Protocol Title: Repetitive Transcranial Magnetic Stimulation Equipment Testing and Pilot Study

Abbreviated Title rTMS equipment testing and pilot

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Principal Investigator:

Elliot A. Stein, PhD	NRB, NIDA-IRP	BRC/ 07A711A	443-740-2650	estein@intra.nida.nih.gov

Medical Advisory Investigator:

Name, Degree	Branch/Institute	Bldg/Rm	Phone	Email
Osama Abulseoud, MD	NRB, NIDA-IRP	BRC/07A705	443-740-2732	abulseoudoa@mail.nih.gov

Associate Investigators: *(list all)*

Name, Degree	Branch/Institute	Bldg/Rm	Phone	Email
Thomas Ross, PhD	NRB, NIDA-IRP	BRC/07A719	443-740-2645	tross@mail.nih.gov
Yihong Yang, PhD	NRB, NIDA-IRP	BRC/07A709	443-740-2648	yihongyang@mail.nih.gov
Karen McCullough, MS	OCD, NIDA-IRP	BRC/01A231	443-740-2363	kmccullo@mail.nih.gov
Betty Jo Salmeron, MD	NRB, NIDA-IRP	BRC/07A717	443-740-2651	bsalmeron@mail.nih.gov
Elise Lesage, PhD	Ghent University, Dept. of Experimental Psychology	Henri Dunantlaan 2, B-9000 Gent, Belgium	+32 (0)9 264 6432	elise.lesage@ugent.be

Research Contact:

Elliot A. Stein, PhD	NRB, NIDA-IRP	BRC/ 07A711A	443-740-2650	estein@intra.nida.nih.gov

Total requested accrual: *(separately specify planned accrual for each subject group)*

140 Healthy Volunteers (140 enrollees for 50 completers)

Project Uses Ionizing Radiation: ☒ No ☐ Yes (*attach RSC/RDRC documentation)*

☐ Medically-indicated only

☐ Research-related only

☐ Both

IND/IDE ☒ No ☐Yes *(attach FDA documentation)*

Drug/Device/#__ __

Sponsor: ____________________________

Durable Power of Attorney ☒ No ☐ Yes

Multi-institutional Project ☒ No ☐ Yes

Data and Safety Monitoring Board ☒No ☐Yes

Technology Transfer Agreement ☐ No ☒ Yes

Agreement type and number __DTA____ Expiration Date____N/A_________

Samples are being stored ☒ No ☐ Yes

Flesch-Kincaid reading level of consent form (s): __8.7___

(exclude boilerplate in assessing reading level)

Medical Coverage Level:

TMS administration session(s): Level 3 - The MAI or covering clinician* must be present within the study building

Other protocol hours (non-TMS days): **Level 5** - The MAI is available by beeper or phone.

**Kathy Lightfoot, PA-C is designated as covering clinician for this protocol.*

Level 1 - The MAI administers all drugs and remains physically present in the experimental room during all or part of study session as determined by the Clinical Director.

Level 2 - The MAI must be physically present in the experimental room during all or part of study session as determined by the Clinical Director.

Level 3 - The MAI must be present within the study building.

Level 4 - The MAI must be on the study campus.

Level 5 - The MAI is available by beeper or phone.

I. Précis

Objective: To establish an effective repetitive transcranial magnetic stimulation (rTMS) protocol for stimulating circuits relevant for addiction. Specifically, we will develop stimulation parameters and outcome measures for rTMS of the anterior cingulate cortex (ACC) with a specialized TMS coil: the HAC coil (Brainsway Ltd.). Various parameters of rTMS stimulation (frequency and intensity) will be varied, and the sensitivity of behavioral tasks and MRI measures to this stimulation will be determined. The objective of this protocol is therefore to allow for the development, assessment and refinement of rTMS parameters for stimulating ACC targets. In addition, outcome measures will be developed to capture the effects of this stimulation. Results from this development protocol will be applied to subsequent cognitive imaging protocols.

Study population: Up to 50 healthy, non-smoking adults will be tested in several conditions over up to two weeks. Subjects must fit exclusion/inclusion criteria for TMS and MRI. We expect 140 subjects to be enrolled to arrive at a number of 50 who complete the protocol.

Design: Within-subject design with each subject completing up to 10 rTMS sessions.

Outcome measures: In a first phase, the outcome measure will be the behavioral response on a task that relies on the ACC. In a second phase, outcome measures will be the effects on MR measures. These will include task-related blood oxygen level-dependent (BOLD) responses, as well as resting state BOLD fMRI. Other MR measures, such as magnetic resonance spectroscopy (MRS) and arterial spin labeling (ASL), will also be explored as potential biomarkers.

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III. Background

A) The problem

Repetitive Transcranial magnetic stimulation (rTMS) is a promising technique to target neural networks in addiction. In particular, the recent development of novel H-coils introduces the ability to reach deeper brain areas that play key roles in addiction, such as the anterior cingulate cortex (ACC). However, an effective set of stimulus parameters for ACC stimulation with the HAC coil has not yet been developed. Therefore, it is crucial that optimal stimulation parameters, and appropriate output measures are established during a pilot phase, before further protocols are developed.

B) Transcranial magnetic stimulation (TMS) and therapeutic developments

Over the last decades, transcranial magnetic stimulation (TMS) has become a prominent method in neuroscience, both as a research tool and recently also as a treatment method (Hallett, 2007). TMS is a non-invasive neurostimulation technique that works by applying magnetic pulses over the scalp. These pulses are produced by passing an electrical current through an electromagnetic coil (TMS coil). The current induces a magnetic field in the underlying brain tissue. Various forms of TMS protocols have been developed, with single-pulse TMS eliciting responses that last about 100microseconds, and repetitive TMS having the potential to induce longer-lasting effects (Hallett, 2007). rTMS can be used to disrupt or enhance processing in the targeted region, depending on the stimulation frequency. Specifically, low low-frequency rTMS (1Hz) is associated with inhibitory effects and high-frequency stimulation rTMS (>5Hz, but more usually 10-20 Hz) is associated with excitatory effects (Hallett, 2007). In fundamental research, TMS has become a prominent tool to study brain physiology, thanks to its ability to causally affect brain function in a non-invasive and relatively pain-free manner. In therapeutic settings, rTMS protocols have been used to induce long-term effects in the tissue targeted and connected regions.

The therapeutic application of rTMS is best described for treatment-resistant depression, but has also been explored in other disorders (Wassermann & Zimmermann, 2012). RTMS has been studied in the treatment of depression for almost two decades and daily rTMS over left dorsolateral prefrontal cortex (DLPFC) is now an FDA-approved treatment (Wassermann & Zimmermann, 2012). George et al. (1995) and Pascual-leone, Rubio, Pallardó, and Catalá (1996) were amongst the first to report an improvement in the symptoms of treatment-resistant depressive patients following rTMS (20Hz and 10Hz respectively, over left dorsolateral prefrontal cortex). By 2010, 141 studies had been published on successful rTMS in the treatment of depression (Polley, Navarro, Avery, George, & Holtzheimer, 2011). Among the more notable was a multi-site randomized placebo-controlled safety and efficacy trial with 301 patients, which found high-frequency rTMS to be an effective treatment for treatment-resistant depression (10Hz, left DLPFC, 4-6 weeks; O'Reardon et al., 2007). A recent meta-analysis of randomized, double-blind and sham-controlled trials also confirms the efficacy of high-frequency rTMS over left DLPFC in treating depression (Berlim, van den Eynde, Tovar-Perdomo, & Daskalakis, 2013). The vast majority of effective stimulation protocols for depression target left dorsolateral prefrontal cortex, use high-frequency TMS (10Hz or 20Hz) at intensities of 100-120% of resting motor threshold (the intensity of stimulus over motor cortex required to obtain a motor response in a muscle at rest) for 3 to 6 weeks; Polley et al., 2011). However, positive effects of rTMS in depression have also been found with low-frequency (1Hz) right DLPFC stimulation (Bares et al., 2009; Menkes, Bodnar, Ballesteros, & Swenson, 1999), with high-frequency dorsomedial TMS (Downar et al., 2013b; Salomons et al., 2013), and in a single study using 3Hz rTMS over posterior parietal cortex (Schutter, Laman, van Honk, Vergouwen, & Koerselman, 2009). Over the years, there has been a clear trend towards longer courses of treatment and higher stimulation intensities, as both parameters have been associated with a better response (Aleman, 2013; Hadley et al., 2011; Polley et al., 2011).

Therapeutic effects of rTMS have also been explored in other conditions. In particular, auditory hallucinations in schizophrenia have been successfully reduced with low-frequency rTMS over the left temporo-parietal cortex (Hoffman et al., 2005; Hoffmann et al., 2000; Slotema, Aleman, Daskalakis, & Sommer, 2012). Therapeutic applications in other areas are sparse and have only very recently started to be studied. For example, high-frequency right DLPFC stimulation has been associated with improvement in the core symptoms of post-traumatic stress disorder (Cohen et al., 2004). In addiction, right high-frequency stimulation of DLPFC was shown to lead to a reduction in craving in a population of cocaine dependent subjects (Camprodon, Martínez-Raga, Alonso-Alonso, Shih, & Pascual-Leone, 2007), while high-frequency left DLPFC stimulation was shown to reduce nicotine cue craving (Li et al., 2013b). RTMS could have significant potential as an interventional tool in addiction (Feil & Zangen, 2010; Jansen et al., 2013).

C) The anterior cingulate cortex as a target for addiction

The ACC is crucially involved in craving (Kühn & Gallinat, 2011), a key predictor for relapse (Doherty, Kinnunen, Militello, & Garvey, 1995). Recruitment of the ACC is related to craving in abstinent smokers (Wang et al., 2007), alcoholics (Wilson, Myles, Grasby, & Nutt, 2006), and cocaine addicts (Goldstein & Volkow, 2011), with increased ACC response predictive of relapse (Wilson et al., 2006). There is evidence for a direct link between ACC hyperactivity and craving. In a real-time fMRI study, nicotine-dependent subjects were able to reduce their craving, which resulted in a reduction of BOLD in the ACC (Li et al., 2013a). A single-case study using TMS over the ACC in an alcoholic patient lead to a transient reduction in craving (De Ridder, Vanneste, Kovacs, Sunaert, & Dom, 2011). These data suggest that an experimental reduction in ACC activity could prevent relapse by reducing craving.

