaluate whether five rTMS treatments would result in the same 30-, 60- and 90-day reduction of opioid cravings demonstrated by Liu and colleagues (2020) after 20 rTMS treatments.

Opioid

Cravings for opioids were reduced by rTMS. Shen and colleagues (2016) and Liu and colleagues (2020) applied 2000 pulses of rTMS at 10 Hz to the DLFPC at 100% MT using a 5-s on and 10-s intra-train pause administration schedule. Shen and colleagues (2016) examined a total of 20 participants while administering five treatments of rTMS, one per day, over five consecutive days, which resulted in a statistically significant reduction of opioid cravings after one and a total of five rTMS treatments. Liu and colleagues (2020) administered a total of 20 rTMS treatments of 2000 pulses each at 100% MT, one treatment per day over 28 days using a Monday – Friday administration schedule, to a much larger sample (n = 118). Liu and colleagues

(2020) found that rTMS significantly reduced opioid cravings, and this effect persisted 30 and 60 days after treatment.

Methamphetamine

Cravings for methamphetamine were also reduced by rTMS. In three randomized, double-blind, experimental studies, high-frequency rTMS was applied to the left DLPFC and a visual cue was used to induce methamphetamine cravings (Liang et al., 2018; Liu et al., 2017; Su et al., 2017). Su and colleagues (2017) applied rTMS at 10Hz for 1500 pulses at 80% MT, which resulted in fewer cravings after one and after a total of five treatments compared to the control group. The lower intensity of 80% MT was used in this study to help reduce scalp discomfort for the participants, although the original treatment protocol was set to be administered at 100% MT, and a reduced number of rTMS pulses were delivered in an attempt to reduce the risk for seizure (Su et al., 2017). Liang and colleagues (2018) applied rTMS at 10 Hz for 2000 pulses, a greater number of pulses than Su and colleagues (2017), at 100% MT for ten treatments and reported statistically significant reductions in withdrawal, cravings, sleep disturbances, anxiety, and depression compared to the control group. Liu and colleagues (2019) also observed a reduction in methamphetamine cravings after 30 and 60 days compared to the control group after applying rTMS at 10 Hz for 2000 pulses at 100% MT for 20 treatments. Lastly, a randomized control trial was conducted by Liu and colleagues (2017) applied rTMS to the left or right DLPFC, using (a) 10 Hz for 5-s on and 10-s off for a total of 2000 pulses at 100% MT or (b) 1 Hz for 10 min for a total of 600 pulses at 100% MT. Both administration protocols resulted in a statistically significant reduction of cravings after a 5-day treatment course compared to the control group, and demonstrated that high and low-frequency on the right or left DLPFC may be effective at reducing methamphetamine cravings (Liu et al., 2017).

Cocaine

Conflicting findings exist regarding rTMS's effect on cocaine cravings. In three studies, rTMS was administered with 2400 pulses at 15 Hz to the left DLPFC, resulting in decreased cocaine cravings (Pettorruso et al., 2018; Pettorruso et al., 2019; Terraneo et al., 2016). First, in a nonrandomized, one-group pilot study, cocaine cravings were decreased after four weeks of rTMS treatment at 100% MT administered twice per day, five days per week for four weeks, followed by one treatment per week for two weeks (Pettorruso et al., 2018). In a quasi-experimental study, Pettorruso and colleagues (2019) used the same treatment protocol and found a reduction in cocaine cravings, depression, anxiety, and anhedonia after four weeks. Employing a randomized, open-label, experimental design, Terraneo and colleagues (2016) applied rTMS at 15 Hz and 100% MT for eight treatments, five days consecutively, then once per week for three weeks, and demonstrated the durability of rTMS using weekly maintenance.

Next, in two randomized studies with a control group, rTMS was administered bilaterally to the DLPFC at a lower frequency of 10 Hz (Bolloni et al., 2016; Martinez et al., 2018). Bolloni and colleagues (2016) administered 1000 pulses of rTMS at 100% MT while Martinez and colleagues (2018) delivered 1200 pulses of rTMS between 90-110% MT. Neither study with rTMS administered at 10 Hz resulted in a significant reduction of cravings for cocaine (Bolloni et al., 2016; Martinez et al., 2018).

Synthesis of rTMS Protocol

Despite the numerous published studies examining the effect of rTMS on SUDs, gaps in this literature remain. This study presents an rTMS treatment protocol that aimed to bridge some of these gaps and increase understanding of rTMS as a treatment option for OUD. In this study and based on the literature reviewed, 10 rTMS treatments were administered. One treatment per

day was delivered Monday-Friday over two weeks using the same treatment protocol as Liu and colleagues (2020). rTMS at 10 Hz was administered to the left DLFPC at 100% MT for 2000 pulses using a 5-s on and 10-s intra-train pause administration schedule. This methodology allowed the Student Investigator (SI) to examine the effect of rTMS on opioid cravings after a single treatment in male and female adults with OUD. Changing the total number of rTMS treatments informs clinicians of the effect of fewer rTMS treatments, which may reduce the cost and time burdens for participants receiving treatment.

Participant Selection

Both of the previously described studies evaluating the impact of rTMS on opioid cravings included only male participants because males more commonly have OUD (Liu et al., 2020). Excluding females from these studies limits understanding of the effect of rTMS on OUD in this population. Liu and colleagues (2017) found that rTMS effectively reduced methamphetamine cravings in females and there was no difference in the effect of rTMS treatment between males and females. This study examines the impact of rTMS on opioid cravings in both males and females in the intervention and control groups.

Cravings

To explore the literature for a more thorough understanding of the role and impact of cravings in OUDs, a separate review of the literature was performed. A search of PubMed, Scopus, and APA Psych Info was performed using the following search terms: “craving,” “opioid craving,” and “substance cravings.” 12 articles were selected by the SI based on their relevance to the topic of this study. A summary of the evaluation of cravings for substances in the rTMS studies previously reviewed will also be examined in this section.

Cravings for substances are a strong predictor of relapse (Tsui et al., 2014). For this reason, cravings are the dependent variable in this study. It is essential for researchers and clinicians to fully understand cravings and their influence on OUD. In fact, the subjective experience of craving has been the focus of multiple research studies (Kleykamp et al., 2019). However, addiction theorists have struggled to conceptualize cravings, resulting in various descriptions of cravings in the literature (Sayette, 2016). Tiffany (1990) described cravings as thoughts motivating drug use. Other authors describe cravings as a desire to use a substance that can be described along a continuum (Abrams, 2000), and some argue that a mild craving is an oxymoron (West & Brown, 2013). Marlatt (1985) described cravings as a desire to experience a substance's effect, while Tiffany and Drobes (1991) suggested that cravings include the anticipation of a drug's effect, the intention to use the drug, and the desire for the drug. Some authors argue that cravings are a conscious recognition of the desire to use a drug (Baker et al., 2006), whereas others suggest cravings can exist subconsciously (Berridge & Robinson, 1995). Of much importance, Franken and colleagues (2002) went further than other researchers and described cravings as the "most characteristic experience in addiction," is a mediator of relapse, and impacts addictive behaviors (p. 675). They additionally described cravings in three domains: desire and intention, control, and negative reinforcement, which will be discussed more in-depth later in this chapter.

Lastly, from a biological perspective, cravings are part of the core psychopathology of various substance use disorders (Kuhn & Gallinat, 2011). When a specific substance such as an opioid is used, dopamine is increased resulting in a pleasurable effect (Kalivas & Volkow, 2005). Once the level of dopamine decreases over time, the desire to obtain that pleasurable effect or craving occurs (Kuhn & Gallinat, 2011). In the brain, the "final common pathway" is the central

area of the brain responsible for these cravings (Kuhn & Gallinat, 2011). This pathway includes projections from the prefrontal cortex, which includes the anterior cingulate cortex and the orbitofrontal cortex, the nucleus accumbens core, and the ventral palladium (Kuhn & Gallinat, 2011). The relationship between this final common pathway and opioid cravings will be further discussed later in this chapter as it relates to the conceptual model guiding this study.

Measurement of Cravings

Because there is such a spectrum of descriptions of cravings in the literature, this study employed a more comprehensive assessment tool than what was used to measure opioid cravings in the two OUD studies with rTMS (Liu et al., 2020; Shen et al., 2016). More specifically, this study employed the Desires for Drug Questionnaire (DDQ) (Franken et al., 2002) to evaluate cravings on three different domains, including desire and intention, negative reinforcement, and control (Yen et al., 2016), whereas the previous researchers utilized a single item measurement tool, such as the VAS (Liu et al., 2020; Shen et al., 2016). The DDQ is a reliable and valid tool that provides data about the three domains of opioid cravings: desire and intention, negative reinforcement, and control (Yen et al., 2016). These three domains align directly with the Biopsychosocial Model, the theoretical framework that will be used to guide this study (Appendix B). Because craving is a key predictor of relapse in OUD (Tsui et al., 2014), this study aimed to evaluate if a reduced cravings score can be maintained 30 days after treatment with rTMS in adults with OUD.

Additionally, previous authors only evaluated opioid cravings after a single treatment or after the full treatment course was completed (Liu et al., 2020; Shen et al., 2016). As a result, the evidence fails to inform clinicians about the longitudinal effect of varying numbers of rTMS treatments on opioid cravings. This study aimed to examine the longitudinal impact of rTMS on

opioid cravings at data points throughout the delivery of rTMS treatments by assessing opioid cravings after one, three, five, eight, and 10 treatments.

Previous OUD studies evaluating the effect of rTMS on cravings used the single-question VAS to evaluate cravings for a particular substance (Liu et al. 2020; Shen et al., 2016). Despite the VAS's established validity and reliability, this tool does not provide clinicians with specific information about the various domains of cravings for substances. This study aimed to measure the effect of rTMS on three domains of opioid cravings by using the DDQ (Franken et al., 2002) (Appendix C). Approval for the use of the DDQ was obtained (Appendix D). This additional information provided by the DDQ about an individual's opioid cravings provides vital information for clinicians in preparing a treatment plan for their clients. It may also guide researchers to further explore the various theoretical domains of opioid cravings.

Finally, Liu and colleagues (2020) examined the longitudinal effect of 20 rTMS treatments on reducing opioid cravings. The researchers collected opioid craving scores at baseline, at the conclusion of treatment (day 30), and again 60 and 90 days after rTMS treatment was complete (Liu et al., 2020). Comparing the VAS scores from baseline to day 30 (Estimate = -29.43, SE = 4.11, $p < 0.001$), day 60 (Estimate = -27.57, SE = 4.26, $p < 0.001$), and day 90 (Estimate = -28.30, SE = 4.94, $p < 0.001$), opioid cravings were significantly reduced, revealing a 60-day lasting reduction of opioid cravings post-treatment (Liu et al., 2020). Based on these findings, this SI anticipated there will not be any further reduction of opioid cravings after day 30 as a result of rTMS. Therefore, this study evaluated whether reduced opioid craving scores could be maintained for 30 days after 10 rTMS treatments using this protocol.

Combined, these gaps in the literature have guided this research development. By examining the effect of a single treatment of rTMS on opioid cravings in both genders,

evaluating the longitudinal effect of rTMS on opioid cravings, measuring the impact of rTMS on the three domains of opioid cravings, and assessing the 30-day stability of opioid cravings after 10 rTMS treatments, this study increases our knowledge of OUD. Linked with theoretical underpinnings and a conceptual understanding of OUD, this protocol reveals a shorter and more effective option for OUD treatment.

Theoretical Framework and Conceptual Model

This study was guided by the Biopsychosocial Model by George Engel (1977), combined with a conceptual and neurobiological understanding of addiction (Koob & Volkow, 2016) (Appendix B). The Biopsychosocial Model was constructed specifically for physicians in caring for patients, expanding the biomedical model (Engel, 1977). Today, this model is utilized as a guiding framework in multiple interdisciplinary professions, including medicine (Kusnanto, 2018), psychology (Darnall et al., 2017), social work (Minimol, 2016), and addiction treatment (Salihu et al., 2019). In sum, the Biopsychosocial Model theorizes that health and illness are impacted by biological, psychological, and social influences (Engel, 1977). Abiding by this model, OUD is influenced by one or more of these factors. This study integrates biological, psychological, and sociocultural influences into the study design.

Addiction, including OUD, is commonly understood to be a result of a three-stage cycle: binge/intoxication, withdrawal/ negative affect, and preoccupation/anticipation (Koob & Volkow, 2016). A significant factor contributing to the difficulty in opioid cessation and abstinence is the presence of cravings for opioids (Kakko et al., 2019). Cravings are directly related to the third phase of the neurobiology of addiction, preoccupation/anticipation, where dopamine, cortisol, and other neurotransmitters and neuromodulators are altered (Fatseas et al., 2011; Koob & Volkow, 2016). The preoccupation/anticipation and binge/intoxication stages may

occur concurrently, feeding into this negative loop (Koob & Volkow, 2016). This negative cycle leads to repetitive use and the desire to use the substance.

Of the various neurotransmitters and neuromodulators impacted in SUDs, a biologic aspect, the most important is the role of dopamine. Dopamine is the main neurotransmitter affected though direct or indirect effects on dopamine neurons (Koob and Volkow, 2016). The mesocorticostriatial dopamine systems play a leading role in producing the rewarding effects of practically all drugs of abuse, including opioids in OUD (Wise, 2009). Specifically, opioids stimulate the mu opioid receptor in the ventral tegmental area and increases striatal dopamine release (Koob and Volkow, 2016). During the binge/intoxication stage of addiction, when opioids are used there is a rapid and sizeable release of dopamine into the ventral striatum (Volkow et al., 2007). When there is such a rapid increase in dopamine, low-affinity D1 receptors are activated, resulting in the feeling of euphoria and other rewarding effects (Koob & Volkow, 2016). Overtime, this increase of dopamine leads to dysregulation within the prefrontal cortex and a loss of control of the dopamine-reward system.

Drugs of abuse, including opioids, have a significant effect on the response to previously stimulated neutral stimuli (Koob & Volkow, 2016). Moreover, those neutral stimuli become augmented to match specifically with the drug of abuse; this phenomenon is called condition reinforcement (Koob & Volkow, 2016). Through this process, the neutral stimuli reinforce behaviors, a sociocultural aspect, to elicit the same response to activate their own reward called incentive salience (Koob &Volkow, 2016). Incentive salience, a psychological aspect, is broadly defined as “motivation for rewards derived from both one’s physiological state and previously learned associations about a reward cue that is mediated by the mesocorticolimbic dopamine system” (Koob & Volkow, 2016, p. 4). Having “executive control over incentive salience is

essential to maintain goal-directed behavior and flexibility of stimulus-response associations" (Koob & Volkow, 2016, p.4). As a result of both conditioned reinforcement and incentive salience, the learned association with repeated exposure to the opioid, created a strong motivation to seek the reward. In sum, the ability of these conditioned stimuli to trigger various circuits strengthens the addiction cycle and helps to explain the intense desire for the drug, opioid cravings (Koob & Volkow, 2014).