The dorsal ACC is plays a major role in cognitive control and response inhibition, which are compromised in addiction (Garavan, Ross, & Stein, 1999; Kaufman, Ross, Stein, & Garavan, 2003). In contrast to its hyperactivity when presented with drug-related cues, the dorsal ACC is hypoactive in addicted individuals when they engage in inhibitory control tasks, which strongly recruit ACC in control subjects (Goldstein et al., 2007; Hester & Garavan, 2004). From a network perspective, the ACC is thought to be part of the salience network, which modulates the relative salience of external cues (such as a cognitive task) or internal cues (such as hunger or craving; Sutherland, McHugh, Pariyadath, & Stein, 2012). The imbalance between internally cued and externally cued networks has been proposed to underlie some of the negative cognitive consequences of addition (Sutherland et al., 2012). TMS may have the potential to restore functional connectivity with ACC which may be compromised during addiction. An avenue worth exploring is therefore whether TMS can normalize the connectivity patterns between these networks and thus alleviate the cognitive side-effects of abstinence.

In sum, the modulation of the ACC could have therapeutic benefits in addiction. Notably, modulation of the ACC response to drug-relates cues could reduce craving and thereby prevent relapse. Moreover, if ACC stimulation can normalize the balance between externally and internally cued neural networks, the negative cognitive side-effects of abstinence may be reduced.

D) The H-coil for "deep rTMS"

Transcranial magnetic stimulation of the ACC is challenging because the structure lies several centimeters below the cortical surface. To reach such deeper regions with TMS, increased current must be passed through the coil. This has the consequence of producing a much greater magnetic field (and thus greater stimulation) in superficial brain regions as well, with potentially negative effects. The need for TMS coils that can stimulate deeper regions while minimizing the effects in more superficial regions has led to the development of novel coil types, such as the H-coils (Brainsway, Ltd.). The H-coil was designed to stimulate deep regions of the brain without requiring high voltage (Roth, Zangen, & Hallett, 2002). With this configuration, the magnetic field does not diminish as quickly as a function of distance. Therefore, functional activation of deep regions can occur at lower voltage settings and with less activation of more superficial regions (Zangen, Roth, Voller, & Hallett, 2005). The H-coil has recently been FDA-approved for the treatment of depression (FDA, January 2013).

E) Safety data on the H-coil

Initial tests:

An initial study of safety using healthy volunteers used two types of H-coil, one stimulating primarily the left prefrontal region and one stimulating bilaterally (Levkovitz et al., 2007). All subjects received 3 days of 10Hz (1s every 20s, repeated 42 times) and 20Hz stimulation (1s every 20s, repeated 42 times), each for 3 days. This double-blind, randomized, controlled study demonstrated that the stimulation was well-tolerated at frequencies of 10Hz and 20Hz with no significant adverse effects, no changes in cognitive abilities, and no changes in mood.

The coil was then tested in several different patient groups to assess safety and potential therapeutic effects. First, a double-blind, randomized study of 65 patients with Major Depressive Disorder (MDD) randomized patients to different coils and different stimulation parameters (Levkovitz et al., 2009). Stimulation was administered for 2 seconds (40 pulses) and this train was repeated 42 times with an inter-train interval (ITI) of 20sec, for a total of 1680 pulses daily, 5 times/week for 4 weeks. The results demonstrated that the stimulation with the H-coil was well-tolerated in this population, and that left DLPFC stimulation at 20Hz and 120% of motor threshold (MT) was effective in decreasing depressive symptoms.

In a second open label, safety and feasibility add-on study of 19 bipolar patients, 20 Hz stimulation at 120% MT was administered for 2 seconds (40 pulses) and this train was repeated 42 times with an intertrain interval (ITI) of 20sec, for a total of 1680 pulses daily, 5x/week for 4 weeks (Harel et al., 2011). One patient suffered a generalized seizure lasting 10 seconds on the 19th treatment day. She was taking Lithium for her bipolar disorder. Of note, this stimulation protocol employed high-frequency 20Hz stimulation, which has been shown to increase the risk of seizures (Wassermann, 1998). There were no other complications or adverse events.

A third double-blind, randomized, controlled study of 12 patients with blepharospasm (dystonia of eyelid opening/closing) received stimulation with the H-coil at 100%MT at 0.2Hz (Kranz, Shamim, Lin, Kranz, & Hallett, 2010). The position of the H-coil was adjusted to target the anterior cingulate cortex and a low stimulation rate was chosen to decrease excitability in this region. There were no adverse events, and no changes in blood pressure, heart rate, or respiratory rate.

Finally, an open label study of 8 patients with schizophrenia used a left-sided H-coil positioned over the temporoparietal junction to determine if stimulation could decrease the occurrence of auditory hallucinations (Rosenberg, Roth, Kotler, Zangen, & Dannon, 2011). The protocol used 1Hz (inhibitory) stimulation at 110% MT for 10 minutes daily for 10-20 days. The stimulation was well tolerated, with one patient experiencing a transient headache. Overall, when used with stimulation parameters that are within safety guidelines (Rossi, Hallett, Rossini, & Pascual-Leone, 2009), the H-coil appears to be safe and well-tolerated.

Summary data from Brainsway

From 2003 through Spring, 2010, 455 patients and healthy volunteers have been treated in Brainsway studies using the TMS H-coil device for different clinical conditions, including major depressive disorder (MDD), schizophrenia, bipolar disorder, addiction (cigarette smoking, cannabis), blepharospasm, Parkinson's disease, and post-traumatic stress disorder (PTSD) (Brainsway, Ltd., unpublished data).

345 of these 437 subjects were treated with high frequency (10-20 Hz) and high intensity ($\leq$120% MT) TMS, for a total of 5760 sessions and 241,014 pulse trains.

138 of these 345 subjects received TMS treatments (1,682 sessions, 71,800 pulse trains) without concomitant psychotropic medications that may lower the seizure threshold. One of these subjects experienced a tonic-clonic seizure lasting 2 minutes after receiving rTMS 20 Hz and 120% MT to the prefrontal cortex (Levkovitz et al., 2009).

207 of these 345 subjects received TMS treatments (4,078 sessions, 169,214 pulse trains) in addition to concomitant medications that may lower the seizure threshold. Three of these subjects experienced seizures, all of whom received TMS at high frequency (20 Hz).

110 of these 455 subjects were treated with low frequency (0.2-1 Hz), high intensity TMS (including 5 who also received high frequency treatment), for a total of 538 sessions (average session duration 15 min) and 1449 pulses. None of these subjects experienced a seizure or any serious adverse event.

Recent published studies using the H-coil

A clinical study compared the MT of the abductor pollicis brevis (APB) muscle with the H-coil and figure 8 coil in 6 healthy volunteers (Zangen et al., 2005). One subject reported a mild, transient headache. There were no other side effects, including no change in cognitive or hearing abilities.

In a subsequent experiment, the H-coil was used to deliver pulses at 1 Hz over 20 sec over five different scalp locations in 3 subjects. The intensity of stimulation was 120% of motor threshold, the interval between the 20-s trains was 2 min and the total number of trains was 10. One of the three subjects experienced a 30 dB hearing loss at 4000 Hz in the left ear that was stable for 10 months and appears permanent. The earplug protection had fallen out for a short period of time during the study (Zangen et al., 2005). The H-coil magnetic field penetrated to a depth of 5-6 cm, compared to 1.5-2 cm with a standard figure 8 coil.

A safety study compared the H1-coil, H2-coil, standard figure-8 coil (Quadstim; The Magstim Company, Ltd.), and sham coil in 32 healthy subjects (Levkovitz et al., 2007). Subjects were randomly assigned to one of four groups: H1 coil (n = 9), H2 coil (n = 9), figure eight coil (n = 8), sham coil (n = 9). All subjects participated in three treatment sessions, one session per day on days 1 (0.05 Hz [1 pulse every 20 seconds]), 3 (10 Hz), and 5 (20 Hz). rTMS was well tolerated, with no major side-effects. There were no scalp lesions and no changes in auditory threshold (measured by audiograms). Computerized cognitive tests found no deterioration in cognitive function, except for transient impairment of spatial recognition memory with the H1 coil on the first day of rTMS (i.e., at 0.05 Hz), but not on the following treatment days. There were no significant emotional or mood alterations, except for reports of “detachment” which were experienced by subjects 24-36 hours after the last H1 coil stimulation, but not following stimulation with H2 coil stimulation.

A recently published study evaluated the H coil in the treatment of medication-free patients with treatment-resistant major depressive disorder (MDD) (Levkovitz et al., 2009). Three different H-coil designs were tested: 23 subjects received H1 (predominantly unilateral), 21 H2 (bilateral), and 19 H1L (unilateral). 53 patients completed the study. The treatment protocol consisted of a drug taper period of 10 to 14 days, followed by 5 days a week of prefrontal rTMS (20 Hz, 2 sec on, 20 sec off, for 20 minutes, i.e., 1680 stimuli) for 4 consecutive weeks (i.e., 20 treatment sessions). Eight of the 18 patients who completed the study with the H1L coil received treatment at 110% of MT; the rest received 120% of MT. There were no reports of seizures, neurological problems, hearing loss, visual changes, or changes in blood pressure. Ten patients reported headaches relieved by non-opioid analgesics during the first week of treatment. There was no impairment of cognitive function (sustained attention, visuospatial memory, cognitive planning, spatial working memory) or psychomotor speed between the beginning and end of treatment. One patient committed suicide 5 days after the last treatment. The Ethics Committee concluded that there was no link between the suicide and the rTMS treatment.

A recently completed study evaluated 5 days a week rTMS treatment for 4 weeks with the H1 coil (20 Hz at 120% of motor threshold over the DLPFC) in patients with treatment-resistant MDD who are also taking anti-depressants (Isserles et al., 2011). The study protocol consists of an initial phase of daily treatment for four weeks, followed by a maintenance phase of once weekly treatments for four consecutive weeks. 57 patients enrolled in the study, with 46 receiving at least 10 TMS sessions and 20 completers. One patient suffered a brief, self-limiting seizure during his second treatment (see above). The only other side effect was mild, transient headaches, some requiring treatment with "common analgesics," in several patients, usually during the first week. One patient withdrew because of headaches.