To stop this negative loop in addiction, treatment should target the area of the brain that plays a significant role in the development of OUD. Specifically, the DLPFC should be targeted. Human brain imaging studies demonstrate that stimulation of dopamine receptors is positively associated with baseline metabolic activity in frontal cortical regions, and is inversely associated with the rewarding effects of drugs, resulting in decreased drug consumption (Volkow et al., 2019). Particularly, decreased activation of dopamine receptors is associated with decreased metabolic activity in the DLFPC, among other areas in the same region (Volkow et al., 2019). Because these regions are responsible for incentive salience, inhibitory control, and decision-making, one can hypothesize that a decrease in dopamine receptor activation would result in an increased motivational value of drugs, loss of control over drug intake, and compulsive drug intake (Volkow et al., 2019).

In sum, targeting the DLPFC with rTMS can help stabilize multiple neurotransmitters and neuromodulators, disrupting the addiction cycle, by eliciting the depolarization of neurons and the modulation of neural circuitry (McClintock et al., 2018). Appendix E presents the various neurotransmitters affected by rTMS in the treatment of OUD.

Research Question, Hypotheses, and Specific Aims

This research was designed to answer the following research question: Is there a

significant change in opioid cravings between treatment and control groups among patients with OUD due to treatment with rTMS. To answer this research question, the following specific aims were developed:

Aim 1. To evaluate the effect of rTMS on reducing opioid cravings.

H1. The intervention group's cravings for opioids will be reduced compared to the control group after a single rTMS treatment.

H2. The intervention group's cravings for opioids will be reduced after one rTMS treatment compared to baseline.

H3. The control group's cravings for opioids will be similar to their baseline after a single rTMS treatment.

Aim 2. To evaluate whether a reduced cravings score is sustained 30 days after treatment with rTMS in adults with OUD.

H4. The cravings for opioids in the intervention group 30 days after treatment will be similar to the cravings for opioids immediately after 10 rTMS treatments and will remain reduced compared to control group.

Aim 3. To examine the longitudinal effect of rTMS on reducing opioid cravings throughout the delivery of rTMS treatments delivered once per day, Monday - Friday, in adults with OUD by assessing opioid cravings after one, three, five, eight, and 10 treatments.

Aim 4. To measure the effect of rTMS on three domains of opioid cravings: desire and intention, control, and negative reinforcement.

H5. The intervention group's cravings for opioids will be reduced in one or more domains of opioid cravings at each craving measurement compared to baseline.

Hypothesis 5 will be used to predict and evaluate both Aims 4 and 5.

Chapter Summary

In this chapter, the literature that is available supporting rTMS as a promising treatment strategy was presented. Opioid cravings were explained in their relationship to OUD, demonstrating their significance as the dependent variable in this study. Due to the complexity of cravings in SUDs, and to reduce opioid cravings and the prevalence of OUD, innovative interventions guided by theoretical and conceptual frameworks are needed. Therefore, the Biopsychosocial Model and a conceptual model of addiction were presented with particular attention to the role of neurotransmitters and their connection to opioid cravings. Given the complexity of OUD, comprehensive strategies must be employed to significantly address the biological, psychological, and sociocultural factors of the disorder to help to curb the disorder.

Chapter 3: Methods

Introduction

To evaluate the effect of rTMS on reducing opioid cravings in adults with OUD, a comprehensive research methodology was employed to address this study's specific aims and answer the study's research question. This chapter will explain the research methodology used, the study design and procedures, and describe the intended sample, measurements, data collection methods, and data analysis.

Study Design

This study employed a randomized, single-blind, experimental design. Participants were randomly assigned to two groups using a computer-based randomization program: intervention and control groups. Only the SI knew to which group the participants are assigned, and the participants were informed that they may have been assigned to either the intervention or control group. Multiple studies evaluating the effect of rTMS on SUDs utilized a single-blind approach as was used in this study, including the two studies specific to opioids (Shen et al., 2016; Liu et al., 2020). This approach directly allowed the SI to pursue the study's aim to examine the effect of rTMS on reducing opioid cravings in adults with OUD.

Additionally, this study was guided by the Biopsychosocial Model (Engel, 1997). None of the previous research identified in the literature review studying the effect of rTMS on SUDs described a theoretical framework to guide their study. By incorporating this model, the research design focused on the biological, psychological, and sociocultural influences in OUD by administering rTMS treatment and evaluating opioid cravings in adults with OUD.

Procedures

A comprehensive research plan was developed to evaluate the effect of rTMS on opioid cravings. In this section, the intended sample, setting, measurements, recruitment, protection of human subjects, data collection methods, intervention, and data analysis will be described.

Sample

To examine the effect of rTMS on reducing opioid cravings in adults with OUD and fully answer the research question, we included participants who represent the population we were examining: adults with OUD. Convenience sampling was used to recruit participants. Table 1 lists the study inclusion and exclusion criteria.

Table 1: Participant Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Persons aged 18—64	Currently prescribed pharmacotherapy for a substance use disorder.
Used heroin in the past 30 days.	Diagnosis of a psychotic disorder or bipolar I disorder.
Have a history of opioid use for at least one year.	Comorbid diagnosis of another substance use disorder (excluding nicotine).
Meets DSM-5 criteria for OUD (Appendix A).	History of seizures or other relevant neurological disorders including organic brain disease, epilepsy, stroke, brain lesions, multiple sclerosis, previous neurosurgery, or personal history of head trauma that resulted in a loss of consciousness for > 5 min and retrograde amnesia for > 30 min.
	Presence of non-fixed metal in body 30 cm to treatment coil and clinician clearance using the TMS Patient Screening Form (Appendix F).

Note: Opioid cravings are described in the DSM-5 clinical criteria for a diagnosis of OUD and have been shown to predict relapse and recurrent substance use in those with SUDs (APA, 2013; Courtney et al., 2016; Fatseas et al., 2011; McHugh et al., 2014).

Based on the outcomes from Shen and colleagues' (2016) study, a power analysis was conducted using the estimated effect size of 1.5, alpha = 0.05, and a power of 95%, which yielded a minimum sample size of 8 participants per group (Appendix G). The effect size was selected based on the average effect size of the two measurements, after a single rTMS treatment and after 5 rTMS treatments, in the Shen and colleagues (2016) study. Also, none of the previous studies used the DDQ to measure cravings, instead, the VAS was used; therefore, craving data measured by the VAS was used to calculate the effect size used in this current study (Shen et al., 2016; Liu et al., 2020). Although no participants left the study conducted by Shen and colleagues (2016), a larger-scale study demonstrated an attrition rate of approximately 13% (Liu et al., 2020). Whereas both Shen and colleagues' (2016) and Liu and colleagues' (2020) studies took place in inpatient rehabilitation programs, the current study took place in an outpatient setting. To account for a possibly higher attrition rate, we included an additional four participants in each group to allow for possible attrition of 33%. Thus, the control and intervention groups each included 12 participants, for a total sample size of 24.

Setting

This study took place in an outpatient mental health clinic. This clinic is located in Reno, NV, in Washoe County, and is comprised of Psychiatric Mental Health Nurse Practitioners, Family Nurse Practitioners, Marriage and Family Therapists, and Licensed Clinical Social Workers. rTMS is currently used at this location to treat various mental health disorders. Primary care, medication management for mental health and SUDs, psychotherapy, and case management are services offered in this location.

To help mitigate the spread of coronavirus, anyone entering the clinic was screened by the clinical staff for any signs, symptoms, or recent exposure to someone diagnosed with

coronavirus. Anyone with recent exposure or current signs or symptoms of the coronavirus (fever, chills, loss of taste or smell, cough, shortness of breath) was not allowed to enter the clinic. Facemasks were required for anyone permitted access to the clinic and must wear the facemask for the entirety of the visit. Those who did not have a facemask were offered one free of charge. The rTMS device was placed in a room approximately 14x14 feet in size. There was a maximum of two people in the room at any given time (participant and SI). This room is of ample size to allow for one participant and the SI to maintain a six-foot distance from each other except when closer contact is required for the setup of the rTMS device. All participants were made aware of the potential risks for exposure regardless and notified of access to care as needed.

Measurements

Gender, age, method of heroin use, length of heroin use, and time since the last heroin intake were collected as potential factors associated with the outcome of treatment. The level of opioid cravings was evaluated using DDQ, which has been validated by Franken and colleagues (2002). The DDQ contains 13 items to evaluate cravings on three different domains, including desire and intention, negative reinforcement, and control (Yen et al., 2016). The domain scores and total scores were calculated based on the original scoring method (Appendix C). This tool has been used in other studies to effectively measure cravings (Ashrafioun, 2016; De Jong, 2006; Jafari et al., 2017; Tsui et al., 2014). The DDQ demonstrated reliability using Cronbach's alpha > 0.79 after removing the seventh question due to low alpha = 0.37 (Franken et al., 2002). The test-retest reliability using intraclass correlation coefficient (ICC) is > 0.70 (Franken et al., 2002). In this study, the 12-item DDQ, without the item #7 from the original version, was self-

administered before and after rTMS treatment on day one, after treatment on day 3, before treatment on day 8, after treatment on days 10 and 12, and again on day 42 (Appendix I).

Recruitment

Study participants were recruited after the IRB approval at the University of Nevada, Las Vegas. The SI initiated recruitment, which was multi-faceted. The first stream of participants was recruited from within the outpatient mental health clinic described above. The nurse practitioners in this practice were informed of the study details, inclusion and exclusion criteria, and instructions on how to refer participants to the study. In addition, the SI informed specific community providers about the research study, and the inclusion and exclusion criteria, and elicited referrals from those medical offices for possible inclusion in the study. These community providers included, but were not limited to, Advanced Practice Primary Care, Quest Counseling and Consulting, Bristlecone Family Resources, and New Frontier Treatment Center. Upon informing these recruitment sources, they were provided with a printout of the inclusion and exclusion criteria, and information about how to refer the participant for potential inclusion in the current study.

Informed Consent

The SI obtained informed consent from each participant at the initial interview after determining if they met the inclusion and exclusion criteria. The informed consent form included and addressed all of the potential risks and benefits of the study, in addition to the study details (Appendix H). Every participant signed the informed consent form if they agreed to participate after they were given an opportunity to ask any questions related to the study.

Data Collection Methods

During the initial interview, the SI collected each participant's gender, age, method of heroin use, length of heroin use, and time since their last use of heroin. All participants in the intervention and control groups completed the DDQ for opioid cravings during the administration of rTMS treatment or sham treatments. All subject data were de-identified and coded to protect the anonymity of the study participants, and were recorded and stored in the UNLV secured cloud drive.

The DDQ for opioid craving was administered before and after rTMS treatment on day 1, after treatment on day 3, before treatment on day 8, after treatment on days 10 and 12, and lastly on day 42 (Appendix I). This specific timeline for opioid craving measurement using the DDQ was selected to evaluate the longitudinal effect of rTMS at various time intervals. Opioid craving levels at baseline enabled the SI to evaluate the hypothesis that the intervention group's craving scores would be reduced after one rTMS treatment. Opioid craving level after the first treatment (day 1) was selected to assess the effectiveness of rTMS after a single treatment compared to the control group. This measurement helped to support or refute the hypothesis that the intervention group's craving scores will be reduced compared to the control group after a single treatment and that the control group's craving scores will be the same compared to baseline. Opioid craving levels on day 5 allowed the SI to assess the effectiveness of rTMS after five rTMS treatments and compare the results of this study to the positive results demonstrated by Shen and colleagues (2016).

Opioid craving levels on days 3, 5, and 8 were used in the analysis to test the hypothesis that the intervention group cravings will be reduced at the various time intervals throughout treatment. Opioid craving levels on day 3 informed clinicians on the effectiveness of more than

one, but less than five rTMS treatments, potentially reducing the time commitment of patients and clinicians and decreasing any risk associated with additional treatments. Opioid craving levels before treatment on day 8 allowed the SI to assess whether the five treatments had a lasting effect over two days without treatment, which informs clinicians of the short-term durability of the craving reduction, which has not yet been demonstrated in the literature. Opioid craving levels on day 12 allowed the SI to evaluate the effectiveness of 10 rTMS treatments, which is half the number of treatments administered in the study by Liu and colleagues (2020), potentially reducing the time commitment, cost, and risk associated with additional 10 treatments. Finally, opioid craving levels on day 42 inform the SI and clinicians of the lasting effect of rTMS at reducing cravings over 30 days post-treatment and compare those findings to the results from a similar study (Liu et al., 2020).

Intervention

The SI, who is a Psychiatric Mental Health Nurse Practitioner with extensive training in administering rTMS, administered all rTMS treatments according to the study procedures and protocol to facilitate consistency and fidelity. For two continuous sets of Monday through Friday, each participant received one rTMS or control treatment per day for a total of 10 days. During the administration of treatment, participants were instructed to watch calming images of nature (e.g., bodies of water, animals, other persons meditating) on the television screen and were listening to nature sounds (e.g., waves, birds, soft tones). They were not allowed to use electronics, read books, or any other extracurricular activity throughout the treatment administration.

rTMS Intervention Group. The resting motor threshold was determined by observing a visual twitch in the contralateral abductor policis brevis at the beginning of each participant's

first rTMS treatment. The coil was positioned over the area of the skull corresponding to the motor cortex and will be adjusted at 0.1cm intervals along the sagittal plane until the point of maximum visual twitch is identified. Then, the coil was adjusted one degree along the coronal plane until each pulse resulted in an isolated movement of the contralateral (right) abductor policis brevis. Finally, the intensity of each pulse was reduced to the lowest intensity that reliably produced movement in the contralateral hand (Li and colleagues, 2013).

Active rTMS treatment was delivered at 10 Hz, 100% resting motor threshold, 2000 pulses delivered in five seconds per train with 10-second intra-train pause, delivered once daily five days per week, Monday through Friday for 10 days (10 total treatments). This protocol was adapted from Shen and colleagues (2016), who did not report any adverse events. Liu and colleagues (2020) also used the same protocol and only reported mild side effects of dizziness, headache, and insomnia, which were resolved by the 30-day follow-up. However, it is unclear whether these side effects resolved sooner than the 30-day follow-up (Liu et al., 2020).

Control Group. The control group underwent the same seat positioning and comfort measures but did not have a resting motor threshold determination. The coil was turned 90 degrees counterclockwise, and the side of the coil rested on the scalp over the area of the skull corresponding to the motor cortex, so the participant felt the coil making contact (Liu et al., 2020). The same treatment protocol in the active rTMS group was initiated to mimic the sound of rTMS treatment, though no pulses were delivered to the participant because of the coil rotation (Li, 2013).

Data Analysis

In this study, SPSS (version 28) was used for analyzing the data. The specific statistical analysis plan used for evaluating the hypotheses is displayed in Table 2.

Table 2: Statistical Analysis

Aim	Hypothesis	Statistical Analysis
1. To evaluate the effect of rTMS on reducing opioid cravings.	H1. The intervention group's cravings for opioids will be reduced compared to the control group after a single rTMS treatment.	Independent T-test
	H2. The intervention group's cravings for opioids will be reduced after one rTMS treatment compared to baseline.	Paired T-Test
	H3. The control group's cravings for opioids will be similar to their baseline after a single rTMS treatment.	Paired T-test
2. To evaluate whether a reduced cravings score is sustained 30 days after treatment with rTMS in adults with OUD.	H4. The cravings for opioids in the intervention group 30 days after treatment will be similar to the cravings for opioids immediately after 10 rTMS treatments and will remain reduced compared to control group.	Mixed Regression Model
3. To examine the longitudinal effect of rTMS on reducing opioid cravings throughout the delivery of rTMS treatments delivered once per day, Monday - Friday, in adults with OUD by assessing opioid cravings after one, three, five, eight, and 10 treatments. 4. To measure the effect of rTMS on three domains of opioid cravings: desire and intention, control, and negative reinforcement.	H5. The intervention group's cravings for opioids will be reduced in one or more domains of opioid cravings at each craving measurement compared to baseline.	Mixed Regression Model

The distribution of the data was evaluated before conducting the analysis to ensure the data meets the required test assumptions. The nonparametric analysis method was used when the

data did not meet the assumptions. The chi-squared test was used to ensure statistical equivalence in the distribution of gender between the treatment and control groups. Independent t-tests measured the equivalence of age, length of use of opioids, and days since the last opioid intake between the groups.

The SI utilized various statistical analyses to answer the major research question: Is there a significant change in opioid cravings between treatment and control groups among patients with OUD due to treatment with rTMS? Appendix G shows each hypothesis aligned with the specific statistical analysis with rationale. Specifically, independent-samples T-tests compared baseline craving scores in the treatment and control groups at baseline. The SI then employed paired T-tests to evaluate the change in opioid cravings between baseline and after a single treatment of either rTMS or sham treatment in the intervention or the control group, respectively. A mixed regression model examined the longitudinal effect of rTMS on reducing opioid cravings at the specified time intervals and compared cravings scores using the three domains of opioid cravings. A mixed regression model was also conducted to examine the effect of rTMS on opioid cravings on days throughout treatment delivery and 30 days after the last treatment (days 1, 3, 5, 8, 10, 12, and 40) in adults with OUD.

A mixed regression model is useful for measuring research questions related to differences in participants over time. Mixed regression can also measure changes due to time-variant (number of treatments received) and time-invariant variables (group, age, gender). The model with the smallest Akaike information criterion (AIC), which indicates the fitness of data, was reported as the final model.

Chapter Summary

This chapter presented the methodology used to evaluate the effect of rTMS on opioid cravings. An experimental, single-blind approach was described which includes the major elements of the study design: procedures, sample, setting, measurements, data collection, and data analysis. By evaluating the effect of rTMS on opioid cravings using this comprehensive approach guided by a theoretical and conceptual framework, a potential treatment strategy for OUD may be supported.

Chapter 4: Findings

Introduction

Based on the available evidence, rTMS may be a possible solution for individuals with OUD. A randomized, single-blind, experimental research study was conducted to evaluate the effect of rTMS on reducing opioid cravings in adults with OUD. The overarching research question for this study was as follows: Is there a significant change in opioid cravings between treatment and control groups among patients with OUD due to treatment with rTMS?

In this chapter, the results of the data analyses will be thoroughly described including the demographic characteristics of the sample and the analysis of each hypothesis. The chapter will end with a description of mild side effects reported by 4 participants and a summary of the analyses employed.

Demographic Characteristics of the Sample

IBM's SPSS software (Version 28) was used to conduct all of the statistical analyses reported in this study. Twenty-six participants enrolled in the study, but two participants voluntarily terminated their participation in the study after consenting and before the initial data measurement; these two participants were lost with no specific explanation for the termination. The final sample included a total of 24 participants. All 24 participants completed the DDQ at all data collection points. After double-checking the data, there were no discrepancies found in the data entered into SPSS.

Each of the 24 participants was randomly assigned to the intervention or control group. Each group consisted of an equal number of participants (n = 12). The average age of the intervention and control groups were 30.25 (SD = 8.80) and 27.58 (SD = 6.49) years of age,

respectively; the mean age between the two groups is not significantly different (p = .41). Each group consisted of 8 male and 4 female participants.

In the intervention group, 9 participants inhaled heroin and 3 participants injected heroin intravenously. The intervention group used heroin for an average of 8.86 years (SD = 7.30) and last used heroin 5.67 (SD = 2.27) days prior to enrollment into the study. In the control group, 8 participants inhaled heroin and 4 participants injected heroin intravenously. The control group used heroin for an average of 7.74 years (SD = 5.88) and last used heroin 5.33 days (SD = 2.93) prior to enrollment into the study. There were no differences between the two groups in the method of heroin use, mean years of heroin use, and days since the last use of heroin. The demographic characteristics of each group are presented in Table 3.

Table 3: Demographic Characteristics of the Sample

Characteristic	rTMS (*n* = 12)	Control (*n* = 12)	*x2* or *t*	*p*
Age in years[a]			-.845	.41
Mean ± SD	30.25 ± 8.8	27.58 ± 6.49		
Median	28	26		
Gender[b]			0	1
Male	8	8		
Female	4	4		
Years of Heroin Use[a]			-.413	.68
Mean ± SD	8.86 ± 7.30	7.74 ± 5.88		
Days Since Last Heroin Use[a]			-.311	.76
Mean ± SD	5.67 ± 2.27	5.33 ± 2.93		
Method of Heroin Use[b]			.202	.67
Inhaled	9 (75%)	8 (67%)		
Intravenous	3 (25%)	4 (33%)		

[a], Independent t-test; [b], Chi-Square test

Results

Statistical analyses were performed to evaluate the craving scores between the treatment and control groups among three domains of craving: desire, control, and negative reinforcement.

Aim 1

Hypotheses 1-3 were analyzed to achieve Aim 1, to evaluate the effect of rTMS on reducing opioid cravings.

Hypothesis 1

We hypothesized that the intervention group's cravings for opioids will be reduced compared to the control group after a single rTMS treatment. Independent-samples t-tests were

conducted to compare craving scores between the intervention group and the control group after a single rTMS treatment. There were no differences between the two groups at baseline. After single treatment, there was a significant difference in the desire domain score between the intervention group (M = 3.14, SD = .75) and control group (M = 5.82, SD = .50), $t(22) = 9.3$, $p < .001$; and a significant decrease in the negative reinforcement domain score between the intervention group (M = 5.74, SD = .45) and control group (M = 6.06, SD = .52), $t(22) = 2.9$, $p = .01$. There was no significant difference in the control domain score between the two groups.

Hypothesis 2

We hypothesized that the intervention group's cravings for opioids will be reduced after one rTMS treatment compared to baseline. A paired-samples t-test was conducted to compare the intervention group's craving scores before and after a single rTMS treatment. There was a significant decrease in the desire and negative reinforcement domain scores, and a significant increase in control scores before and after a single rTMS treatment (Table 4).

Hypothesis 3

Next, we hypothesized the control group cravings for opioids will be similar to their baseline after a single sham-rTMS treatment. A paired-samples t-test was conducted to compare the control group's craving scores before and after a single rTMS treatment (Table 4). There was a significant reduction in desire domain score before (M = 6.23, SD = .39*)* and after a single sham rTMS treatment (M = 5.82, SD = .50), $t(12) = 4.09$, $p = .002$, and there was an increase in control domain score before (M = 1.33, SD = .44) and after a single sham rTMS treatment (M = 1.58, SD = .52), $t(12) = -2.57$, $p = .026$. There was not a significant difference in negative reinforcement scores ($p = .37$).

Table 4: Paired T-Test

	T1	T2	Mean Difference	*df*	*t*	*p*
Intervention group						
Mean ± (SD)						
Desire	6.10 ± .44	3.14 ± .75	-2.68 ± .61	11	15.27	**<.001**
Negative Reinforcement	6.40 ± .41	5.48 ± .45	-.92 ± .51	11	6.17	**<.001**
Control	1.42 ± .63	1.88 ± .80	.46 ± .40	11	-4.01	**0.002**
Control Group						
Mean (SD)						
Desire	6.23	5.82	-.41 ± .10	12	4.09	**.002**
Negative Reinforcement	6.15	6.06	-.08 ± .30	12	.94	.368
Control	1.33	1.58	.25 ± .34	12	-2.57	**.026**

Note: Mean difference: T2-T1

Aim 2

Hypothesis 4 was analyzed to achieve Aim 2, to evaluate whether a reduced craving score was sustained 30 days after treatment with rTMS in adults with OUD.

Hypothesis 4

Hypothesis 4 stated the cravings for opioids in the intervention group 30 days after treatment will be similar to the cravings for opioids immediately after 10 rTMS treatments and will remain reduced compared to control group. A paired-samples t-test was used to compare craving scores between day 12, after 10rTMS treatments, and again 30 days after the last rTMS treatment in the intervention group (day 42). There was a significant reduction in the desire domain score from day 12 (M = 2.22, SD = .44*)* to day 42 (M = 2.04, SD = .57), $t(11) = 2.29$, $p =$

.042, and a significant decrease in the negative reinforcement domain score from day 12 (M = 5.29, SD = .61) to day 42 (M = 5.04, SD = .64), $t(11) = 2.87$, $p = .015$. There was not a significant difference in the control domain score ($p = .275$).

Next, independent t-tests were conducted to compare the craving scores between the intervention and control groups on day 42, which was 30 days after the last rTMS treatment. The desire domain score was significantly lower in the intervention group (M = 2.04, SD = .57) than in the control group (M = 4.53, SD = .57, $p < .001$). The negative reinforcement score was also significantly lower in the intervention group (M = 5.04, SD = .64) than in the control group (M = 5.54, SD = .58, $p = .057$). There was no significant difference in the control score between the two groups on day 42 ($p = .59$).

Aims 3 & 4

Hypothesis 5 was evaluated to carry out both Aims 3 and 4 of the study. Aim 3 was to examine the longitudinal effect of rTMS on reducing opioid cravings throughout the delivery of rTMS treatments delivered once per day, Monday - Friday, in adults with OUD by assessing opioid cravings after one, three, five, eight, and 10 treatments. Aim 4 was to measure the effect of rTMS on three domains of opioid cravings: desire and intention, negative reinforcement, and control.

Hypothesis 5

We hypothesized that the intervention group's cravings for opioids will be reduced in one or more domains of opioid cravings at each craving measurement compared to baseline. We used mixed-effect regression analysis to evaluate this hypothesis to see if there is a time and group interaction, which indicates if the intervention affects the outcome differently over the treatment time between the control and intervention groups.

Table 5: Mixed Effect Regression Analysis

Domain	Category	Estimate	Standard Error	*p*
Desire				
	Intercept	3.208	0.317	**<.001**
	Group			
	Control	2.384	0.176	**<.001**
	Intervention	0	0	
	Sex			
	Female	-0.090	0.083	.283
	Male	0	0	
	Route			
	Inhaled	0.425	0.087	**<.001**
	IV	0	0	
	Age (years)	0.048	0.011	**<.001**
	Years of Use	-0.044	0.011	**<.001**
	Days since Last Use	-0.121	0.014	**<.001**
	Timepoint	-0.242	0.024	**<.001**
	Control x Timepoint	0.146	0.034	**<.001**
	Intervention x Timepoint	0	0	
Negative Reinforcement				
	Intercept	5.823	0.348	**<.001**
	Group			
	Control	0.207	0.165	.214
	Intervention	0	0	.
	Sex			
	Female	-0.069	0.093	.462
	Male	0	0	.
	Route			
	Inhaled	0.216	0.098	**.028**
	IV	0	0	.
	Age (years)	0.022	0.012	0.067
	Years of Use	-0.037	0.013	**0.004**
	Days since Last Use	-0.049	0.015	**0.002**
	Timepoint	-0.121	0.024	**<.001**
	Control x Timepoint	0.048	0.033	0.151
	Intervention x Timepoint	0	0	.

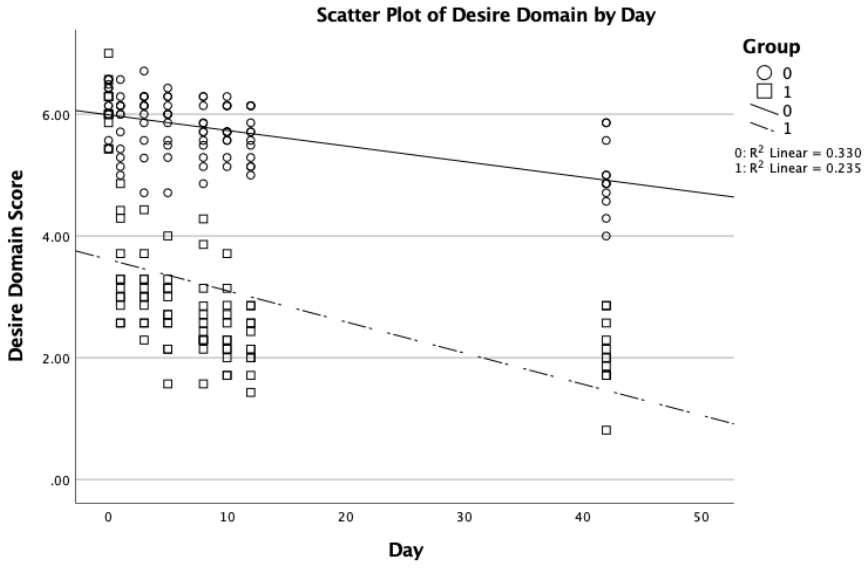
Control				
	Intercept	1.904	0.366	**<.001**
Group				
	Control	-0.191	0.175	.277
	Intervention	0	0	.
Sex				
	Female	-0.131	0.098	.185
	Male	0	0	.
Route				
	Inhaled	-0.203	0.102	**.049**
	IV	0	0	.
Age (years)		-0.033	0.013	**.012**
Years of Use		0.057	0.014	**<.001**
Days since Last Use		0.055	0.016	**.001**
Timepoint		0.057	0.023	**.017**
Control x Timepoint		0.002	0.033	.957
Intervention x Timepoint		0	0.000	.

Desire Domain.

There was a significant interaction between time and group, which indicates that the intervention group experienced decreased craving scores on the desire domain significantly more than the control group over the time ($p < .001$) (Table 5). The control group's desire domain score was approximately 2.38 ($p < .001$) points higher than the intervention group, and the intervention group's desire domain score decreased by approximately .24 at each time point measurement ($p < .001$). At each time point, the control group's desire domain score was approximately .15 points higher than the intervention group ($p < .001$). If the participant inhaled heroin, their desire domain score was likely to be .43 points higher than if they intravenously injected heroin ($p < .001$). For each year of age increase, the desire domain score was predicted

to be .05 points higher ($p < .001$). For each year increase in the length of heroin use, the desire domain score was expected to decrease by .04 points ($p < .001$). For every day since the participant's last use of heroin, their desire domain score was expected to decrease by .04 points ($p < .001$). There were no significant differences in the desire domain scores between males and females ($p = .283$).