Two recently published case series involved 13 depressed outpatients (3 taking concurrent anti-depressants) treated with the H-1 coil over the DLPFC at 20 Hz (120% of MT) (Rosenberg, Shoenfeld, Zangen, Kotler, & Dannon, 2010a; Rosenberg, Zangen, Stryjer, Kotler, & Dannon, 2010b). The following adverse events occurred (each in one subject): worsening insomnia (leading to study withdrawal), transient dizziness and nausea, transient numbness in right temporal and cervical zones, trembling of lower limbs (resolved with lowering intensity to 100% of MT), foul smell and sensation of bad taste (with the former continuing for 40 days after treatment cessation). No subject had seizure or other serious adverse event.

In summary, present data indicate that the use of the H-coil is associated with the same risk profile as other TMS coils.

F) An H-coil for anterior cingulate stimulation: the HAC coil

Over 15 H-coil designs have been created thus far, each tailored to stimulate a specific brain region (Roth, Pell, & Zangen, 2013b). Tests by the manufacturer indicate that tissue up to 6cm deep can be stimulated with these coils, based on measurements in phantom model of the human head (Levkovitz et al., 2009; Roth et al., 2013a; Roth, Amir, Levkovitz, & Zangen, 2007).

The HAC coil is specifically designed to target medial prefrontal regions including the ACC. Given the role of medial prefrontal cortical structures in the integration of reinforcing stimuli and goal-directed behavior and its role in addiction, ACC stimulation has therapeutic potential in cue craving and addictive behaviors.

Tests of the HAC coil in a phantom indicate that these medial prefrontal cortex structures can indeed be effectively reached (see Figure 1), and the HAC coil is being used for experimental purposes in a number of laboratories. However, the ability of the HAC coil to effectively stimulate ACC tissue has not been assessed. Specifically, the conditions under which these target regions can be successfully stimulated are yet to be determined. Moreover, appropriate behavioral and neuroimaging outcome measures for ACC stimulation have not yet been identified. Thus, prior to using the HAC coil in further protocols to evaluate potential addiction treatments, a feasible and effective stimulation protocol must be developed.

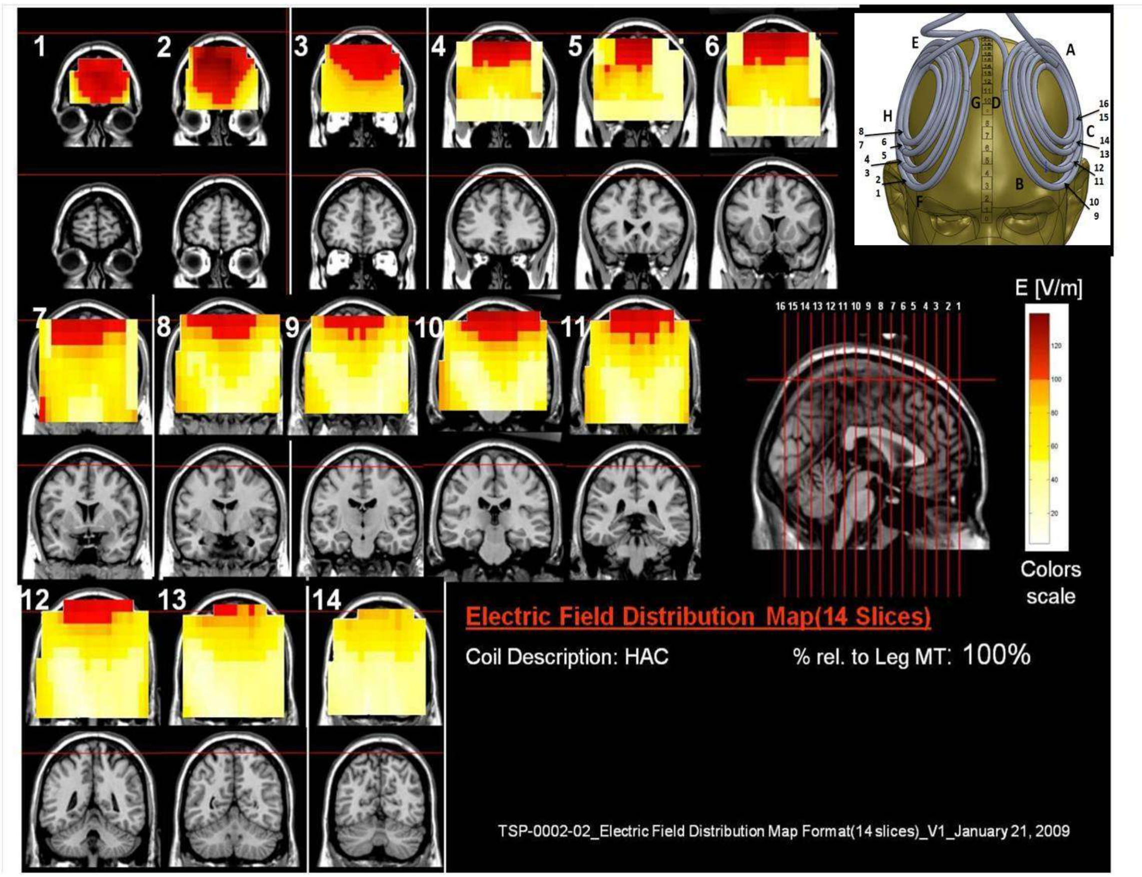

Figure 1: Pseudocolored field maps for the HAC H-coil indicating the electrical field in a saline phantom (Brainsway, LTD.). Regions in red indicate regions induced currents of 100V/m, the level required to activate neuronal tissue (Roth et al., 2007).

IV. Study Objectives

The aim of these pilot investigations is to establish an anterior cingulate cortex rTMS protocol with the HAC coil, and to determine which behavioral and MRI measures can capture the effects of this stimulation. The objective is to establish of a set of effective stimulation parameters for the use of the HAC coil, to establish a behavioral task that is sensitive to the TMS stimulation, and to assess which MRI measures are affected by TMS stimulation. These pilots will form the basis of further investigations, which will use the stimulation parameters and outcome measures obtained under this protocol.

The pilot study will consist of two phases. In the Phase A of the pilot, TMS parameters will be modulated, and TMS effects on behavioral tasks that recruit the ACC will be assessed. This phase will result in (1) a set of stimulus parameters that effectively affect behavior on an ACC-sensitive behavioral task, and (2) the behavioral task. In Phase B of the pilot, the TMS parameters will be applied between two MRI scanning sessions, and TMS effects on MRI measures will be assessed. In both phases, we will test for short-term after-effects following a single dose of rTMS. Candidate outcome measures will be compared prior and immediately following TMS. Participants will be observed for two hours after stimulation.

Following the determination of an effective ACC stimulation protocol, a hypothesis-driven protocol will be submitted that will apply this stimulation protocol in with the general aim of better understanding the underlying circuitry in addiction.

V. Study Design and Methods

A) Study overview

Two phases can be distinguished (see Figure 2). In a first behavioral phase (Phase A), stimulation parameters will be varied in order to establish a protocol that effectively stimulates ACC, as demonstrated by an effect in a behavioral task that is ACC-dependent. The second phase (Phase B) of the pilots will assess the sensitivity of various MRI measures to the stimulation. At least, these fMRI measures will include task-based fMRI (using an MRI-adapted version of the behavioral task) and resting state fMRI. The resting state BOLD signal can be used to assess changes in functional connectivity between the targeted tissue and other brain areas, as well as to measure fractional ALFF, a proxy for the intensity of regional spontaneous activity (Zou et al., 2008). Other MR measures will include MR spectroscopy and ASL. Both of these MR measures have been used to capture TMS effects (Michael et al., 2003; Moisa, Pohmann, Uludağ, & Thielscher, 2010) and have potential as biomarkers of effective rTMS. Using MR spectroscopy, levels of glutamate and other neurometabolites can be compared before and after stimulation. There is some evidence for rTMS-induced modulation of glutamate levels following high-frequency rTMS (Luborzewski et al., 2007; Michael et al., 2003). ASL is used as a proxy for neuronal activity, and different rTMS protocols have been linked to modulations of neuronal activity in the targeted tissue as well as connected regions in an interleaved TMS/fMRI design (Moisa et al., 2010).

In the unlikely event that a behavioral effect is found in Phase A, but no MR effect is found in Phase B, this would indicate that the behavioral effect may have been spurious. In this case, we may reiterate the first step (Phase A). If the range of stimulation parameters for the first behavioral task is exhausted and no behavioral effect is found, a number of MRI sessions may be undertaken to assess whether the most intensive stimulation of the range (120% of motor threshold) is able to affect the ACC, as assessed by ASL or resting state BOLD (fALFF) measures.

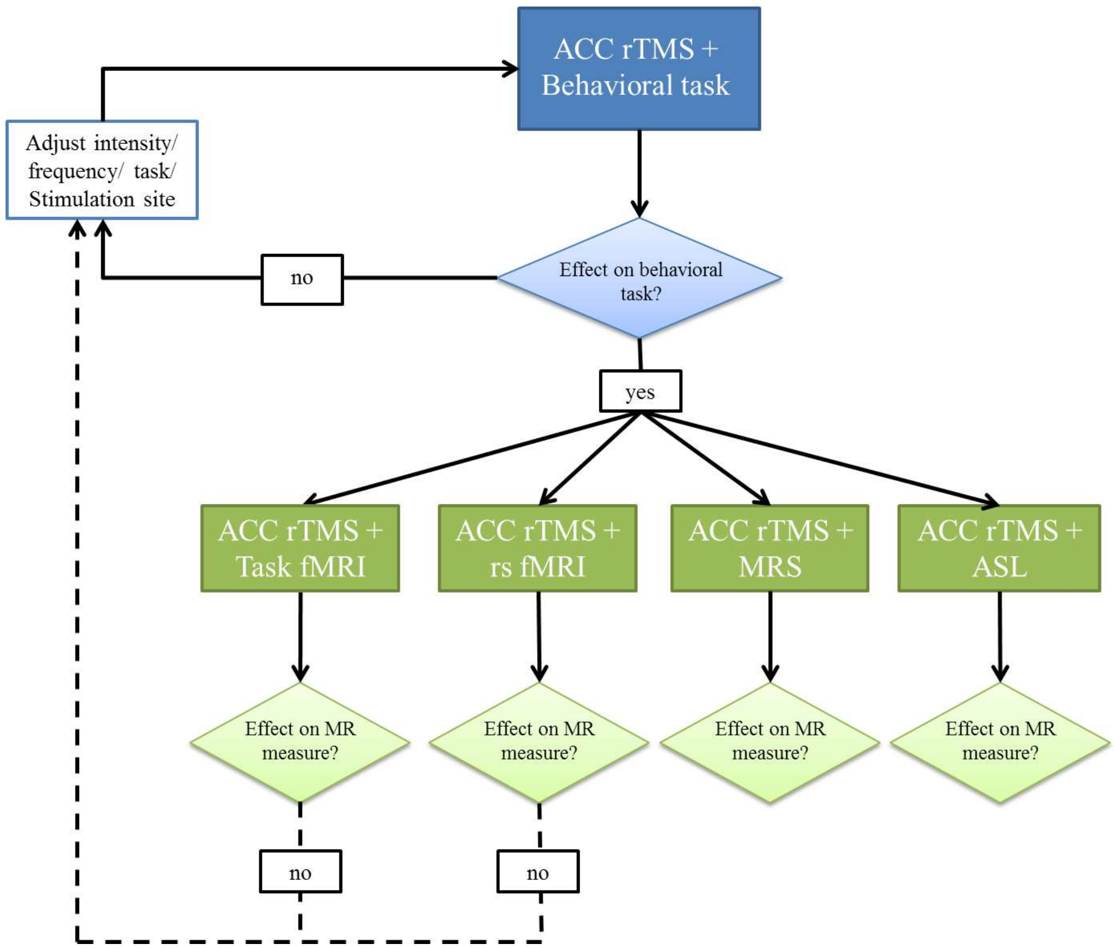

Figure 2. Two phases of pilot tests for repetitive transcranial magnetic stimulation (rTMS) over the anterior cingulate cortex (ACC). In Phase A (blue) stimulation parameters will be varied until an effect on a behavioral ACC-dependent task is seen. Phase B (green) will explore whether the neural correlates of rTMS stimulation can be captured using various MR measures. Solid lines represent planned tests. Dashed lines represent the reprisal of Phase A in the unlikely event that behavioral effects cannot be replicated in the MRI scanner, which would indicate that initial Phase A behavioral results were likely spurious.

Due to the nature of single-session rTMS, stimulation effects are expected to be transient, with effects lasting 15-30 minutes after stimulation (Chen et al., 2003). Therefore, a single session cannot all of the proposed outcome measures. Due to the exploratory nature of the pilot sessions, the precise stimulation parameters are yet to be determined (see Phase A). At a minimum, we will investigate the effectiveness of both 1Hz and 10Hz rTMS, at intensities of 100% and 110% of MT. The initial parameter range is outlined in Table 1.

	1Hz rTMS				10Hz rTMS			
	Sham	100%	110%	120%	Sham	100%	110%	120%
Flanker	A	B	C	D	E	F	G	H
MR Flanker	A*	B*	C*	D*	E*	F*	G*	H*
MR Rest	A**	B**	C**	D**	E**	F**	G**	H**
ASL/MRS	A***	B***	C***	D***	E***	F***	G***	H***

Table 1. Frequency and intensity range (expressed as % of motor threshold) and assessment tools. Letters and asterisks represent the conditions, with the letter representing the stimulus parameters and the asterisk representing the type of outcome measure. Blue indicates behavioral phase, Green indicates MRI phase.

While stimulation parameters such as intensity and frequency will be varied, clear boundaries are put in place with regards to stimulation parameters and number of sessions per person. These boundaries seek to minimize the possibility of adverse events. They will also avoid potential stimulation aftereffects lasting longer than the day of the experiment.

Parameter boundaries:

- **Number of rTMS visits:** Subjects will not participate in more than 10 rTMS sessions under this protocol. There will be no more than 3 consecutive days with an rTMS session. If subjects have participated in this or other rTMS studies, there must be at least two weeks between the time of the last TMS session and the time of first rTMS session under this protocol. Note that the baseline session is not included in this total of 10, because this session will not include rTMS. There is no evidence to suggest that more or more frequent rTMS sessions would lead to adverse effects or effects lasting beyond the sessions, but we chose these parameter boundaries to maximize compliance and not to unduly burden participants.
- **Number of rTMS sessions per day**: Subjects will not receive more than 1 rTMS session per day. There will be at least 20 hours between stimulation sessions. As a rule of thumb, single session rTMS effects are expected to extend past the end of the stimulation for about the same time as the duration of the session (Chen et al., 2003; Thut & Pascual-Leone, 2010).
- **Number of consecutive days with rTMS sessions:** There will be no more than 3 TMS sessions on consecutive days. In studies investigating effects of rTMS on depression, therapeutic effects lasting longer than 24 hours have been reported from 5 consecutive days of active rTMS onwards (Conca et al., 2002; Polley et al., 2011). Restricting the number

of consecutive TMS days to 3 (of which at least one is a Sham session) minimizes the probability of inducing longer-term effects.

- **Length of rTMS stimulation session**: The length of rTMS stimulation will not exceed 30 minutes. No explicit guidelines exist regarding the absolute length of a session, but there are no data to suggest that longer TMS sessions are associated with larger risk, provided other parameters (number of pulses, pulses per train, inter-train duration) are within guidelines (Rossi et al., 2009).
- **Stimulation intensity**: Stimulator intensity shall not exceed 120% of tibialis anterior (leg) motor threshold (MT). Because our stimulation target, like the motor representation of the lower extremities, is situated on the medial longitudinal fissure, we will measure leg motor threshold. The 2009 TMS safety guidelines (Rossi et al., 2009) do not speak to the use of intensities relative to leg motor threshold. However, TMS studies targeting ACC have safely used stimulus intensities ranging from 100% to 120% of leg motor threshold (Downar et al., 2013a; Harmer, Thilo, Rothwell, & Goodwin, 2001; Hayward et al., 2007; Hayward, Goodwin, & Harmer, 2004; Kranz et al., 2010; Salomons et al., 2013). Dr. Jonathan Downar has stimulated ACC with the highest intensity of this range in over 300 patients thus far, without serious side-effects (Jonathan Downar, personal communication). We also consulted with Dr. Mark Hallett, co-author of the most recent safety guidelines, on the use of stimulus intensities relative to leg motor threshold and he agreed it is reasonable to think that these parameters would be appropriate, but, in the absence of published literature, there is no assurance. (Mark Hallet, personal communication). Dr. Hallett is a TMS expert, co-inventor of the H-coil, and Independent Safety Monitor for this protocol.
- **Stimulation frequency**: Frequency of the TMS pulses will vary between 1Hz and 10 Hz. Safety guidelines recommend using frequencies under or equal to 20Hz (Rossi et al., 2009).
- **Pulse train and inter-train interval**: appropriate inter-train intervals and pulse durations will be used as per the safety guidelines for rTMS (Rossi et al., 2009) and parameters used in previous studies with H-coils (Krause, Enticott, Zangen, & Fitzgerald, 2012). For example, for the 10 Hz stimulation the pulse train duration will not exceed 32 pulses and there will be 20 second inter-train intervals (Rossi et al., 2009). For the 1 Hz session there will be continuous 1 Hz stimulation, similar to that used in Krause et al. (2012).

B) Recruitment

Participants will be recruited from the general population through advertising in city, regional or campus newspapers, flyers, via referrals, or radio and television advertisements (See Appendix 2 for recruitment advertisements) under the aegis of protocol 06-DA-N415). Participants will also be recruited from among past candidates for NIDA-IRP studies if written consent to be re-contacted has been obtained.

C) Screening

Screening will be conducted using the basis of screening tools under the NIDA screening protocol, 06-DA-N415. Candidate participants will be screened for participation based on the Inclusion/Exclusion criteria listed above. Informed consent will be obtained from prospective participants prior to the commencement of any screening procedures in a private area where participants are free to ask questions. During screening, participants will be given some initial information regarding the study (see Appendix 3 "Fact Sheets") to determine if they are interested in possible participation. Results of screening evaluations will be reviewed by the Medical Advisory Investigator (MAI) of the protocol who will determine if the individual meets the inclusion /exclusion criteria and qualifies for the study.

D) Study procedures

Before each study session, a nursing assessment will be done which includes vital signs, assessment of recent medical history, medications, drug use, breathalyzer, urine toxicology screen, MRI safety form (if the study session includes MRI scanning), TMS safety questionnaire and for females, a urine pregnancy test. Participant will also be asked when they last had TMS, and whether this was at NIDA or elsewhere. If breathalyzer is positive for alcohol or if urine is positive for THC, subjects will be rescheduled. Other positives will be evaluated by the MAI against known reasons for false positives. In case of a suspected false positive and if there are no safety concerns, the subject may be allowed to participate at the discretion of the MAI. Otherwise, the subject will be rescheduled. Urine samples of suspected false positives will be sent to the laboratory for analysis.

RTMS procedures have been used for over 10 years in a wide variety of settings and there are no published data to suggest that the procedure would have adverse effects on the cardiovascular system. Nevertheless, vital signs will be taken again prior to daily discharge.

In general, participants will partake in one baseline session (orientation visit) and up to 10 rTMS visits. We may invite participants back for additional behavioral training if required. This may be the case if an alternative behavioral task is introduced or if several months have passed between sessions. If for some reason a session is not completed (such as equipment failure) we may bring a participant back to repeat or complete a session. We will not exceed 10 rTMS sessions.

1. <u>Baseline session:</u>

After signing informed consent, there will be a baseline session involving the following:

- *Structural MRI scan.* This scan will be used to locate the stimulation target for TMS on the participant's individual anatomy.. If a structural scan for the subject has been obtained under Protocol 10-DA-N457, this structural will be used, and no structural scan will be acquired during the baseline session.
- *A single pulse TMS session* will be performed where motor hotspot is determined and motor threshold will be taken. This initial TMS session will provide the subject with the

opportunity to experience TMS pulses and withdraw from the study if he or she is uncomfortable with the sensation of TMS pulses. If the motor hotspot cannot be determined within 1 hour, or if the leg active motor threshold is higher than 83% (therefore, if 120% of AMT exceeds the maximum stimulator output of the TMS apparatus), the participant may be discharged at the discretion of the lead investigator. Motor threshold determination is performed using single pulse TMS, which has no effect lasting beyond the pulse itself.

- *Habituation session:* Following the determination of motor threshold, the TMS coil will be placed over the ACC region and a number of test stimuli will be administered. Intensity will be gradually increased according to the subjects' subjective discomfort levels as assessed with a verbal pain rating scale ("Please rate your discomfort level using a number from 0 to 10, with 0 being no pain, 5 being moderate pain and 10 worst possible pain") . The total time stimulated will be 10 minutes or less. Scalp pain due to TMS pulses has been documented to decrease over sessions (Conca et al., 2002; O'Reardon et al., 2007), and similar habituation procedures have been used for ACC rTMS (Downar et al., 2013b). This session does not count towards the number of rTMS sessions.