Figure 1: Scatter Plot of Desire Domain by Day

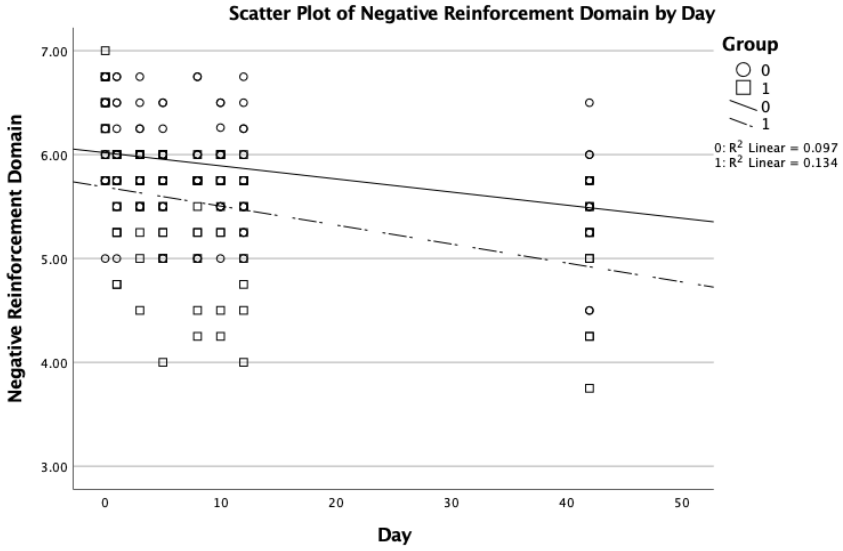


Negative Reinforcement Domain.

Both the intervention and control groups' negative reinforcement domain scores decreased significantly over time ($p < .001$), but the change in the control group was decreasing similarly to the intervention group ($p = 0.15$) (Table 5). For each year increase in the length of heroin use, the negative reinforcement domain score was predicted to be .04 points lower ($p =$

.004), and for each day since the participant's last use of heroin, their score was predicted to decrease by .05 points (p = .002). If the participant inhaled heroin, their negative reinforcement domain score was likely to be .22 points higher than if they intravenously injected heroin (p = .028). For each year of age increase, the negative reinforcement domain score was predicted to be .02 points higher (p < .1). There were no significant differences in the negative reinforcement domain scores between male and female participants (p = .462).

Figure 2: Scatter Plot of Negative Reinforcement Domain by Day

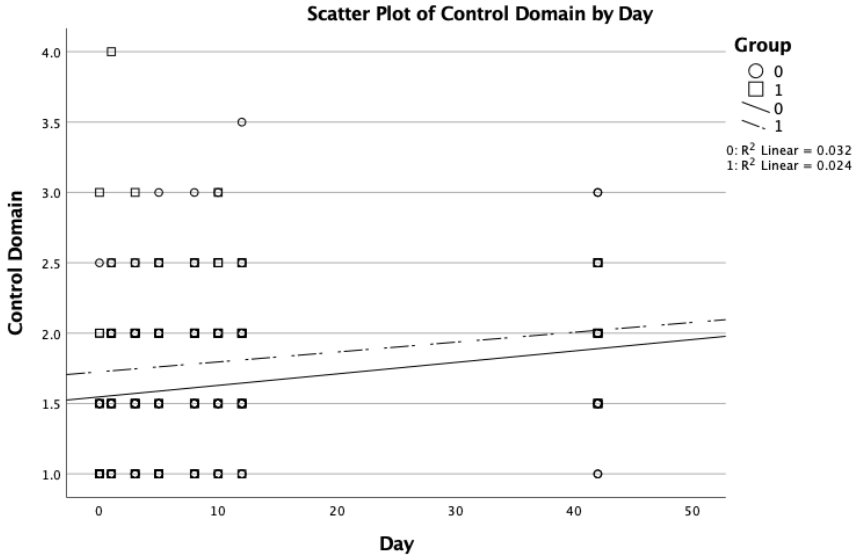


Control Domain.

Oppositely, the intervention and control group's control domain scores increased significantly over time (p = .017), but the change in the control group was increasing similarly to the intervention group (p = 0.957) (Table 5). If the participant inhaled heroin, their control

domain score was predicted to decrease by .20 points compared to those who intravenously injected heroin (p = .049). For each year of age increase, the control domain score was expected to decrease by 0.3 points (p = 0.012). For each year increase in the length of heroin use, the control domain score was predicted to be .06 points higher (p < .001). For every day increase since the last use of heroin, the control domain score was expected to increase by .06 points (p = .001). There were no significant differences in the control domain scores between male and female participants (p = .185).

Figure 3: Scatter Plot of Control Domain by Day



Side Effects

Mild side effects were reported by 4 participants in the rTMS group. These side effects included temporary scalp pain under the side of the coil and headache, both of which are common side effects reported during rTMS treatment (Rossi et al., 2009). The scalp pain was

reported by 3 participants and resolved immediately after each rTMS treatment was complete; this complaint was only reported during the first and second rTMS treatment and all participants chose to continue with the study. One participant complained of a headache during and after the first rTMS treatment, which was reported to have resolved within one hour after the initial rTMS treatment. No side effects were reported by participants in the control group.

Chapter Summary

This chapter presented the data analyses and findings of the study. Demographics including age, gender, years of heroin use, days since the last heroin use, and route of heroin use were provided. The analyses for each hypothesis were presented, and the craving scores of the two groups were statistically analyzed. Finally, the side effects reported by the participants were described.

Chapter 5: Discussion

Introduction

In this study, we sought to evaluate the effectiveness of rTMS on opioid cravings using a randomized, single-blind, experimental design with a control group to test the effect of rTMS on opioid cravings among adult patients with OUD. This chapter will present a summary and discussion of the study findings. Demographics of the study participants will be reviewed, each research question will be individually addressed, implications for nursing practice and research will be presented, and the limitations of the study will be identified.

Discussion of Study Findings

Opioid Use Disorder is a major public health concern in the U.S. and around the globe. Many individuals and families are affected by the disorder and its repercussions. The prevalence of OUD remains high, and a major contributing factor to the disorder is the use of heroin. Evidence-based treatments such as MAT are available for the treatment of the disorder, but there are many barriers and challenges to accessing these resources (Bell & Strang, 2020; Chilcoat et al., 2019). New, innovative, and comprehensive strategies are needed to combat OUD. Based on the findings in this study and the previously documented literature, high-frequency rTMS applied to the left DLPFC is a well-tolerated effective method for decreasing opioid cravings in adults with OUD.

Demographic Characteristics

Descriptive statistics on study participants did not show any significant differences between the control and intervention groups. There was an equal number of participants in each group (n = 12). Twenty-four participants completed the study. The ratio of males to females was the same in each group; neither of the previously documented studies evaluating rTMS on OUD

included any females in the study design. There were no statistically significant differences in years of use, days since last use, and the method of heroin use between the control and intervention groups at baseline.

Evaluating the Effect of a Single Treatment of rTMS on Opioid Cravings

Aim 1 of the study was achieved by evaluating the effect of rTMS on reducing opioid cravings based on the DDQ domain scores. Aligned with the hypothesis, the effect of a single rTMS treatment reduced opioid cravings in adults with OUD who used heroin. A single rTMS treatment was previously documented to reduce opioid cravings in adult males with OUD when applied to the DLPFC (Shen et al., 2016). The current study findings reaffirm that result and demonstrate a significant reduction in opioid cravings on the desire and negative reinforcement domain scores in adults with OUD. This reduction was demonstrated in the intervention group compared to its baseline craving scores, and there were greater reductions in the desire and negative reinforcement domain scores compared to the control group. These results may provide evidence that even a single treatment with high-frequency rTMS to the DLFPC reduces opioid cravings. Given cravings for opioids are a strong predictor of relapse, a single treatment of rTMS may reduce opioid cravings, and thereby help to prevent relapse, in adults with OUD (Tsui et al., 2014).

There was also a significant increase in the control domain scores of opioid cravings in the intervention group after a single treatment with rTMS. When using the DDQ, after removing item number 7 to ensure the reliability of the tool, the control domain is measured by only a single item: *If I started using heroin now, I would be able to stop* (Franken et al., 2002). This item may be interpreted that once a person starts to actively use heroin, they would be able to stop using heroin while in the process of using heroin or in the future. Because of the ambiguity

in interpreting this single item measuring the control domain of opioid cravings, the implications for this specific domain in this measure cannot be assumed.

After a single sham-rTMS treatment, the control group experienced a significant reduction in the desire domain score and a significant increase in the control domain score. There may have been a placebo effect on these craving domains. Increased attention from the SI and/or their healthcare provider, along with their own expectation to improve as a result of participating in this study, may have also contributed to the change in opioid cravings. However, there was still a significantly greater reduction in desire domain scores in the intervention group compared to the control group after a single rTMS treatment, confirming that a single rTMS treatment may reduce the desire domain cravings in adults with OUD. The time effect on opioid cravings will be discussed later in this section.

Durability of rTMS Reducing Opioid Cravings 30 Days after Treatment

Aim 2 was achieved by evaluating whether a reduced craving score would be sustained 30 days after treatment with rTMS in adults with OUD. 30 days after the last rTMS treatment there was a significant reduction of desire and negative reinforcement scores for craving in the intervention group. In addition, the desire and negative reinforcement scores in the intervention group were significantly lower than the control group 30 days after the last rTMS treatment. Liu and colleagues (2020) found that opioid cravings were reduced 30 days after 20 rTMS treatments. This current study demonstrates that a lesser number of rTMS treatments, 10, also results in a sustained reduction of opioid cravings 30 days after treatment. Though this current study did not measure opioid cravings longer than 30 days after the last treatment, a reduction of cravings may be sustained in this population given the durability of the reduction of cravings 60 days after treatment previously demonstrated in the study by Liu and colleagues (2020).

Longitudinal Effect of rTMS on Opioid Cravings

Examining the longitudinal effect of rTMS on reducing opioid cravings throughout the delivery of treatment was another aim of the study. Opioid cravings were measured throughout the delivery of rTMS treatment in the current study, which was not fully evaluated in previous studies (Shen et al., 2016; Liu et al., 2020). Given that there was a significant reduction of craving in both the control and intervention groups throughout the study, opioid cravings are likely to be reduced with abstinence alone over time. However, there was a significantly greater reduction of desire domain scores in the intervention group compared to the control group, which demonstrates the effectiveness of rTMS treatments on opioid cravings. Also, for each specific time point during the treatment (i.e., days 1, 3, 5, etc.), we found continuous reductions in the desire to use opioids and negative reinforcement as well as increases in the perceived that control one has over using heroin. These findings demonstrate that the 10 rTMS treatments may have a cumulative effect in reducing opioid cravings. This reduction could be explained by a theorized increase in dopaminergic circuitry and synaptic plasticity in the reward system, thereby decreasing desire and reducing negative reinforcement (Koob & Volkow, 2014; Razza et al., 2018; Volkow et al., 2019).

In previous studies, either 5 or 20 treatments were administered (Shen et al., 2016; Liu et al., 2020). In this current study, 10 rTMS treatments were administered to evaluate if more than 5 treatments resulted in a greater effect than 5 rTMS treatments. The specific effect in this study cannot be directly compared to the effect reported by Shen and colleagues (2016) because a different tool for measuring craving was used. The additional rTMS treatments administered in this study may result in or lead to reduced cravings for opioids in all domains compared to after only 5 rTMS treatments alone administered by Shen and colleagues (2016). In addition, there

was a meaningful reduction in opioid cravings in the intervention group 30 days after the last rTMS treatment, similar to that observed in the study by Liu and colleagues (2020), which demonstrates the durability of this particular treatment protocol. Given the sustained effect demonstrated after 10 rTMS treatments, this protocol offers lesser time commitment than the 20-rTMS treatment protocol (Liu et al., 2020) and therefore reduced cost and burden when treating adults with OUD.

Evaluating Opioid Cravings among Three Domains

Evaluating the effect of rTMS on opioid cravings among three domains provides a more comprehensive assessment of opioid cravings compared to the single-item VAS. Using this tool provides specific craving measurements related to desire or intention to use heroin, negative reinforcement, and perceived control over one's use of heroin. Because there is a lack of clarity in defining opioid cravings among heroin users and researchers (Sayette, 2016), using a multidimensional and comprehensive approach to measure opioid cravings in the current study may contribute to collecting more accurate craving data in association with the rTMS treatment (Franken et al., 2002). This differentiation of the specific aspects of opioid cravings may also help researchers and clinicians identify targeted interventions to help reduce various aspects of opioid cravings, thus reducing the risk of relapse secondary to uncontrolled opioid cravings (Tsui et al., 2014).

Of most importance in the current study was the effect of rTMS on reducing opioid cravings in the desire domain. This desire domain represents the current, short-term craving state, which informs the SI and clinicians of the here-and-now existence and intensity of one's desire and intent to use heroin (Franken et al., 2002). Therefore, rTMS, even as a single treatment, could be an easily accessible and practical means to decrease desire and intention to

use opioids. Its use could decrease these immediate, here-and-now cravings, potentially preventing relapse, and effectively breaking the 3-stage cycle of addiction explained in the theoretical model used to guide this study.

No studies have been found to use any other measurements than the VAS cue-reactivity cravings on opioid use (Shen et al., 2016; Liu et al.; 2020), which limits the usefulness of the previous results for clinicians in developing a treatment plan for adults with OUD. In this current study, there was a greater reduction in the desire domain of opioid cravings in the intervention group compared to the control group after a single rTMS treatment, after 10 rTMS treatments, and 30 days after the last rTMS treatment. This greater reduction in craving scores was not evident in the negative reinforcement and control domains between the two groups. With these findings, clinicians may be able to better assist adults with OUD in reducing cravings by augmenting rTMS treatment with other interventions specifically addressing the negative reinforcement and control domains of opioid cravings including individual and group psychotherapy, peer support, substance abuse counseling, and MAT.

Limitations

The current study findings contribute to the body of knowledge and may inform further research and application of rTMS in the treatment planning for adults with OUD, but there are limitations to this study. First, there is a potential bias in this study related to the recruitment methods used. The SI used multiple outreach methods into the community for recruitment, but the majority of the inquiries for participation came from a single community organization. This community organization has a residential treatment program for substance abuse disorders, and each person admitted to this program undergoes intense psychosocial interventions, including group therapy, individual psychotherapy, substance abuse counseling, and medication

management for substance use disorders. These additional interventions may have contributed to the improvement of opioid cravings among the three domains and may also explain the improvement of opioid cravings in the control group. In addition, although these psychosocial interventions in the community organizations are considered outpatient treatments, the clients participating in these programs have many resources available that other people in outpatient settings may not have. These additional resources include case management, psychotherapy, substance abuse counseling, physical examinations, and other medical and psychosocial resources. Lastly, because most of the participants were referred from a single community organization, there is a potential that the participants referred had a more severe OUD or higher levels of opioid craving than what would be seen in the general OUD population, which possibly resulted in a greater potential for reduction of opioid cravings. Therefore, the sample used in this study may not be a true representation of all persons with OUD in outpatient settings.

A second limitation of this study is the small sample size used. Both the intervention group and the control group enrolled a total of 12 participants each. Because of the small number of participants, there is an increased risk for a Type II Error to occur. However, the study findings were similar to those presented previously with a larger sample size (Liu et al., 2020). In addition, this study included 12 participants in each group, which was greater than the number needed (n = 8) based on the power analysis calculated using the estimated effect size of 1.5, alpha = 0.05, and a power of 95%.