Depending on the design and phase of the pilot, the baseline session may also include the following:

- A behavioral task may be practiced in the TMS chair or in the Mock scanner to assess baseline performance.
- A simple fMRI task may be performed to functionally define a stimulation region of interest (for example a functional localizer for dorsal anterior cingulate cortex, or a functional localizer for leg motor cortex).
- In Phase B of the pilots, other MRI measures may be taken in the baseline session. These will include resting-state fMRI and task-related fMRI, which may be supplemented with Magnetic Resonance Spectroscopy (MRS), and arterial spin labeling (ASL).

2. rTMS sessions 1-10

A typical experimental session will entail a pre-test on a relevant outcome measure, a TMS session and a post-test on the measure used (see Figure 3). We may explore small variations on the structure of the TMS sessions, such as have the participant perform the task during TMS to probe for immediate effects, or ask the subject to perform more than one behavioral task if the timeframe allows. Pilots will use a within-subject design, whereby performance on a task or a neural response is compared before and after real rTMS or sham rTMS. To enable a direct comparison of different stimulation parameters, the same subjects will partake in several sessions, whereby the task or stimulation parameters will be varied. Under these conditions, it is unlikely that any long-term changes will be induced. Typically, an rTMS session will produce an aftereffect proportional to the length of the session. For example, an rTMS stimulation protocol which lasts 15 minutes is expected to produce an aftereffect for 15 minutes (Chen et al., 2003). Aftereffects lasting over 24 hours have been reported from 5 consecutive real rTMS days onwards (Polley et al., 2011). Here, we limit consecutive testing days to three, of which at least one is a sham session. Subjects will partake in a minimum of three sessions to be deemed completers, and will participate in up to 10 TMS sessions.

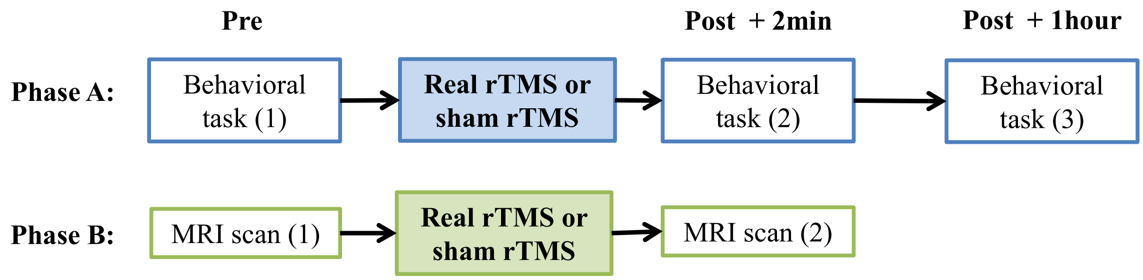

Figure 3. The simplified structure of an rTMS session for Phase A (top) and Phase B (bottom). The behavioral task (Phase A) or type of scan (Phase B) is always the same at all time points.

- *Pre-TMS questionnaires*: Participants are asked to fill in a questionnaire about possible side-effects since the last rTMS session (the TMS monitoring questionnaire), and a questionnaire about their affect (the PANAS) See Appendix 5).

- *TMS calibration*: The subject will be comfortably seated. Motor threshold of the TA muscle will be measured with the H-coil. Motor threshold is defined as the lowest intensity needed to evoke a visible muscle twitch.

- *Pre-stimulation measure (1)*: The participant will be assessed on a pre-stimulation measure. Depending on the design and session, this could be a computer-based behavioral task or an fMRI scanner session which could include resting state fMRI, task fMRI, ASL or MRS. In Phase A of the pilot, the subject will perform the task in the TMS room or the Mock scanner room at NIDA. In Phase B, the subject will perform the pre-stimulation measures in the MRI scanner at NIDA.

- *rTMS*: The subject will be comfortable seated. The H-coil will be placed over the participants ACC. A brief habituation procedure will take place, whereby a small number of test stimuli[1] will be administered to allow the subject to get used to the sensation of rTMS. Intensity will be ramped up according to the subject's discomfort level (as indicated with a verbal pain rating scale; "Please rate your discomfort level using a number from 0 to 10, with 0 being no pain, 5 being moderate pain and 10 worst possible pain") until the target intensity for that session is reached (between 100-120% of motor threshold). The length of this procedure will depend on the individual's responses, but will take no more than 5 minutes of stimulation. After the habituation procedure, there will be a rest period

[1] The test stimulus will consist of 20 seconds of 1Hz TMS or 2 trains of 10hz TMS (with one train consisting of a maximum of 32 pulses, and the intertrain interval at least twice the duration of the train, according to safety guidelines (Rossi et al., 2009). Intensity will be started at motor threshold level and then adjusted upward or downwards dependent on the subject's response.

of approximately 1 minute for every minute of the stimulation to any possible TMS effects to wear off. After this pause, rTMS will be administered. Precise stimulus parameters are to be determined in Phase A, but will remain within the clear boundaries set out in the Study overview section.

- *Post-stimulation measure (2)*. The post-stimulation measure will be identical to the pre-stimulation measure.

- *Post-stimulation measure (3)*. In Phase A of the pilot, a second post-stimulation measure may be taken to assess whether the behavioral effects have returned to baseline. This will be one hour after the stimulation.

- *Post-TMS questionnaires:* At the end of the visit, participants are asked to fill in a questionnaire about possible side-effects (the TMS monitoring questionnaire) and a questionnaire about their affect (the PANAS; See Appendix 5). Vital signs will be taken before daily discharge.

3. Task

The task used to capture ACC function will be the Eriksen Flanker task (Eriksen & Eriksen, 1974). This task engages areas thought to be involved in error monitoring or conflict, robustly activates the anterior cingulate (Bunge, Hazeltine, Scanlon, Rosen, & Gabrieli, 2002), and has been shown to be dysfunctional in drug abusers (Sokhadze, Stewart, Hollifield, & Tasman, 2009). It is one of the most sensitive ACC-related tasks known and is easily taught to subjects. It can be repeated almost indefinitely and continues to activate the region so that there are no expected habituation effects of the task.

In a flanker task, participants respond according to the central item/letter (e.g., H or S) of a congruent (HHHHH or SSSSS) or incongruent (HHSHH or SSHSS) stimulus array. On incongruent trials, the participant is required to suppress the response associated with the flankers and select the response associated with the central item. Participants are presented with a fixation mark on the screen, after which the stimulus array appears. Participants are instructed to respond as fast as possible to avoid feedback indicating that their response was too slow according to a preset reaction time (RT) deadline. Whenever participants respond too slowly, feedback (e.g., "!") is presented indicating that they need to respond faster on future trials.

In Phase A, the aim is to detect increases and decreases in performance in the flanker task due to rTMS. We therefore need as sensitive a performance measure as possible. The flanker task can be made easier of more difficult by varying the number of flankers (with more flankers a more difficult), and by adjusting the timing of the task. We will titrate the level of difficulty to a level at which the subject reaches a certain level of performance. Titrating the difficulty will have the added advantage that the task will be optimally challenging for every subject.

In Phase B, the aim is to find BOLD differences in the ACC when subjects perform a flanker task. The task will be adjusted to be an effective and efficient MRI design. Due to the delayed nature of the BOLD response and the noisy nature of the signal, the timing of the task will be adjusted and the number of trials will be changed to allow proper estimation of the BOLD responses.

In the event that ACC stimulation does not result in behavioral differences with the flanker task, other behavioral tasks that have been found to recruit ACC will be employed (See Figure 2). These tasks are a Stroop task, a multiple source interference task (MSIT), and a Stop Signal Reaction Time (SSRT) task. If performance on none of these tasks is modulated by TMS, we will request an amendment to this protocol before using other tasks.

The Flanker task, Stroop task, MSIT and SSRT task are simple computer-based tasks whereby the subject looks at letters and/or symbols on a screen and responds by means of a button press on a response keypad. Performance is not linked to any monetary gains and the subject is not exposed to any affective stimuli.

4. rTMS procedures

Apparatus and tests: A bilateral HAC-coil (Brainsway Inc, Israel) and a Magstim Rapid2 magnetic stimulator (Magstim, Whitland, Dyfed, UK) will be used to apply rTMS. Each study visit day will start with a nursing assessment that includes urine drug screen, vital signs, and urine pregnancy test for females. If breathalyzer is positive for alcohol or if urine is positive for THC, subjects will be rescheduled. If urine is positive for other illicit drugs, these positives will be evaluated by the MAI against known reasons for false positives. In case of a suspected false positive and if there are no safety concerns, the participants may be allowed to participate at the discretion of the MAI. Otherwise, subjects will be rescheduled. Pregnant females will not be allowed to participate in the study. Vital signs will be assessed again before daily discharge. All study visits will be done at National Institute on Drug Abuse Intramural Research Program (NIDA IRP)

Localization of stimulation area: Structural MRI data will be acquired and the location of the stimulation will be determined using the structural image.

Motor threshold determination:

In determining motor threshold, first the scalp position closest to the motor representation (the “motor hot spot”) is sought. Then the motor threshold (MT) at this location is determined. The hotspot is located during the baseline session, whereas the motor threshold is measured every session. In accordance with the manufacturer’s instructions and other studies that have stimulated the anterior cingulate cortex (Downar et al., 2013b; Salomons et al., 2013), we stimulate leg motor cortex to obtain motor threshold.

Determination of the optimal site (hot spot) for motor cortex stimulation and active motor threshold (AMT): Subjects will be seated in a recliner in a comfortable resting position and fitted with earplugs. The TMS H-coil connected to a magnetic stimulator (Magstim Rapid 2; Magstim Co. Ltd., Whitland, Wales, UK) will be placed over the leg-associated primary motor cortex. While suprathreshold stimuli will be applied, the coil will be moved to determine the optimal scalp position for producing motor evoked potentials (MEP) of maximal amplitude (lowest threshold) in the contralateral target leg muscle.