Next, there is a possibility in this study for experimenter bias. Even though the participants were randomized into the two groups and a sham treatment was used in the control group to mimic the rTMS treatment, the SI was not blinded and was fully aware of which

participants belonged to each group. In this study, the SI may have unintentionally acted, communicated, or behaved differently with the participants, possibly influencing the outcome.

Another limitation to this study is the fact that the term OUD encompasses those who use various forms of opioids including heroin and opioids such as fentanyl and many other types of opioids. In this study, only people with OUD from the use of heroin were admitted to the study. Therefore, the findings from the study may not be representative of the entire OUD population.

Finally, another limitation of this study was a flaw in the original study design and selection of time points of data collection. Initially, the SI planned to perform 10 rTMS treatments on a Monday-to-Friday schedule over two consecutive weeks. Data was to be collected before and after treatment on day 1, after treatment on day 3, before treatment on day 8, after treatment on days 10 and 12, and again on day 42. However, it was not originally specified if treatment must be initiated on a Monday. This was not specified in the previous studies either (Shen et al., 2016; Liu et al., 2020). Because of the unpredictability of recruitment and the SI's desire to enroll participants into the study before they lost interest, 4 participants in the control group and 2 participants in the intervention group started their initial treatment on a Tuesday, Wednesday, or Thursday. No participants were started on Friday. When participants started rTMS treatment on different days of the week, the 2-day break in treatment that was supposed to occur after rTMS treatment 5 (i.e., days 6-7) did not always fall on days 6-7 of the study. In addition, following this Monday – Friday schedule, the participants who started rTMS treatment on a Tuesday, Wednesday, or Thursday had two 2-day breaks before completing all 10 rTMS treatments. However, the SI adapted the data collection protocol mid-study to collect data after the same number of rTMS or control treatments delivered rather than on the specific day of the

study. This, inadvertently, could have impacted the intervention effectiveness and the opioid cravings scores.

Implications

Opioid Use Disorder is a multi-faceted, complex ailment that affects people of all ages. It is influenced by biological, psychological, and social factors, which emphasizes the need for a comprehensive, multi-modal approach to treatment. Currently, the literature published on opioid cravings and OUD as a whole is robust. However, there is a dearth of literature specifically evaluating the use of rTMS in OUD and opioid cravings, and there is limited literature on OUD treatment from a nursing perspective. The findings of this current study are particularly relevant because the study was guided using a theoretical framework, the Biopsychosocial Model, which is closely aligned with the nursing approach to patient care.

In the two previous studies published on the topic (Shen et al., 2016; Liu et al., 2020), cue-induced cravings were used as the dependent variable. In this study, a video or other method to induce cravings was not utilized in order to capture the typical day-to-day cravings that might be experienced by adults with OUD. Because a cue was not used prior to data measurement to induce cravings in this current study, the measurement of opioid cravings at various timepoints may be more representative of the day-to-day cravings experienced by individuals with OUD than what was previously examined (Shen et al., 2016; Liu et al., 2020).

In this current study, cravings were also measured among three domains of opioid cravings, rather than with a single question (Shen et al., Liu et al., 2020). This method of measurement provides additional perspective as to the scope of opioid cravings, which may be used by nurses and other clinicians in the development of individualized treatment plans for patients with OUD. For example, clinicians may recommend a combination of rTMS treatment

and substance use counseling together to reduce relapse. Another possible combination for treatment may include rTMS accompanied with MAT, the current gold standard for OUD treatment (Bell & Strang, 2020), or other pharmacotherapies to reduce opioid cravings. Further research is needed specifically examining the dual effect of some of these combination therapies. Also, none of the participants in this study used heroin less than 3 days before starting rTMS treatment. Additional research is needed specifically looking at the effect of rTMS in individuals who last used heroin less than three days ago, which would offer an opportunity to examine opioid withdrawal symptoms and how they may be affected by rTMS treatment.

Nursing Practice

Nurses are often at the forefront of providing care to all populations with various diseases and disorders. This is true for nurses in the treatment of OUD. In particular, Advanced Practice Registered Nurses are prepared to diagnose and formulate treatment plans for individuals with the disorder. Though more research is needed to support a particular treatment protocol, rTMS should be considered a viable treatment option for OUD. It is a safe, non-invasive treatment that does not have the risks of diversion, abuse, or misuse as does MAT, the current gold standard (Bell & Strang, 2020). It may be used as one of many interventions used when developing a comprehensive plan for the treatment of OUD. Also, because rTMS is a non-invasive treatment, it could be offered to clients who desire a non-pharmacological treatment alternative. It is also a nursing role to educate the public about health and all levels of prevention strategies. Educating their patients and the public about rTMS as a treatment option may increase awareness and improve access to rTMS as a treatment option for OUD.

Nursing Research

Nursing researchers should pursue further examination regarding the use of rTMS in various populations to better represent the diversity of adults who suffer from OUD. In addition, this study only examined the use of rTMS on adults with OUD from heroin use, but OUD can result from the use of multiple other types of opioids; subsequent research should focus on the effectiveness of rTMS with other forms of opioids are used.

Although the two previous studies (Shen et al., 2016; Liu et al, 2020) and this current study demonstrated the effectiveness of rTMS at reducing opioid cravings, each study administered a different number of rTMS treatment sessions. Therefore, additional research is needed to further examine the most efficacious treatment regimen and clarify the number of treatment sessions needed to both reduce opioid cravings and maintain that reduction over the long-term. Further research should also be pursued to examine the need for maintenance rTMS treatments after the initial treatment regimen is administered, which may help maintain the reduction of opioid cravings over the long term.

Next, MAT continues to be the gold standard for treatment of OUD, and psychotherapy and substance abuse counseling has been a mainstay for treatment in SUDs. Further studies should focus on the usefulness of rTMS as an augmentation strategy for one or more of these interventions at reducing opioid cravings. This focus may help to identify the most appropriate strategy for every individual given the worldwide prevalence of OUD.

Conclusion

Opioid Use Disorder is a major public health concern that must be addressed. In this chapter, the findings of the current research study were discussed. Using a randomized, single-blind experimental design methodology, the findings of this study suggest that 10 rTMS may be

an effective treatment for reducing cravings in OUD. This treatment regimen has demonstrated effectiveness after a single treatment, both a cumulative and durable effect in reducing opioid cravings; therefore, clinicians should consider rTMS as a viable treatment in OUD. Though there were multiple limitations identified, the results of this study contribute to the body of knowledge available for the treatment of OUD. Further research is needed to better understand the effect of rTMS on the various domains of opioid cravings and must be pursued.

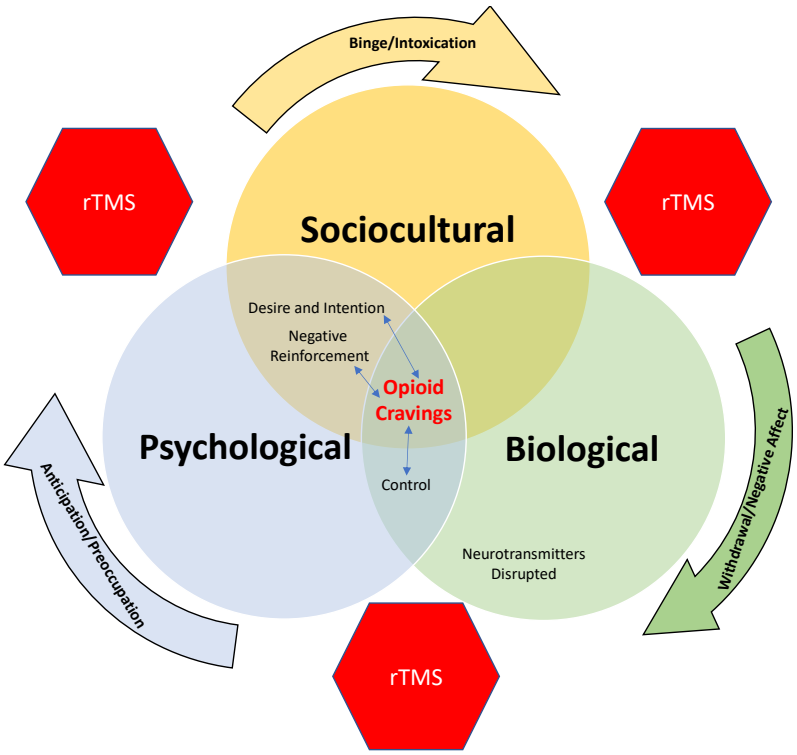
Appendix A: DSM-V Criteria for OUD

A. A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect.
    b. A markedly diminished effect with continued use of the same amount of an opioid.
    Note: This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision.
11. Withdrawal, as manifested by either of the following:
    a. The characteristic opioid withdrawal syndrome (refer to Criteria A and B of the criteria set for opioid withdrawal, pp. 547–548).
    b. Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.
    Note: This criterion is not considered to be met for those individuals taking opioids solely under appropriate medical supervision.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). American Psychiatric Association.

Appendix B: Theoretical Framework



Appendix C: Desires for Drug Questionnaire

DDQ Heroin

Please indicate to what extent you agree or disagree with each of the following statements. Do so by inserting an X mark on the line between "STRONGLY DISAGREE" and "STRONGLY AGREE". The closer you insert the X to one or the other side indicates to what extent you agree or disagree. Please don't skip any statements. We want to know how you think and feel at THIS MOMENT, so the moment you complete this questionnaire.

FOR EXAMPLE:
STRONGLY DISAGREE |____|____|__ _|____|____|_ X__|____| STRONGLY AGREE
/

1. Using heroin would be satisfying now

STRONGLY DISAGREE |____|____|____|____|____|____|____| STRONGLY AGREE

2. I would consider using heroin now

STRONGLY DISAGREE |____|____|____|____|____|____|____| STRONGLY AGREE

3. If I started using heroin now I would be able to stop

STRONGLY DISAGREE |____|____|____|____|____|____|____| STRONGLY AGREE

4. I would do almost anything to use heroin now

STRONGLY DISAGREE |____|____|____|____|____|____|____| STRONGLY AGREE

5. I would feel less worried about my daily problems if I used heroin now

STRONGLY DISAGREE |____|____|____|____|____|____|____| STRONGLY AGREE

6. My desire to use heroin now seems overwhelming

STRONGLY DISAGREE |____|____|____|____|____|____|____| STRONGLY AGREE

~~**7. I could easily limit how much heroin I would use if I used now**~~

~~STRONGLY DISAGREE |____|____|____|____|____|____|____| STRONGLY AGREE~~

8. I would feel as if all the bad things in my life had disappeared if I used heroin now

STRONGLY DISAGREE |____|____|____|____|____|____|____| STRONGLY AGREE

9. I want heroin so much I can almost taste it

STRONGLY DISAGREE |____|____|____|____|____|____|____| STRONGLY AGREE

10. Using heroin now would make me feel less tense

STRONGLY DISAGREE |____|____|____|____|____|____|____| STRONGLY AGREE

11. Even major problems in my life would not bother me if I used heroin now

STRONGLY DISAGREE |____|____|____|____|____|____|____| STRONGLY AGREE

12. Using heroin would be pleasant now

STRONGLY DISAGREE |____|____|____|____|____|____|____| STRONGLY AGREE

13. I am going to use heroin as soon as I possibly can

STRONGLY DISAGREE |____|____|____|____|____|____|____| STRONGLY AGREE

THANK YOU VERY MUCH FOR YOUR COOPERATION!!!!

SCORING BY DOMAIN

STRONGLY DISAGREE |_1_|_2_|_3_|_4_|_5_|_6_|_7_| STRONGLY AGREE

DDQ_DESIRE = (D1 + D2 + D4 + D6 + D9 + D12 +D13) / 7.
DDQ_NEG = (D8 + D11 + D5 + D10) / 4.
DDQ_CONTROL = (D3) ~~+ D7) / 2.~~

Appendix D: Approval for DDQ Use

From: **Ingmar Franken** franken@essb.eur.nl
Subject: Re: Request to use the DDQ
Date: October 6, 2020 at 2:23 AM
To: Cameron Duncan duncac5@unlv.nevada.edu

IF

Sure, good luck with your study!
Best Ingmar Franken

On 06/10/2020, 01:54, "Cameron Duncan" <duncac5@unlv.nevada.edu> wrote:

Hello Dr. Franken,

My name is Cameron Duncan and I am a PhD student at the University of Nevada, Reno. I would like to use the Desires for Drug Questionnaire for my dissertation studying the effect of a novel intervention called Transcranial Magnetic Stimulation at reducing opioid cravings in patients with Opioid Use Disorder. May I please have permission to use the DDQ, and will you please provide me with a copy of the tool.

Thank you so much for your consideration!
Cameron Duncan DNP, MS, APRN, FNP-C, PMHNP-BC
PhD Student
(775) 843-8428


Scoring_DDQ.doc


DDQ_SHORT-her ne...ish.doc

Appendix E: Neurotransmitters Disrupted in OUD

Stage	Neurotransmitter	Response
Binge/Intoxication		
	Dopamine	Increase
	Opioid Peptides	Increase
	Serotonin	Increase
	y-aminobutyric acid	Increase
	Acetylcholine	Increase
Withdrawal/Negative Affect		
	Corticotropin-releasing factor	Increase
	Dynorphin	Increase
	Norepinephrine	Increase
	Hypocretin	Increase
	Substance P	Increase
	Dopamine	Decrease
	Serotonin	Decrease
	Opioid peptide receptors	Decrease
	Neuropeptide Y	Decrease
	Nociceptin	Decrease
	Endocannabinoids	Decrease
	Oxytocin	Decrease
Preoccupation/Anticipation		
	Dopamine	Increase
	Glutamate	Increase
	Hypocretin	Increase
	Serotonin	Increase
	Corticotropin-releasing factor	Increase

Koob, G. F., & Volkow, N. D. (2016). Neurobiology of addiction: A neurocircuitry analysis. *The Lancet Psychiatry*, *3*(8), 760-773.

Appendix F: Screening Form

JOHNS HOPKINS
MEDICINE
THE JOHNS HOPKINS HOSPITAL
600 NORTH WOLFE STREET
BALTIMORE, MD 21287

DEPARTMENT OF PSYCHIATRY AND BEHAVIORAL SCIENCES

for addressograph plate

TMS Patient Screening Form

This section is to be filled out by the PATIENT/patient representative.
Please indicate if you have any of the following:

Aneurysm clips or coils	☐Yes	☐No	Wearable cardioverter defibrillator	☐Yes	☐No
Cardiac pacemaker or wires	☐Yes	☐No	Implanted insulin pump	☐Yes	☐No
Internal cardioverter defibrillator (ICD)	☐Yes	☐No	Programmable shunt or valve	☐Yes	☐No
Carotid or cerebral stents	☐Yes	☐No	Hearing aid	☐Yes	☐No
Deep brain stimulator	☐Yes	☐No	Cervical fixation devices	☐Yes	☐No
Metallic devices implanted in your head	☐Yes	☐No	Surgical clips, staples, or sutures	☐Yes	☐No
Dental implants	☐Yes	☐No	VeriChip microtransponder	☐Yes	☐No
Cochlear implant/ear implant	☐Yes	☐No	Wearable monitor (e.g., heart monitor)	☐Yes	☐No
CSF (cerebrospinal fluid) shunt	☐Yes	☐No	Bone growth stimulator	☐Yes	☐No
Eye implants	☐Yes	☐No	Wearable infusion pump	☐Yes	☐No
Cardiac stents, filters, or metallic valves	☐Yes	☐No	Radioactive seeds	☐Yes	☐No
Tattoo	☐Yes	☐No	Portable glucose monitor	☐Yes	☐No
Vagus nerve stimulator (VNS)	☐Yes	☐No	Tracheostomy	☐Yes	☐No
Blood vessel coil	☐Yes	☐No	Medication patch/nicotine patch	☐Yes	☐No
Shrapnel, bullets, pellets, BBs, or other metal fragments	☐Yes	☐No	Other implanted metal or device If yes, please specify:_____	☐Yes	☐No

Age: _____ Weight (lbs): _____ Height: _____ Last menstrual period: _____

Have you ever been a machinist, welder, or metal worker? ☐Yes ☐No

Have you ever had a facial injury from metal and/or metal removed from your eyes? ☐Yes ☐No

Are you pregnant? ☐Yes ☐No

Have you ever had complications from an MRI? ☐Yes ☐No

Signature of person completing this form: _____ Date: _____

Signature of physician or health care provider: _____ Date: _____

02-849-0008 (9/09)

Appendix G: Statistics Table

Hypotheses	H1. The intervention group's cravings for opioids will be reduced compared to the control group after a single rTMS treatment.	H2. The intervention group's cravings for opioids will be reduced after one rTMS treatment compared to baseline. H3. The control group's cravings for opioids will be similar to their baseline after a single rTMS treatment.	H4. The cravings for opioids in the intervention group 30 days after treatment will be similar to the cravings for opioids immediately after 10 rTMS treatments and will remain reduced compared to control group.	H5. The intervention group's cravings for opioids will be reduced in one or more domains of opioid cravings at each craving measurement compared to baseline.
Independent Variable	Categorical Dichotomous rTMS & control			
Dependent Variable	Continuous DDQ			
Number of Measurements	2	2		8
Estimated Effect Size	2.1 rTMS 40 +/- 11.4 Sham 62 +/- 9.5 (Shen et al. 2016)	0.85 rTMS Baseline: 60 +/- 11.2 1 day: 40 +/- 11.4 (Shen et al. 2016)		3.26 rTMS 5 day: 25 +/- 9.2 Sham 5 day: 55 +/- 9.2 (Shen et al. 2016)
Power	95%			
Alpha	0.05			
Statistical Test	Independent T-test	Paired T-Tests		Mixed Regression Repeated Measures ANOVA, between factors
Power Analysis	n=8	n=6		n=8

Appendix H: Consent Form

INFORMED CONSENT

Department of Nursing

TITLE OF STUDY: Evaluating Repetitive Transcranial Magnetic Stimulation to Reduce Opioid Cravings in Adults Who Use Heroin

RESEARCHER(S): Dr. Cameron Duncan and Dr. Hyunhwa Lee
For questions or concerns about the study, you may contact Cameron Duncan (Student Investigator) at 775-843-8428 or Hyunhwa Lee (Principal Investigator) at 702-895-3492.

For questions regarding the rights of research subjects, any complaints or comments regarding the manner in which the study is being conducted, contact **the UNLV Office of Research Integrity – Human Subjects at 702-895-2794, toll free at 888-581-2794 or via email at IRB@unlv.edu.**

It is unknown as to the level of risk of transmission of COVID-19 if you decide to participate in this research study. The research activities will utilize accepted guidance standards for mitigating the risks of COVID-19 transmission: however, the chance of transmission cannot be eliminated.

Purpose of the Study

You are invited to participate in a research study. The purpose of this study is to test the effect of repetitive transcranial magnetic stimulation (rTMS) on opioid cravings among adult patients with Opioid Use Disorder (OUD). The use of rTMS for OUD is investigational.

Participants

- You are being asked to participate in the study because you fit these criteria:
- Adult aged 18-64, used heroin in the past 30 days;
- have a history of heroin use for at least one year;
- meets the clinical criteria for OUD (only heroin use will be considered to meet these criteria);
- meets the clinician clearance using the rTMS Patient Screening Form.

You also:

- do not currently take any medications for a substance use disorder such as methadone, buprenorphine, naltrexone, acamprosate, disulfiram;
- do not have a psychotic disorder;

- do not have a diagnosis of another substance use disorder;
- do not have a history of seizures or other neurological disorders including organic brain disease; epilepsy, stroke, brain lesions, multiple sclerosis, previous neurosurgery;
- do not have a personal history of head trauma that resulted in a loss of consciousness for more than 5 minutes and retrograde amnesia for more than 30 minutes;
- have not taken any medication for a substance use disorder within the last 72 hours before the first rTMS treatment;
- are not pregnant or think you may be pregnant.

Procedures

If you volunteer to participate in this study, you will be asked to do the following:

Screening Visit- On the initial appointment, the Student Investigator will provide an explanation of the procedures of the study and will explain all possible risks and benefits. You will be asked a series of questions to determine if you meet the eligibility criteria. In addition, you will be asked for your full name, date of birth, and phone number; these personal details are needed to verify your identity. This information will be saved until the last day of the study, Day 42. You will be allowed to ask any questions throughout the process. You will also be encouraged to continue any medical, mental health or substance use treatment with your current healthcare provider throughout the study. If you do not have a current healthcare provider, you will be provided the contact information for three community agencies.

At any time throughout the study, if you use an illicit substance, use heroin again, or start a medication for substance use disorders, you will not be allowed to continue to participate in the study and your personal identifying information will be immediately permanently deleted from the master list so the data can never be linked back to you. Any partial data will be deidentified and used in the final results.

Day 1 (60-90 minutes)**:**

When you come to the office at your scheduled time, you will be allowed to ask any questions you might have. You can ask questions at any time throughout the study.

You will complete a one-page form called the Desires for Drug Questionnaire (DDQ). This questionnaire contains 13 questions and should take less than 5 minutes to complete.

Next, you will be explained through the procedure of setting up the Neurostar rTMS treatment by the Student Investigator.

Once you are comfortable and have had all your questions answered, you will be asked to remove any metal jewelry on your body, you will be asked to put in earplugs, and you will have a seat in the Neurostar rTMS chair (see Figure 1).

The Student Investigator will place a paper strap with adhesive onto your forehead and secure the strap to the chair. The strap will be secured with Velcro making it easy to remove if needed. The strap is used to help you keep your head positioned in one place throughout the treatment.

Next, the Student Investigator will place the rTMS device on the left side of your scalp. The intensity of the treatment will be determined by observing the movement of your right thumb. The Student Investigator will move the device forward, back, up, and down, until movement is seen. You may not feel or see the movement.

Once the intensity and location are determined by the Student Investigator, the treatment will start. The Neurostar rTMS will pulse loudly and deliver the treatment over approximately 12 minutes. Your face, eye, forehead, and ear may twitch. The pulses may feel uncomfortable, but should not hurt.
When the treatment is complete, the Student Investigator will remove the device and loosen the paper strap. You will remove the strap from your forehead and your earplugs and dispose of them. You will then, again, be asked to complete the DDQ form.

Days 2-12 (45-60 minutes)**:** You will receive the same procedure described on day 1. However, the Student Investigator will not determine the intensity and placement of the device again. Rather, the device and intensity will be positioned in the same position and intensity determined on Day 1. You will also complete the DDQ form after treatment on days 3, 5, 10 and 12, and before treatment on day 8.

Day 13-41 (0 minutes)**:** No treatment or forms to complete. You may contact the researchers at any time with questions.

Day 42 (15-20 minutes)**:** You will be contacted by telephone and asked to complete the DDQ form again, and the Student Investigator will confirm that you did not take any medications or use heroin since Day 1. You will also be allowed to ask any questions. Lastly, you will be encouraged again to continue to seek any medical, psychiatric, or substance use treatment from your regular healthcare provider. If you do not have a regular healthcare provider or wish to start care with one, you will be given the contact information for three community healthcare agencies. You will also be advised that if you experience cravings for heroin you should reach out to one of these healthcare providers for additional support. Immediately after this phone call all personal identifying information including your full name, phone number and date of birth will be permanently deleted from the master list so the data can never be linked back to you.

At any time throughout the study, if you use an illicit substance, use heroin again, or start a medication for substance use disorders, you will not be allowed to continue to participate in the study and your personal identifying information will be immediately permanently deleted from the master list so the data can never be linked back to you.

Figure: **Neurostar rTMS system**

Benefits of Participation

There may be direct benefits to you as a participant in this study. The main benefit of the study will be that you may experience fewer cravings for opioids, which may also help you to avoid using heroin again. We hope to learn if rTMS does reduce cravings for opioids in adults with OUD.

Risks of Participation

There are risks involved in all research studies. This study may include only minimal risks.

The most common side effect is pain or discomfort at or near the treatment site. Headaches were reported in half of the patients who participated in the clinical trial for the NeuroStar. These events are transient (they come and go quickly); they occur during the TMS treatment course and do not occur for most patients after the first week of treatment. You should inform the researchers or their staff if this occurs.

It is not likely that treatment with rTMS will result in an increased desire to use heroin. However, cravings are a common symptom present in OUD, so it is possible you may experience increased cravings spontaneously on any day of the study. You should inform the researchers if this occurs.

Seizures (sometimes called convulsions or fits) have been reported with the use of TMS devices. No seizures were observed with the use of the NeuroStar rTMS Therapy System in clinical trials involving about 500 patients and over 15,000 treatments. Since the introduction of the NeuroStar rTMS System into clinical practice, seizures have been rarely reported. The estimated risk of

seizure under ordinary clinical use is approximately 1 in 30,000 treatments or 1 in 1000 patients (<0.1% per patient). In the case of a seizure, the Duncan Family Healthcare Procedure for Managing Medical Events or Emergencies Occurring During Transcranial Magnetic Stimulation Therapy (attached) will be followed. A copy of this procedure will be provided to you. To protect you further in the case of a seizure, the Student Investigator who is also a licensed Advanced Practice Registered Nurse will be in the room with you while rTMS is being delivered. Any adverse events will be reported by phone to the Principal Investigator immediately after they occur. Also, the Principal Investigator and the Student Investigator will meet every other week to discuss the research study progression during data collection.

At any time during the study, particularly when being asked questions about your medical and psychiatric history, you may experience stress or undesirable memories. If this occurs, the Student Investigator is a licensed Advanced Practice Registered Nurse and is specifically trained to support you using guided imagery, deep breathing, and grounding techniques. You will also be provided with the contact information for three community healthcare agencies for additional support.

There is a risk for the loss of confidentiality for your participation. Employees or other employees accessing care at Duncan Family Healthcare might recognize you from a past interaction. They may recognize that you entered the facility and may greet you and introduce themselves. This may encourage you to disclose your name, losing confidentiality. However, the employees of the agency will not ask which services you entered the office for, nor is this standard practice in the office for them to ask. You can choose to disclose your name, but your information will not be found in the Duncan Family Healthcare system unless you previously accessed care at this organization. To minimize interaction with other persons inside Duncan Family Healthcare, you will be given specific instructions as to where to present at the scheduled time (eg. in the waiting room in the chair next to the tree). The employees of the agency will not have access to any of the data or personal information from this study.

To help mitigate the spread of COVID-19, anyone entering the clinic is screened by the clinical staff for any signs, symptoms, or recent exposure to someone diagnosed with coronavirus. Anyone with recent exposure or current signs or symptoms of the coronavirus (fever, chills, loss of taste or smell, cough, shortness of breath) will not be allowed to enter the clinic. Facemasks are required for anyone permitted access to the clinic and must wear the facemask for the entirety of the visit. Those who do not have a facemask will be offered one free of charge. The Neurostar rTMS device is placed in a room approximately 14x14 feet in size. There will be a maximum of two people in the room at any given time (participant and Student Investigator). This room is of ample size to allow for one participant and the Student Investigator to maintain a six-foot distance from each other except when closer contact is required for the setup of the rTMS device.

Cost /Compensation

There will not be any financial cost to you to participate in this study. There will be a time commitment. For two continuous sets of Monday through Friday, each participant will spend approximately 60 minutes per day over 10 days in the office filling out a form and completing rTMS treatment. Thirty days after the final rTMS treatment you will be contacted by the Student

Investigator by phone for approximately 15 minutes. This will be a total of approximately 10 hours and 15 minutes. You will not be compensated for your time.

Confidentiality

All information gathered in this study will be kept as confidential as possible. No reference will be made in written or oral materials that could link you to this study. All data will be managed by the researchers. The privacy of the information we collect about you will be very carefully protected.

The researchers will create a master list which will include your full name, date of birth, and phone number. This information will be saved on the UNLV secured cloud service. This information will be required to verify your identity before each treatment and on Day 42 when you are contacted by phone. On day 42, after the phone call, your data will be permanently deleted from the master list so the information can never be traced back to you.

All other subject data will be de-identified and coded using a random number generator to protect the anonymity of the study participants. Specific data regarding the seat and coil positioning settings, the number of pulses delivered, and your resting motor threshold will be saved locally on the Neurostar rTMS Device under your randomly assigned number. On the 12th day of the study, after your last treatment, your data will be permanently deleted from the Neurostar rTMS device. All other data will be de-identified, linked to your randomly assigned number, and stored on the UNLV secured cloud service for ten (10) years after completion of the study. After the storage time of 10 years, the information gathered will be destroyed by the Principal Investigator.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Voluntary Participation

Your participation in this study is voluntary. You may refuse to participate in this study or in any part of this study. You may withdraw at any time without prejudice to your relations with UNLV. You are encouraged to ask questions about this study at the beginning or any time during the research study.

Participant Consent:

I have read the above information and agree to participate in this study. I have been able to ask questions about the research study. I am at least 18 years of age. A copy of this form has been given to me.

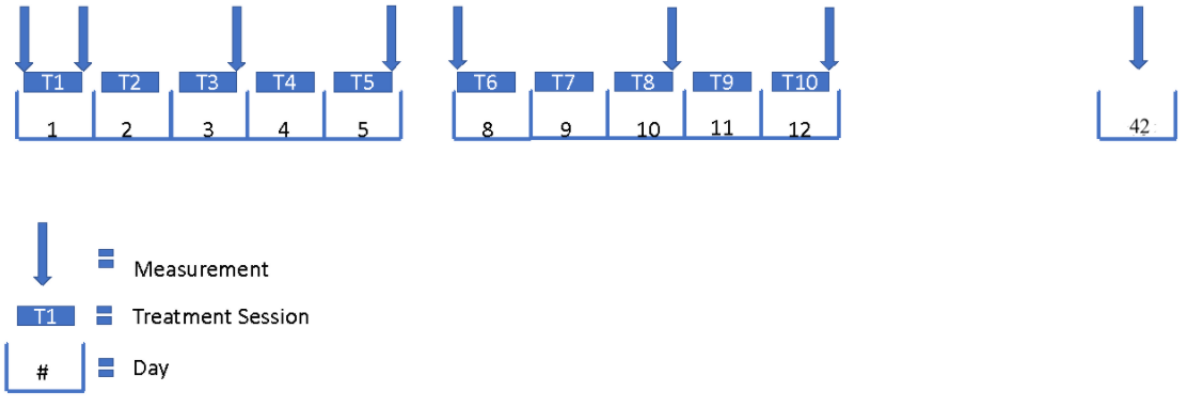
_____ _____

Signature of Participant Date

_____

Participant Name (Please Print)

Appendix I: Treatment Timeline



References

Abrams, D. B. (2000). Transdisciplinary concepts and measures of craving: Commentary and future directions. *Addiction*, *95*(8s2), 237-246.