Subsequently motor threshold will be taken with the H-coil. This is done by using the single pulse mode and applying a series of 10 pulses at least 3 seconds apart. Stimulus intensities start at the level with which the motor hotspot was determined and will then be reduced in steps of 2% of maximal stimulator output. AMT is defined as the lowest stimulus intensity (in percentage of maximum stimulator output) that elicited at least five visible twitches out of 10 consecutive stimulations.
This entire procedure (hotspot determination and threshold determination) can take 30 minutes to 1.5 hour. If the hotspot is difficult to determine using the H-coil, a figure-of-eight coil may be used to find the hotspot location. If no motor hotspot can be determined within 1 hour or if the motor threshold exceeds 83% of maximal stimulator output, the participant may be discharged at the discretion of the lead investigator. The 83% of maximal output is used to allow for stimulation intensities as proscribed to reach 120% of MT. Motor threshold will be measured at the beginning of each rTMS session.

Sham Stimulation:
The selection of the operation mode (active or sham) is done using a magnetic treatment card individually assigned to each subject. Each card is pre-programmed to activate either the active or sham TMS pulse mode when inserted into the card reader attached to the device. Study personnel will not know which mode is being activated by any particular card, thus preserving the double-blind. The H sham coil setting is designed to mimic the auditory artifact and the scalp sensations evoked by the real H coil, and to produce activation of facial muscles similar to the effect of a real H coil, without stimulating the brain itself. However, in experienced subjects, the difference between real and sham TMS, as well as the difference between different intensities of TMS is likely to be noticeable. In an attempt to avoid placebo effects, it is emphasized to the subject that the sensation is related to the stimulation of scalp nerves and muscles, and brain stimulation itself cannot be felt.

Noticeable effects of the stimulation such as facial twitches could give away real TMS to the experimenter. Therefore, while efforts are taken to preserve the double-blind, it is possible that subject or the experimenter can become unblinded to the treatment condition.

Session video recording: If a potential adverse event occurs during TMS stimulation, video footage of the session can help determine the nature of the incident. Thus, video will be recorded during threshold determination and during rTMS, barring any technical difficulties with recording instrumentation. If the session progresses without incident, this footage will be deleted within a week of the session. Should a possible adverse event occur, the footage may be used by the MAI, the ISM, and any experts they wish to consult to determine the nature of the event. Participants will not be given the option to opt out of the video recordings. If they do not wish to be recorded, the alternative is to not participate in the study.

5. Relationship to other protocols

All participants in this protocol will first enter the NIDA IRP screening protocol 06-DA-N415. Data from the screening protocol will be used by investigators in this study to determine eligibility. In line with current NIDA-IRP practice, every subject that is in a NIDA-IRP protocol will be invited to participate in protocol 10-DA-N457. Data obtained under 10-DA-N457 may be shared with this protocol. The anatomic localization scans needed for this protocol may be served by those obtained under10-DA-N457.

E) End of participation

Participation in the study will be terminated once a subject has completed 10 sessions (per this protocol), or if their participation is no longer required. Tonic effects of rTMS can be expected from 2-3 weeks of daily treatment (10-15 sessions) onwards (Wassermann & Zimmermann, 2012). Therefore no lasting effects should be expected from the herein proposed 10 sessions spaced over several weeks; with no more than three sessions on consecutive days and with 33%-50% of sessions not involving real rTMS (sham sessions).

Re-entry into the protocol will be allowed after two weeks following discharge. No published data indicate that there should be an upper limit to the number of TMS sessions in a lifetime; indeed a recent report noted no adverse effects of daily TMS over 40 and up to 80 sessions (Hadley et al., 2011). Nevertheless, we will maintain a period of two weeks where no TMS is undergone before re-entry into the protocol is allowed.

Participants can withdraw from the study at any time should they no longer wish to participate. Typically, no data obtained during the course of this study will be shared with the individual participant or their health care providers.

VI. Inclusion and Exclusion Criteria

A) Description of the study population

We will enroll up to 140 healthy adults who meet the exclusion/inclusion criteria in order to complete 50 subjects. Screening will be conducted using the basis of screening tools under the NIDA screening protocol, 06-DA-N415.

B) Inclusion criteria

Subjects must:

1. Be able to give valid informed consent
2. Be 18 – 55 years of age.
    a. Justification: Many neural processes change with age, and these changes could introduce unwanted variability in both behavioral and MRI signals. In addition, the risk of difficult-to-detect medical abnormalities such as silent cerebral infarcts increases with age.
    b. Screening tool: History. Government-issued forms of identification (e.g. driver's license, birth certificate) will be required when participant appears to be out of age range.
3. Be in good health.
    a. Justification: Many illnesses may alter neural functioning as well as fMRI signals.
    b. Screening tools: Medical Assessment, Medical History and Physical Examination. Medical assessments include: Vital Signs, EKG, oral HIV test, height/weight measurements, urinalysis and blood sample. Tests on the blood sample include CBC, complete metabolic profile, TSH, ESR, STS and HIV (if needed to confirm a positive salivary test for HIV). The following individual laboratory results will independently disqualify individuals: Cholesterol >250 mg/dl, Hemoglobin < 10.5 g/dl, WBC < 2400/µl, LFTs > 3Xnormal, HCG positive, Casual serum glucose > 200 mg/dl, Urine protein > 1+. The MAI will retain discretion to exclude at less extreme values, depending on the clinical presentation. (Serum glucose over 140 mg/dl will be followed up with a fasting serum glucose assessment. Those with fasting glucose below 100 mg/dl may be considered for the protocol. Others will be rejected and referred for work-up.) MAI will make the final judgment on any questionable lab results.
4. Right-handed.
    a. Justification: Using right-handed individuals will reduce variability in BOLD MRI data.
    b. Screening tool: Edinburgh Handedness Inventory.
5. Estimated IQ ≥ 85
    a. Justification: Subjects must be able to perform a cognitively challenging task to a high standard.
    b. Screening tool: Wechsler Abbreviated Scale of Intelligence.

C) Exclusion criteria

1. Personal history of stroke, brain lesions, previous neurosurgery, any personal history of seizure or fainting episode of unknown cause, or head trauma resulting in loss of consciousness, lasting over 30 minutes or with sequela lasting longer than two days.
    a. Justification: Stroke or head trauma can lower the seizure threshold, and are therefore contra-indications for TMS. Fainting episodes or syncope of unknown cause could indicate an undiagnosed condition associated with seizures.
    b. Screening tool: TMS safety questionnaire, Medical History.

2. First-degree family history of any neurological disorder with a potentially hereditary basis, including migraines, epilepsy, or multiple sclerosis.
    a. Justification: Neurological disorders can lower the seizure threshold, and are therefore contra-indications for TMS. First-degree family history of certain neurological disorders with a hereditary component increases the risk of the subject having an undiagnosed condition that is associated with lowered seizure threshold.
    b. Screening tool: TMS safety screening, Medical History.
3. Cardiac pacemakers, neural stimulators, implantable defibrillator, implanted medication pumps, intracardiac lines, or acute, unstable cardiac disease, with intracranial implants (e.g. aneurysm clips, shunts, stimulators, cochlear implants, or electrodes) or any other metal object within or near the head that precludes MRI scanning.
    a. Justification: Any metal around the head is a contraindication for both MRI and TMS, as both methods involve exposure to a relatively strong magnetic field.
    b. Screening tool: TMS safety screening, MRI safety screening, Medical History.
4. Noise-induced hearing loss or tinnitus.
    a. Justification: individuals with noise-induced hearing problems may be particularly vulnerable to the acoustic noise generated by TMS and MRI equipment.
    b. Screening tools: TMS safety screening.
5. Current use (any use in the past 4 weeks, chronic use within 6 past six months) of any investigational drug or of any medications with psychotropic, anti or pro-convulsive action.
    a. Justification: The use of certain medications or drugs can lower seizure threshold and is therefore contra-indicated for TMS.
    b. Screening tools: MRI safety screening questionnaire, Medical history, Medical Assessments: Urine toxicology analyzes for presence of a broad range of prescription and nonprescription drugs.
6. Lifetime history of major depressive disorder, schizophrenia, bipolar disorder, mania, or hypomania.
    a. Justification: The population of interest here is a healthy control population with no psychiatric disorders. In subjects with depression, bipolar disorder, mania or hypomania, there is a small chance that TMS can trigger (hypo)manic symptoms.
    b. Screening tools: SCID Screen Patient Questionnaire. Potential diagnoses will be further evaluated by a counsellor.
7. Meet current DSM V criteria for moderate to severe substance use disorder (excluding nicotine), smoke daily, or urine toxicology positive for any illicit substance inconsistent with history given.
    a. Justification: The population of interest here is a healthy control population with no substance use disorder. Current use of illicit substances could impact on seizure threshold and is therefore contra-indicated for TMS.
    b. Screening tools: SCID Screen Patient Questionnaire. Potential diagnoses will be further evaluated by a counsellor, Drug Use Survey (DUS), Substance Use Disorder Evaluation, Medical Assessments: urine qualitative drug screen is performed for methadone, benzodiazepines, cocaine, amphetamine/methamphetamine, opiates, barbiturates, and tetrahydrocannabinol.

8. Have met DSM V criteria for moderate to severe substance use disorder (excluding nicotine, alcohol and cannabis) in the past, or have met DSM V criteria for moderate to severe substance use disorder for cannabis or alcohol in the past 5 years.
    a. Justification: the population of interest here is a healthy control population with no present or past substance use disorder.
    b. Screening tools: SCID Screen Patient Questionnaire. Potential diagnoses will be further evaluated by a counsellor. Drug Use Survey (DUS), Substance Use Disorder Evaluation.
9. History of myocardial infarction, angina, congestive heart failure, cardiomyopathy, stroke or transient ischemic attack, or any heart condition currently under medical care.
    a. Justifications: the risk of TMS for individuals with a heart condition is unknown.
    b. Screening tool: physical assessment (EKG), medical history.
10. Pregnant women or women with reproductive potential who are sexually active and not using an acceptable form of contraception.
    a. Justification: it is unknown whether TMS poses a risk to fetuses.
    b. Screening tool: Medical assessments (urine pregnancy test) at the beginning of each visit that involves TMS or MRI.
11. History of learning disability or current ADHD
    a. Justification: Subjects should be able to perform cognitive tasks to a high degree of accuracy, both in the MRI scanner and outside the scanner. Subjects with ADHD/LD may engage different neural circuitry even if they can perform the tasks.
    b. Screening tool: Wechsler Abbreviated Scale of Intelligence, Medical history, Adult ADHD Self-Report Scale.
12. Participation in an rTMS session less than two weeks ago.
    a. Justification: in order to limit exposure to TMS, we will not enroll subjects who have received TMS less than two weeks ago.
    b. Screening tool: TMS safety screening questionnaire.

VII. Clinical and Laboratory Methods

Screening samples will be collected and processed as indicated in protocols 06-DA-N415. No other samples are collected for this protocol.

VIII. Collections and Storage of Human Specimens or Data

Clinical data will be stored in the Clinical Data Warehouse (CDW) and in clinical research charts. Research charts will be stored in locked filing cabinet, in a locked room at the NIDA-IRP. Imaging data are stored on a password protected drive on a UNIX server, which is maintained by the NRB. One copy of the consent form is kept in the participant's NIDA-IRP medical chart, the other is kept in a limited access, locked cabinet with other consent forms from the same protocol. Summaries of data analyses (e.g. demographics, laboratory results, consent audit) are stored on a password protected shared NRB data drive. Participant data contained within files on the NRB data drive are identified by ARC number, and not by other personal identifiers such as name. No samples are stored as part of this protocol.

IX. Statistical Analysis

Statistical methods will be chosen as most appropriate to the type of data collected for each phase of the protocol and for each task individually. We propose to test 50 individuals, each of which will partake in up to 10 conditions. Participants should complete at least three sessions in order to be deemed completers (a sham session and two levels of real TMS using the same behavioral task would constitute a useable piece of data).

At a minimum, we plan to test (against a Sham TMS baseline) the efficacy of rTMS at 1 and 10Hz, using intensities of 100% and 110% of motor threshold (and 120% if the former are ineffective) on the Flanker (or Stroop or SSRT) task and on a number of MRI measures (see Study overview, Table 1). Planned group sizes are 10 subjects per condition, but an interim futility analysis will be undertaken when data for 6 subjects are available. A condition will be considered ineffective if fewer than 4 out of 6 subjects show a positive effect. A positive effect is defined as a 6% [2] change in error rate on the Flanker task. In the group of 10 subjects, a condition will be aborted of fewer than 6 out of 10 subjects show an effect. A group size of 10 will allow us to detect large effects (Cohen's d of 1.4) at an alpha level of 0.05. We will employ a within-subjects design to minimize interindividual variability. If the true effect size is smaller than a Cohen's d of 1.4, we should still be able to observe trends.

Accrual Request:

Due to the nature of this pilot protocol, the number of participants needed will depend greatly on the results of the initial tests. To go through the intensity range with one stimulus frequency and

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[2] We derive this estimate from a two-drug double-blind, placebo-controlled study performed at NIDA in which smokers and non-smokers performed a Flanker task on nicotine, varenicline or neither (Carroll, Sutherland, Salmeron, Ross, & Stein, 2013). In this study, the administration of nicotine led to a 9% change in performance (increase in errors on incongruent relative to congruent trials). We use this as an indication of how an intervention (here nicotine) can affect performance on a Flanker task. We take 2/3 of this change (6%) as indicative of an effect of TMS.

one task (see Figure 5), a minimum of 16 subjects are required (if all subjects perform 10 sessions and all tests indicate a positive effect). To assess the proposed range of conditions (see Study overview, Table 1) for one behavioral task, 32 to 40 subjects will be needed if all subjects perform 10 sessions. To accommodate the likelihood that some subjects may not be able to complete 10 sessions, we estimate that we will need 50 subjects to complete this pilot.

Thus, we will enroll 140 subjects to arrive at a number of 50 completers. Participants should complete at least three sessions in order to be deemed completers (a sham session and two levels of rTMS using the same behavioral task. In accordance with NIH guidelines, a person who is readmitted into the protocol (a minimum of 6 month after the participant is discharged, see the parameter boundaries outlined in V.A), he or she will be considered as the same individual for the enrollee count. Official enrollment reports will therefore reflect the number of unique individuals enrolled in the study. However, to retain transparency we will also report the number of re-enrolled subjects along with the number of TMS sessions to the IRB.

If more than 50 subjects are required (for example this is likely to occur if performance on the Flanker task appears not to be modulated by medial prefrontal TMS) we will seek permission from the IRB to recruit additional subjects.

For conditions that show positive trends using a group of 10, a power analysis will be performed, and we will seek IRB approval to recruit an appropriate number of subjects to gain the statistical power needed to assess the effects of the stimulation paradigm with sufficient sensitivity and specificity.

In the event that TMS stimulation appears entirely ineffective (that is, if none of the intensities at 1Hz or 10 Hz elicit effects on the Flanker task or MRI measures), we will amend the protocol and seek permission from the IRB before continuing.

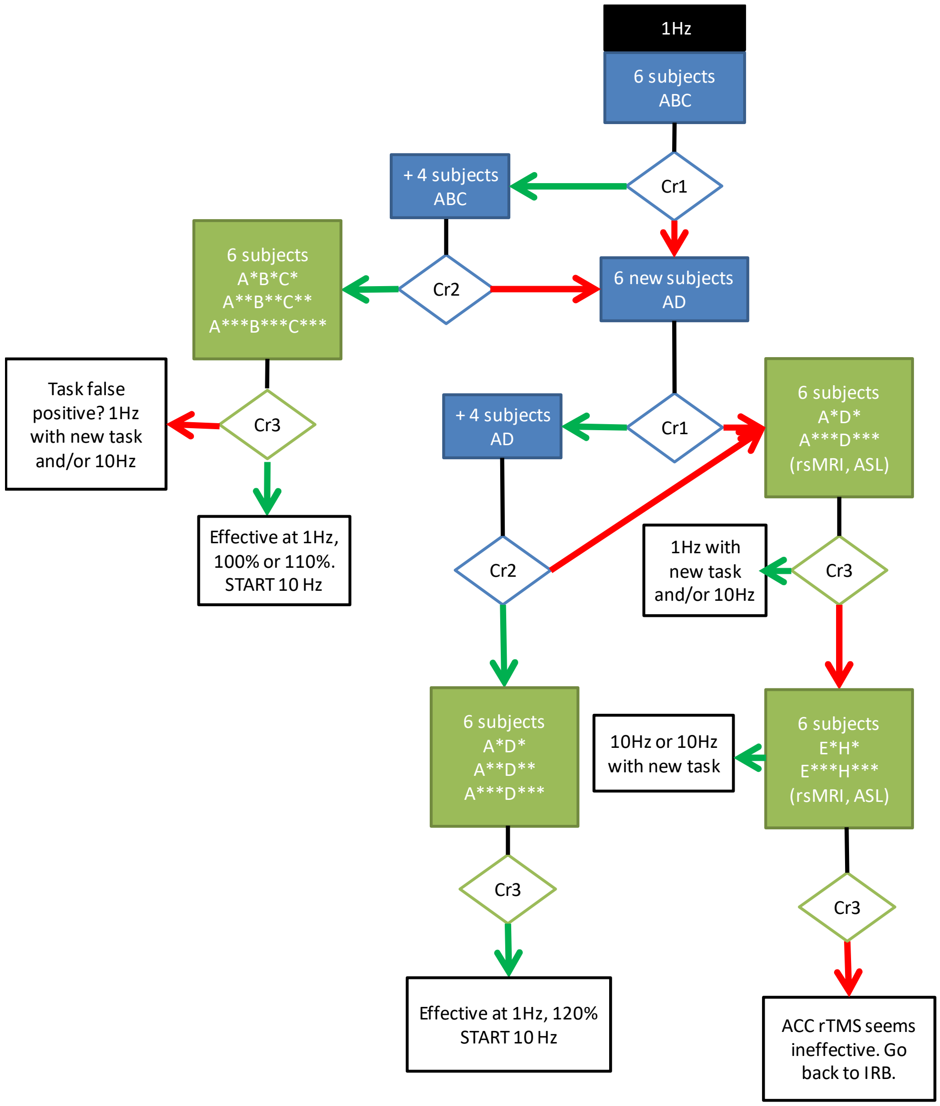

Figure 5. Example flowchart for 1Hz stimulation with the Flanker task. Letters and asterisks represent conditions outlined in Table 1 (Study overview section). Cr 1: Criterion 1; 4 out of 6 subjects show an effect. Cr 2: Criterion 2; 6 out of 10 subjects show an effect. Cr 3: Criterion 3; difference in ACC against sham significant at p<0.001 uncorrected in 2/3 of subjects. Blue: behavioral sessions. Green: MRI sessions. Green arrow: criterion is met. Red arrow: criterion is not met.

X. Additional considerations

This protocol does not intend to determine the safety or efficacy of the HAC coil. Rather, it seeks to establish optimal stimulation parameters for and appropriate behavioral markers and biomarkers of anterior cingulate rTMS. This protocol is therefore exempt from CRF Title 21, part 812, and does not require an IDE. A previously approved protocol (Protocol 479) also uses the HAC coil and has received an exemption from CRF Title 21, part 812, for the same reason.

XI. Subject Safety monitoring

A) Parameters to be monitored

Seizure monitoring procedures: At screening and on each study day involving a TMS session, subjects will fill out the TMS safety form to ensure that there is no change in the subject's suitability for TMS. They will also have a urine drug screen and pregnancy test (females). If urine drug screen is positive, they will be rescheduled; if pregnant, females will be notified, referred if necessary for care, and discontinued from participation in the study. Subjects will be monitored throughout each rTMS session by trained staff. Study staff will be trained in TMS safety using the most recent TMS practice and safety guidelines (Rossi et al., 2009). Study staff will visually monitor subjects at all times during rTMS application for possible signs of seizures, such as involuntary muscle movements, generalized tonic stiffing of muscles, salivary frothing, or loss of consciousness. In the event of a seizure, staff will have immediate access to life support equipment and antiepileptic drugs.

Seizure management procedure: In the event of a seizure, the following procedure (Towne & DeLorenzo, 1999) will be followed by staff in order to minimize additional trauma:

1. Protect patient's head and limbs from injury.
2. Ensure an adequate airway.
   - When jaws are clenched do not attempt to pry open the mouth to insert a mouth gag. At no time should anything be placed in the patient's mouth.
   - When safely able, turn the patient to the side to prevent aspiration and promote drainage of mucus and saliva. Do not force any part of the patient's body during the seizure.
   - Loosen any constrictive clothing.
3. Immediately call the on-call study physician or approved covering clinician (available in the building during TMS sessions). When appropriate, call for medical assistance by dialing 911 in order to have the patient transferred to Johns Hopkins Bayview emergency room
4. Observe patient for:
   - Initial movements/ sensations
   - Progression of movements.
   - Change in respiratory status.
   - Skin color.
   - Incontinence.
   - Level of consciousness:
   - Ability to communicate.
   - Level of orientation.