American Association of Colleges of Nursing. (2010). *The research-focused doctoral program in nursing: Pathways to excellence*. Retrieved from https://www.aacnnursing.org/Portals/42/Publications/PhDPosition.pdf

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). American Psychiatric Association.

Ashrafioun, L. (2016). Prescription opioid craving: Relationship with pain and substance use-related characteristics. *Substance Use & Misuse*, *51*(11), 1512-1520.

Baker, T. B., Japuntich, S. J., Hogle, J. M., McCarthy, D. E., & Curtin, J. J. (2006). Pharmacologic and behavioral withdrawal from addictive drugs. *Current Directions in Psychological Science*, *15*(5), 232-236.

Bell, J. & Strang, J. (2020). Medication treatment of opioid use disorder. *Biological Psychiatry, (87)*1, 82-88.

Bellamoli, E., Manganotti, P., Schwartz, R. P., Rimondo, C., Gomma, M., & Serpelloni, G. (2014). rTMS in the treatment of drug addiction: An update about human studies. *Behavioural Neurology*, *2014*, 815215.

Berridge, K. C., & Robinson, T. E. (1995). The mind of an addicted brain: Neural sensitization of wanting versus liking. *Current Directions in Psychological Science*, *4*(3), 71-75.

Bolloni, C., Panella, R., Pedetti, M., Frascella, A. G., Gambelunghe, C., Piccoli, T., Maniaci, G., Brancato, A., Cannizzaro, C. & Diana, M. (2016). Bilateral transcranial magnetic stimulation of the prefrontal cortex reduces cocaine intake: A pilot study. *Frontiers in*

Psychiatry, *7*, 133.

Camprodon, J. A., Martínez-Raga, J., Alonso-Alonso, M., Shih, M. C., & Pascual-Leone, A. (2007). One session of high frequency repetitive transcranial magnetic stimulation (rTMS) to the right prefrontal cortex transiently reduces cocaine craving. *Drug and Alcohol Dependence*, *86*(1), 91-94.

Center for Disease Control and Prevention. (2018). Opioid overdose: Understanding the epidemic. Retrieved from https://www.cdc.gov/drugoverdose/epidemic/index.html

Chilcoat, H. D., Amick, H. R., Sherwood, M. R., & Dunn, K. E. (2019). Buprenorphine in the United States: Motives for abuse, misuse, and diversion. *Journal of Substance Abuse Treatment*, *104*, 148-157.

Cochran, G., Bruneau, J., Cox, N., & Gordon, A. J. (2020). Medication treatment for opioid use disorder and community pharmacy: Expanding care during a national epidemic and global pandemic. *Substance Abuse, 41*(3), 269-274.

Courtney, K. E., Schacht, J. P., Hutchison, K., Roche, D. J., Ray, L. A. (2016). Neural substrates of cue reactivity: Association with treatment outcomes and relapse. *Addiction Biology, (21)*, 3–22.

Darnall, B. D., Carr, D. B., & Schatman, M. E. (2017). Pain psychology and the biopsychosocial model of pain treatment: Ethical imperatives and social responsibility. *Pain Medicine*, *18*(8), 1413-1415.

De Jong, C. A., Gongora, V. C., Engelhardt, P., & Breteler, M. H. (2006). Effects of craving self-report measurement on desire for heroin in opioid dependent individuals. *Substance Use & Misuse*, *41*(13), 1695-1704.

Engel, G. L. (1977). The need for a new medical model: A challenge for biomedicine. *Science*,

196(4286), 129-136.

Faul, M., Bohm, M., & Alexander, C. (2017). Methadone prescribing and overdose and the association with medicaid preferred drug list policies—United States, 2007–2014. *MMWR. Morbidity and Mortality Weekly Report*, *66*(12), 320.

Fatseas, M., Denis, C., Massida, Z., Verger, M., Franques-Reneric, P., Auriacombe, M. (2011). Cue-induced reactivity, cortisol response and substance use outcome in treated heroin dependent individuals. *Biological Psychiatry*, *70,* 720–727.

Field, A. (2013). Discovering statistics using IBM SPSS statistics. Sage.

Florence, C. S., Zhou, C., Luo, F., & Xu, L. (2016). The economic burden of prescription opioid overdose, abuse, and dependence in the United States. *Med Care*, *54*(10), 901-906.

Franken, I. H., Hendriks, V. M., & van den Brink, W. (2002). Initial validation of two opiate craving questionnaires: The Obsessive-Compulsive Drug Use Scale and the Desires for Drug Questionnaire. *Addictive Behaviors*, *27*(5), 675-685.

Geisler, S., & Wise, R. A. (2008). Functional implications of glutamatergic projections to the ventral tegmental area. *Reviews in the Neurosciences*, *19*(4-5), 227-244.

Gorelick, D. A., Zangen, A., & George, M. S. (2014). Transcranial magnetic stimulation in the treatment of substance addiction. *Annals of Ney York Academy of Science, 1327,* 79–93.

Hassani-Abharian, P., Mokri, A., Ganjghani, H., Oghabian, M. A., & Ekhtiari, H. (2016). Validation for Persian versions of “desire for drug questionnaire” and “obsessive compulsive drug use scale” in heroin dependents. *Archives of Iranian Medicine, 19*(9), 659-665.

Horvath, J. C., Mathews, J., Demitrack, M. A., & Pascual-Leone, A. (2010). The NeuroStar TMS device: Conducting the FDA approved protocol for treatment of depression. *Journal of*

Visualized Experiments, (45), 2345. https://doi.org/10.3791/2345

Jafari, S., Khajehpour, S., Razzaghi, E. M., Heidari, K., Soleimani, M., & Ghaeli, P. (2017). Craving and drug reward: A comparison of celecoxib and ibuprofen in detoxifying opiate addicts. *Iranian Journal of Psychiatry*, *12*(4), 229.

Jones, C. M., Campopiano, M., Baldwin, G., & McCance-Katz, E. (2015). National and state treatment need and capacity for opioid agonist medication-assisted treatment. *American Journal of Public Health*, *105*(8), e55-e63.

Kakko, J., Alho, H., Baldacchino, A. M., Molina, R., Nava, F. A., & Shaya, G. (2019). Craving in opioid use disorder: From neurobiology to clinical practice. *Frontiers in Psychiatry*, *10*, 592.

Kalivas, P. W. & Volkow, N. D. (2005). The neural basis of addiction: A pathology of motivation and choice. *American Journal of Psychiatry, 162*(8), 1403-1413.

Kleykamp, B. A., De Santis, M., Dworkin, R. H., Huhn, A. S., Kampman, K. M., Montoya, I. D., Preston, K. L., Ramey, T., Smith, S. M., Turk, D. C., Walsh, R., Weiss, R. D., & Strain, E. C. (2019). Craving and opioid use disorder: A scoping review. *Drug and Alcohol Dependence*, 107639.

Kluger, B. M., Triggs, W. J., (2007). Use of transcranial magnetic stimulation to influence behavior. *Current Neurology and Neuroscience Reports, 7*, 491–497.

Koob, G. F., & Volkow, N. D. (2016). Neurobiology of addiction: A neurocircuitry analysis. *The Lancet Psychiatry*, *3*(8), 760-773.

Kuhn, S. & Gallinat, J. (2011). Common biology of craving across legal and illegal drugs: A quantitative meta-analysis of cue-reactivity brain response. *The European Journal of Neuroscience, 33*(7), 1318-1326.

Kusnanto, H., Agustian, D., & Hilmanto, D. (2018). Biopsychosocial model of illnesses in primary care: A hermeneutic literature review. *Journal of Family Medicine and Primary Care*, *7*(3), 497.

Li, X., Hartwell, K. J., Owens, M., LeMatty, T., Borckardt, J. J., Hanlon, C. A., Brady, K. T. & George, M. S. (2013). Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex reduces nicotine cue craving. *Biological Psychiatry*, *73*(8), 714-720.

Liang, Y., Wang, L., & Yuan, T. F. (2018). Targeting withdrawal symptoms in men addicted to methamphetamine with transcranial magnetic stimulation: A randomized clinical trial. *JAMA Psychiatry*, *75*(11), 1199-1201.

Liu, Q., Shen, Y., Cao, X., Li, Y., Chen, Y., Yang, W., & Yuan, T. F. (2017). Either at left or right, both high and low frequency rTMS of dorsolateral prefrontal cortex decreases cue induced craving for methamphetamine. *The American Journal on Addictions*, *26*(8), 776-779.

Liu, X., Zhao, X., Liu, T., Liu, Q., Tang, L., Zhang, H., Luo, W., Daskalakis, Z. J. & Yuan, T. F. (2020). The effects of repetitive transcranial magnetic stimulation on cue-induced craving in male patients with heroin use disorder. *EBioMedicine*, *56*, 102809.

Marlatt, G. A. (1985). Cognitive factors in the relapse process. In G. A. Marlatt & J. R. Gordon (Eds.), *Relapse prevention: Maintenance strategies in the treatment of addictive behaviors*, (pp. 128–200). Guilford.

Martinez, D., Urban, N., Grassetti, A., Chang, D., Hu, M. C., Zangen, A., Levin, F. R., Foltin, R. & Nunes, E. V. (2018). Transcranial magnetic stimulation of medial prefrontal and cingulate cortices reduces cocaine self-administration: A pilot study. *Frontiers in Psychiatry*, *9*, 80.

McClintock, S. M., Reti, I. M., Carpenter, L. L., McDonald, W. M., Dubin, M., Taylor, S. F., Cook, I. A., O'Reardon, J., Husain, M. M., Wall, C., Krystal, A. D., Sampson, S. M., Morales, O., Nelson, B. G., Latoussakis, V., George, M. S., Lisanby, S. H., National Network of Depression Centers rTMS Task Group, & American Psychiatric Association Council on Research Task Force on Novel Biomarkers and Treatments (2018). Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. *The Journal of Clinical Psychiatry*, *79*(1), 16cs10905.

McHugh, R. K., Fitzmaurice, G. M., Carroll, K. M., Griffin, M. L., Hill, K. P., Wasan, A. D., & Weiss, R. D. (2014). Assessing craving and its relationship to subsequent prescription opioid use among treatment-seeking prescription opioid dependent patients. *Drug and Alcohol Dependence*, *145*, 121-126.

Minimol, K. (2016). Risk assessment and strengths-based case management in elderly care: Scope of social work practice. *Artha Journal of Social Sciences*, *15*(2), 121-121.

Mishra, B. R., Nizamie, S. H., Das, B., & Praharaj, S. K. (2010). Efficacy of repetitive transcranial magnetic stimulation in alcohol dependence: A sham-controlled study. *Addiction*, *105*(1), 49-55.

Pettorruso, M., Martinotti, G., Santacroce, R., Montemitro, C., Fanella, F., & Di Giannantonio, M. (2019). rTMS reduces psychopathological burden and cocaine consumption in treatment-seeking subjects with cocaine use disorder: An open label, feasibility study. *Frontiers in Psychiatry*, *10*, 621.

Pettorruso, M., Spagnolo, P. A., Leggio, L., Janiri, L., Di Giannantonio, M., Gallimberti, L., Bonci, A. & Martinotti, G. (2018). Repetitive transcranial magnetic stimulation of the left

dorsolateral prefrontal cortex may improve symptoms of anhedonia in individuals with cocaine use disorder: A pilot study. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, *11*(5), 1195-1197.

Pripfl, J., Tomova, L., Riecansky, I., & Lamm, C. (2014). Transcranial magnetic stimulation of the left dorsolateral prefrontal cortex decreases cue-induced nicotine craving and EEG delta power. *Brain Stimulation*, *7*(2), 226-233.

Razza, L. B., Moffa, A. H., Moreno, M. L., Carvalho, A. F., Padberg, F., Fregni, F., & Brunoni, A. R. (2018). A systematic review and meta-analysis on placebo response to repetitive transcranial magnetic stimulation for depression trials. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *81*, 105-113.

Remler, D. K., & Van Ryzin, G. G. (2014). Research methods in practice: Strategies for description and causation (2nd ed.). Sage Publication.

Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., & Safety of TMS Consensus Group (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology*, *120*(12), 2008–2039. https://doi.org/10.1016/j.clinph.2009.08.016

Rong, C., Jiang, H. F., Zhang, R. W., Zhang, L. J., Zhang, J. C., Zhang, J., & Feng, X. S. (2016). Factors associated with relapse among heroin addicts: Evidence from a two-year community-based follow-up study in China. *International Journal of Environmental Research and Public Health*, *13*(2), 177.

Salihu, H. M., Salinas, A., Medina, I., Krishnaswami, J., & Aliyu, M. H. (2019). Biopsychosocial determinants of opioid use disorder (OUD) and implications for

maternal and child health research: A scoping review. *Journal of Opioid Management*, *15*(1), 77-91.

Sayette, M. A. (2016). The role of craving in substance use disorders: Theoretical and methodological issues. *Annual Review of Clinical Psychology*, *12*, 407-433.

Shen, Y., Cao, X., Tan, T., Shan, C., Wang, Y., Pan, J., He, H. & Yuan, T. F. (2016). 10-Hz repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex reduces heroin cue craving in long-term addicts. *Biological Psychiatry*, *80*(3), e13-e14.

Su, H., Zhong, N., Gan, H., Wang, J., Han, H., Chen, T., Li., X., Ruan, X., Zhu, Y., Jiang, H., & Zhao, M. (2017). High frequency repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex for methamphetamine use disorders: A randomized clinical trial. *Drug and Alcohol Dependence*, *175*, 84-91.

Substance Abuse and Mental Health Services Administration. (2019). Medication assisted treatment. Retrieved from https://www.samhsa.gov/medication-assisted-treatment

Substance Abuse and Mental Health Services Administration. (2020). Key substance use and mental health indicators in the United States: Results from the 2019 National Survey on Drug Use and Health. Retrieved from https://www.samhsa.gov/data/report/2019nsduh-annual-national-report

Terraneo, A., Leggio, L., Saladini, M., Ermani, M., Bonci, A., & Gallimberti, L. (2016). Transcranial magnetic stimulation of dorsolateral prefrontal cortex reduces cocaine use: A pilot study. *European Neuropsychopharmacology*, *26*(1), 37-44.

Tiffany, S. T. (1990). A cognitive model of drug urges and drug-use behavior: Role of automatic and nonautomatic processes. *Psychological Review*, *97*(2), 147.

Tiffany, S. T., & Drobes, D. J. (1991). The development and initial validation of a questionnaire

on smoking urges. *British Journal of Addiction*, *86*(11), 1467-1476.

Tsui, J. I., Anderson, B. J., Strong, D. R., & Stein, M. D. (2014). Craving predicts opioid use in opioid-dependent patients initiating buprenorphine treatment: A longitudinal study. *The American Journal of Drug and Alcohol Abuse*, *40*(2), 163-169.

Volkow, N. D., Michaelides, M., & Baler, R. (2019). The neuroscience of drug reward and addiction. *Physiological Reviews*, *99*(4), 2115-2140.

Volkow, N. D., Wang, G. J., Telang, F., Fowler, J. S., Logan, J., Jayne, M., Ma, Y., Pradhan, K., Wong, C. (2007). Profound decreases in dopamine release in striatum in detoxified alcoholics: Possible orbitofrontal involvement. *Journal of Neuroscience, 27*(46):12700-12706.

West, R., & Brown, J. (2013). *Theory of addiction*. John Wiley & Sons.

Wise R. A. (2009). Roles for nigrostriatal--not just mesocorticolimbic--dopamine in reward and addiction. *Trends in neurosciences*, *32*(10), 517–524. https://doi.org/10.1016/j.tins.2009.06.004

Yen, C. F., Lin, H. C., Wang, P. W., Ko, C. H., Lee, K. H., Hsu, C. Y., Chung, K., Wu, H., & Cheng, C. (2016). Heroin craving and its correlations with clinical outcome indicators in people with heroin dependence receiving methadone maintenance treatment. *Comprehensive Psychiatry, 65*, 50–56.

Curriculum Vitae

Cameron G. Duncan DNP, MS, APRN, FNP-C, PMHNP-BC, CNE
drduncandnp@gmail.com

Education
University of Nevada, Las Vegas- Anticipated graduation 4/2022. Doctor of Philosophy, Nursing (PhD)
University of Arizona- 2015: Psychiatric-Mental Health Nurse Practitioner (PMHNP) Post-Masters Certificate
University of Arizona- 2014: Doctor of Nursing Practice (DNP) & Master's Degree of Nursing, Family NP
Grand Canyon University- 2012: Masters of Science in Nursing with an emphasis in Nursing Leadership in Health Care Systems
University of Nevada, Reno- 2010: Bachelors of Science- Nursing
Truckee Meadows Community College- 2009: Associates of Science- General Science

Teaching Experience
University of Nevada, Reno- Dean: Debera Thomas PhD
Position: Associate Professor, Psychiatric-Mental Health Nurse Practitioner Program Director
Employment Dates: 7/2017- Current

Chamberlain College of Nursing- Faculty Manager: Valerie Becker MSN, RN
Position: Visiting Professor (Leadership and Role of the APN, Geriatric Primary Care Clinical and Didactic, Advanced Research Methods: Evidence Based Practice)
Employment Dates: 05/2015- 06/2021

University of Arizona- Director of Nursing: Joan Shaver PhD, RN
Position: Adjunct Professor
Employment Dates: 8/2016- 5/2018

College of the Desert- Director of Nursing: Wayne Boyer DNP, RN
Position: Nursing Instructor (ADN program, clinical and theory, Med/Surg, Fundamentals, Med Dosage Calc)
Employment Dates: 01/2014- 3/2015

California State University of San Bernardino- Director of Nursing: Asma Taha PhD, RN
Position: Nursing Instructor (LPN-to-RN and BSN programs, theory)
Employment Dates: 04/2014 – 06/2014

- Pathophysiology Course Instructor

Carrington College of Reno, NV - Director: Sarah Warmbrodt MSN, RN
Position: Nursing Instructor (Theory & Clinical, Med/Surg, Fundamentals, Curriculum & Faculty Dvlpmnt.)
Employment dates: 09/2012-01/2014
Professional Nursing Experience
Duncan Family Healthcare

Position: Chief Executive Officer, President, Nurse Practitioner
Dates: April 2016- Current
Mental Health Populations Served: Anxiety, Depression, Mood Disorders, Schizophrenia, PTSD, Substance Abuse, Personality Disorders; Ages: 5-100+

Borrego Community Health- Supervisor: Glen Grayman, MD
Position: Family and Psychiatric-Mental Health Nurse Practitioner
Employment Dates: March 2015- April 2016
Mental Health Populations Served: Anxiety, Depression, Mood Disorders, PTSD, Schizophrenia; Ages: 3-100+

Veteran's Health Administration (VAMC) - Supervisor: Andrea Wagner MSN, RN
Position: Registered Nurse (Med/Surg/Telemetry)
Employment Dates: May 2010– December 2013

Life Care Center of Reno- Supervisor: Connie Blackmore RN, DON
Position: Staff Nurse, Admission/Discharge Nurse, Wound Care Nurse & Risk Manager
Employment Dates: March 2008- June 2012

Internships
Dr. John Kohut MD, Psychiatry: January 2015- August 2015
Dr. Nina Maw Maw MD, Family Practice: May – December 2014
Dr. Dimple Agrawal MD, Internal Medicine: January – May 2014
Dr. Roger Green DNP, FNP, Family Practice: January – May 2014

Professional Licenses
Advanced Practice Registered Nurse (FNP, PMHNP): NV Board of Nursing, #APRN001965, 2015-Current
Registered Nurse License: Nevada State Board of Nursing, #RN67966, 2011-Current

Certifications
American Nurses Credentialing Center- Certified Nurse Educator: December 2021
American Association for Nurse Practitioners- FNP Certification: #F1214369
American Nurses Credentialing Center- PMHNP Certification: #2015013210
Telemetry Certification, Learn: Rhythm Adult Online Course: American Heart Association, Current
BLS Certification- American Heart Association, Current
Group Fitness Instructor Certification: American Council on Exercise, June 2007

Volunteer Work
Washoe County Health Department: COVID Vaccine Administration RN, 2/2020
Nevada Advanced Practice Nurse Association: Vice President, 9/2020 – Current
Nevada Advanced Practice Nurse Association: Membership and Communications Officer, 6/2016- 9/2020
The Empowerment Center: Executive Board Member, February 2019- June 2021
Advisory Council on the State Program for Wellness and the Prevention of Chronic Disease Sub- Committee on Patient-Centered Medical Homes: Appointed Member, 2016-2019

Nevada Advanced Practice Nurse Association: Membership and Communications Officer, 6/2016-9/2020
Volunteers in Medicine: RN Volunteer, 2014-2015
Human Rights Campaign: Volunteer, 2008-2012
American Assembly for Men in Nursing: Volunteer, 2010- 2012

Publications

Duncan, C. (2021). Diagnosis: Diverticular disease. In Crowley-Koschnitzki, C., Wallace, C. Kay, K. & Letz, K. (Eds.), ***3 P's: Pathophysiology, Pharmacology, & Physical Assessment (pp. 221-224). ACNPF.***

Duncan, C., Shipman, B., Salvacion, C., Jenkins, V., & Richards, S. (2021). Transcranial magnetic stimulation and depression. ***The Nurse Practitioner, 46*****(2), 13-15.**

Duncan, C., Butler, K., & Loa, L. (2021). Cannabis use disorder: Implications and best practices. ***The Nurse Practitioner, 46*****(3), 12-15.**

Duncan, C., Serafica, R., Williams, D., Kuron, M., & Rogne, A. (2020). Telepsychiatry during the COVID-19 pandemic. ***The Nurse Practitioner, 45*****(12), 6-9.**

Duncan, C., Mellum, N., Cuneo, C., Anukam, D., & Anderson-Monroe, C. (2020). Understanding histrionic personality disorder: A guide for APRNs. ***International Journal of Nursing and Healthcare Research, 3,*** **1983.**

Sheppard, K. G., & Duncan, C. G. (2020). Relative value units in health care: Friend, foe, or necessary evil?. ***Journal of the American Association of Nurse Practitioners*****,** ***32*****(9), 626-629.**

Duncan, C. G. (2019). Nicotine dependence: Identification and recommendations. ***International Journal of Nursing and Healthcare Research, 2*****(8), 1113.**

Duncan, C. G. & Sheppard K. G. (2019). Implications and recommendations for addressing insomnia disorder. ***The Nurse Practitioner, 44*****(1), 19-25.**

Sheppard, K. G. & Duncan, C. G. (2018). Caring for patients with borderline personality disorder: Implications and best practice recommendations. ***The Nurse Practitioner*****, 43(6), 14-17.**

Duncan, C. G. & Sheppard, K. G. (2015). The full practice authority initiative: Lessons learned from Nevada. ***The Journal for Nurse Practitioners, 6*****(11), 610-617. doi:10.1016/j.nurpra.2015.01.020**

Duncan, C. G. & Sheppard, K. G. (2015). Barriers to nurse practitioner full practice authority: State of the science. ***International Journal of Nursing Student Scholarship,*** **(2), 1-12 (Article #8).**

Scholarship

APRN Business Ownership Principles for NURS 764 Practice Development of the DNP-University of
Nevada Reno, September 2021

Expert Reviewer for Manuscript for the Journal of the American Association of Nurse Practitioners-
September 2021; "Development and Implementation of Virtual Clinical Skills Experiences for Psychiatric Nurse
Practitioner Students"

Addressing Opioid Use Disorder using Transcranial Magnetic Stimulation: Psych Congress Elevate Conference Poster Presentation, June 2021

Testify for Senate Bill 420: Revises provisions related to health insurance: Supports the development of a public healthcare option, provides pay parity for APRNs on state Medicaid; May 4, 2021

Expert Reviewer for Manuscript for The Nurse Practitioner- April 2021; "Professional values and role socialization of new nurse practitioners."

Testify in Senate for Assembly Bill 91: Revises certain provisions relating to State Board of Nursing: Support to add APRN member to Nevada State Board if Nursing; April 14, 2021

Expert Reviewer for Manuscript for The Journal of the American Association of Nurse Practitioners- March 2021
"Men and Suicide: Primary Care Prevention in the Era of COVID-19 and Beyond"

Expert Reviewer for American Psychiatric Nurses Association Annual Conference Abstracts (Poster and Concurrent Sessions)- March, 2021

Mental Health in Primary Care Settings, Guest Lecture: University of Nevada, Reno, NURS 716R;
Mar 4, 2021

Testify in Assembly for Assembly Bill 91: Revises certain provisions relating to State Board of Nursing: Support to add APRN member to Nevada State Board if Nursing; February 22, 2021

Evaluating Transcranial Magnetic Stimulation to Reduce Opioid Cravings in Opioid Use Disorder: Western Institute of Nursing, 2021

Expert Reviewer for Manuscript for The Journal of American Academy of Nurse Practitioners-
December 2020 "Rethinking the Advanced Physical Assessment Requirement for Psychiatric Mental Health Nurse Practitioners."

Expert Reviewer for Manuscript for The Nurse Practitioner- November 2020 "NPs seek experiential learning opportunities"

PMHNP Content Review Expert for Barkley & Associates, Inc.- October 2020

Expert Reviewer for Manuscript for Western Journal of Nursing Research- October 2020
"Associations of insomnia symptoms with cognition: The Health and Retirement Study"

Expert Reviewer for Manuscript for The Nurse Practitioner Journal- September 2020
"Suicide Detection and Treatment in a Nurse-Led, Interprofessional Primary Care Practice: A 2-year Retrospective Analysis"

Expert Reviewer for American Psychiatric Nurses Association Annual Conference Abstracts (Poster and Concurrent Sessions)- March 2020

Severe Major Depressive Disorder: Transcranial Magnetic Stimulation- November 2019, NAPNA
Addressing Suicide in Nevada- Mae Orvis Symposium Podium Presentation, UNR, April 2019
I Can't Sleep: Implications and Recommendations for Addressing Insomnia Disorder- Mae Orvis Symposium Podium Presentation, UNR, April 2019
NAPNA Representative for Public Comment: APRN/PMHNP Workgroup- Department of Health and Human Services, Division of Healthcare Financing and Policy, January 2019
NAPNA Representative for Public Comment: APRN Parity- Department of Health and Human Services, Division of Healthcare Financing and Policy, December 2018
Psychiatric Mental Health Nurse Practitioner Role, NV Rural Health Day: Nov. 2018 Univ. of NV Reno
Transcranial Magnetic Stimulation- October 2018, NAPNA
Mental Status Examination, Delirium and Dementia- October 2018, ACNP Podcast at UNR
Identifying and Treating Major Depressive Disorder: New Therapies- March 2018, NAPNA
Expert Reviewer for *The Journal of American Association for Nurse Practitioners*- April 2018
Expert Reviewer for *The Journal of American Association for Nurse Practitioners*- November 2016
Full Practice Authority Initiative: Lessons Learned from Nevada: Western Institute of Nursing, 2015
Expert Reviewer for *The Journal of American Association for Nurse Practitioners*- December 2014
The Path to Autonomous Practice: Identifying Legislative Barriers: Western Institute of Nursing, 2014
Odyssey Conference Abstract Review Committee: Sigma Theta Tau International, 2014
Intake and Output, Implementing the New Flowsheets: VA Medical Center, 2012
Nursing Informatics, Patient Exercise Routine Monitoring: University of Arizona, 2012

Awards
American Academy of Nurse Practitioners 2021 Nevada State Award for Excellence: 2021
NV Advanced Practice Nurses Association and Nevada Nurses Foundation Stellar Nurse Recipient: 2020
Nevada Nurses Foundation "50 under 50"- 2019 & 2020
Estelle F. Schuler Nursing Scholarship Recipient, University of Arizona: 2015
Alumni Council Doctoral Candidate Award Recipient, University of Arizona: 2015
National Nurse Practitioner Symposium Grant Recipient: 2014
Nurse Rookie of the Year, Northern Nevada Nurse of Achievement Nomination: 2013
Nurse Faculty Loan Program Recipient: 2013-2015

Professional Memberships
Sigma- Nu Iota
Nevada Advanced Practice Nursing Association
American Association for Nurse Practitioners
Nevada Alumni Association

Committee Work
APNA Awards and Recognition Committee- American Psychiatric Nurses Association, 2020-

Current
APNA Scholarly Review Committee- American Psychiatric Nurses Association, 2020-Current
LOA Evaluation Committee, University of Nevada, Reno, 2020-Current
Peer Evaluation Committee, University of Nevada, Reno, 2020-Current
Annual Evaluation Committee, University of Nevada, Reno, 2020-Current
QLAB/LGBTQ-IA+ Task Force, University of Nevada, Reno, 2019-Current
Faculty Affairs Committee, University of Nevada, Reno 2018-Current
Graduate Program Committee, University of Nevada, Reno, 2017-Current
Doctor of Nursing Practice Program Committee, University of Nevada, Reno, 2017-Current
APRN Program Committee, University of Nevada, Reno, 2017-Current
Curriculum and Instructional Support Advanced Specialty Practice Committee- Univ. of AZ, 2013-2014
Dean of Nursing Performance Review Search Committee Student Representative- Univ. of AZ, 2014
Medication Administration Proficiency Task Force- Carrington College, 2012-2014
Faculty Development Committee- Carrington College, 2012-2014
Collegiality Committee Member: Veterans Administration Hospital, 2010- 2013
Nursing Faculty Search Committee: Orvis School of Nursing (OSN), 2009- 2010
Nursing Admissions, Progressions & Student Affairs Committee: OSN, 2009- 2010
Retention Committee: Life Care Center of Reno, 2008-2010