- Duration of seizure activity. If after two minutes, the seizure has not resolved, physician or approved covering clinician will order and physician/approved covering clinician or nurse will administer, midazolam IM, 10 mg that is contained in a lock box in the TMS suite.
- Provide supportive care after the seizure resolves.
- Orient patient to time and place.

Investigators will provide to any subject experiencing a seizure a letter documenting that the seizure was experimentally produced.

The investigators, counselors and medical staff will be prepared to address psychological or medical issues that may arise during the study. A physician or approved covering clinician knowledgeable about TMS will be immediately available in the building whenever rTMS is being administered and will be available by telephone or pager 24 hours a day for consultation. NIDA health personnel will be available 24 hours a day in the event of a medical emergency. If immediate medical assessment or intervention is required, the subject will be referred to the appropriate medical facility. Information on all adverse events will be cumulated and reported to the Addiction Institutional Review Board (IRB) with each continuing review application. Unexpected or serious adverse events (defined in accordance with NIH and NIDA policy) will be promptly reported to the NIDA Clinical Director and Addictions IRB in accordance with National Institutes of Health (NIH), and NIDA policy.

fMRI: At screening and on each study day involving an fMRI scan, subjects will fill out an fMRI safety form to ensure that there is no change in the subject's suitability for fMRI scanning. They will also have a urine drug screen and pregnancy test (females). If urine drug screen is positive, they will be rescheduled; if pregnant, females will be notified, referred if necessary for care, and discontinued from participation in the study. At all times during fMRI scanning study clinician and scan operator will be present in the control room and subjects will be able to communicate with them via intercom. Subjects will also have a device they can squeeze to alert the operator in case of an urgent issue.

B) Criteria for individual subject withdrawal from the study:

A participant will be withdrawn from the study if he or she:

- so requests, or withdraws consent.
- requires study visits to be rescheduled more than twice for positive urine triage.
- develops an exclusionary medical condition or medical problem, for which, in the Medical Advisory Investigator's (MAI's) judgment, it is in the participant's best interest to be withdrawn from the study.
- becomes or is found to be pregnant

Participants withdrawn from the study for any medical reason will be referred for appropriate medical follow-up.

XII. Outcome measures:

The sensitivity of several outcome measures will be compared and assessed. These measures will include behavioral tasks and MRI measures. Not all MRI outcome measures mentioned in this section will necessarily be investigated for reasons outlined above (see Figure 2).

Behavioral tasks: A flanker task, with the difficulty level adjusted to the individual's capacity will be used. If the flanker task proves ineffective in showing rTMS effects, other tasks which have been shown to recruit ACC will be used. Performance before TMS will be compared with performance after TMS.

Task fMRI: In Phase B, the task will be performed in the scanner. The recruitment of a stimulated area in a task is expected to change under conditions where that area is used. For example, after stimulation, the ACC may be more or less engaged in the incongruent conditions of the flanker task than before stimulation.

Resting-state fMRI: rTMS could be effective in changing connectivity between the targeted tissue and connected regions in networks relevant to addiction. Resting-state connectivity analysis can be used to detect these differences. In depression, there is evidence that rTMS may influence resting-state functional connectivity between a targeted region and brain areas it is connected with (Salomons et al., 2013; Speer et al., 2003).

Other MRI measures: additional MRI measures may be used to further characterize the effects of TMS. These include MR spectroscopy, which is able to measure changes in glutamate and other neurometabolite levels, and arterial spin labeling (ASL) which is able to indirectly capture absolute metabolic changes, and used as surrogate for neuronal activity. Both of these measures have previously been used to capture effects of TMS (Luborzewski et al., 2007; Michael et al., 2003; Moisa et al., 2010; Stagg et al., 2013)

XIII. Human Subjects Protection

A) Regulatory and ethical consideration

The study will be conducted in accordance with Good Clinical Practice (GCP), 21CFR Parts 50 and 56, and all applicable regulatory requirements.

B) Subject Selection

Applicants who fulfill study criteria will be included regardless of race, ethnicity, socioeconomic status, religious and political affiliations, and similar factors. We will base recruitment demographics similar to that of prior recruitment of a healthy control population in Baltimore. The expected demographic composition is approximately 64% White, 32% Black or African American, 3% Asian, 0.3% American Indian and Alaska Native, 0.04% Native Hawaiian and Other Pacific

Islander and 0.8% some other race (http://www.census.gov/). Of this population (any race), 2% are Hispanic or Latino.

APPROVED STUDY POPULATION						
	FEMALE ENROLLMENT	MALE ENROLLMENT	**TOTAL** ENROLLMENT	FEMALE COMPLETERS	MALE COMPLETERS	**TOTAL** COMPLETERS
APPROVED CEILING	70	70	140	25	25	50

NIH TARGETED/PLANNED ENROLLMENT			
	Sex/Gender		
ETHNIC CATEGORY	Females	Males	Total
Hispanic or Latino	2	2	4
Not Hispanic or Latino	68	68	136
Ethnic Category: Total of All Subjects*	70	70	140
RACIAL CATEGORIES			
American Indian/Alaska Native			
Asian	2	2	4
Native Hawaiian or Other Pacific Islander			
Black or African American	23	23	46
White	45	45	90
Racial Categories: Total of All Subjects*	70	70	140

*The “Ethnic Category: Total of All Subjects” must be equal to the “Racial Categories: total of All Subjects.”

C) Exclusion of children

Children under the age of 18 are excluded from this study because safety of rTMS in children has not been studied. In addition, this study is more than minimal risk and presents no direct benefit. Minors can therefore, not be enrolled.

D) Exclusion of other vulnerable populations

Pregnant women will be excluded as it is not known if TMS or fMRI have deleterious effects to pregnant mother or fetus. Those who are unable to understand and provide their own consent will also be excluded, as compliance with study procedures is essential to the integrity of the study.

E) Justification of sensitive procedures

The use of sham (placebo) stimulation is necessary to evaluate the effects of rTMS. This is necessary to evaluate the action of rTMS with respect to study hypotheses.

F) Safeguards for vulnerable populations

No vulnerable populations are recruited into this study. Pregnancy testing is used to prevent fetal drug exposure.

G) Qualifications of investigators

Elliot A. Stein, Ph.D., (PI) is a behavioral neuroscientist and the Chief of the Neuroimaging Research Branch, NIDA/IRP. His background in motivation and reinforcement began as a NIDA postdoctoral fellow with Dr. James Olds at the California Institute of Technology. His laboratory at the Medical College of Wisconsin was one of the first to apply fMRI to the study of human drug abuse. He will share responsibility for the design and implementation of experimental paradigms and procedures and will assist in interpreting and presenting findings and preparing manuscripts. He will not obtain consent.

Osama Abulseoud, M.D. (MAI), is a staff clinician in the Neuroimaging Research Branch. He received his MD degree from Cairo University in Egypt then went through an extensive series of clinical and research training in eminent institutes. He was the sole psychiatrist at Mayo Clinic that established and successfully treated patients with refractory mental illness with deep brain stimulation. He will be responsible for the medical aspects of the protocol, is ACLS certified and will share responsibility for the implementation of experimental paradigms and procedures as well as the interpreting and presenting of findings and preparing of manuscripts. He will obtain informed consent for this protocol.

Betty Jo Salmeron, M.D., is Board-Certified in psychiatry and is a Staff Clinician in the Neuroimaging Research Branch, NIDA/IRP. She trained at the Massachusetts General Hospital, where she was a chief resident. She will be responsible for the medical aspects of the protocol and is ACLS certified. She will share responsibility for the design and implementation of experimental paradigms and procedures as well as the interpreting and presenting of findings and preparing of manuscripts. She will oversee all medical aspects of the protocol and obtain informed consent.

Elise Lesage, PhD, (Guest Researcher at NIDA) is a FWO/Marie Curie Postdoctoral Fellow in the Department of Experimental Psychology at Gent University, Belgium. Prior to her current position, she was a post-doctoral visiting fellow at the Neuroimaging Research Branch at NIDA-IRP. She has extensive experience using neurostimulation techniques (TMS, tDCS), neuroimaging techniques (fMRI), and various cognitive tasks to investigate the neural basis of cognitive processing, and has worked with both clinical and non-clinical groups. She has been trained in TMS procedures, has over 3 years' experience administering TMS. Dr. Lesage will assist in data analysis and manuscript preparation for data from this protocol. Dr. Lesage is fully credentialed with clinical access and her required trainings are kept up-to-date. As such, she is currently able to access and analyze identifiable data directly on NIH systems via VPN. No data is transferred directly to her and she does not store data offsite. These activities are covered by a signed FWA agreement. Dr. Lesage has also been given a copy of SOP 16 - Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations.

Thomas Ross, Ph.D., earned his doctorate in Experimental Plasma Physics and holds the position of Staff Scientist at NIDA-IRP. He has spent the last 20 years involved in the acquisition and modeling of noisy signals. He also spent 2 years as a professional computer programmer and has extensive hardware and instrumentation experience. He will hold primary responsibility in all aspects of the acquired fMRI data including the development and application of novel analysis techniques. He serves as systems administrator on this computationally demanding project and is responsible for the integrity of all data storage and backup, hardware and software implementations and will program and assist in the development of new scanner-compatible cognitive tasks. He will not obtain informed consent.

Yihong Yang, Ph.D. is an Investigator and Chief of the MRI Physics Unit, Neuroimaging Research Branch. Dr. Yang has extensive experiences in the development of functional and structural MRI techniques. He, with his colleagues, has developed fast spiral BOLD imaging, multislice arterial spin labeling perfusion imaging, event-related ASL perfusion imaging, silent fMRI for auditory studies, a novel diffusion tensor imaging, and methods for reduction of susceptibility artifacts. Dr. Yang will be responsible for the development and implementation of functional and structural MRI techniques employed in this protocol. He will not obtain informed consent.

Karen McCullough, B.S., is a research associate at NIDA IRP, with 26 years' experience in clinical research. She has been trained in TMS procedures, is BLS certified and has experience conducting TMS sessions. She will be conducting rTMS sessions in this protocol. She will not obtain informed consent.

H) Consent documents and process

Designation of those obtaining consent

Study investigators designated as able to obtain consent in Qualifications of Investigators section above, will obtain informed consent. In addition to completion of all required NIH and institutional required clinical access and consent trainings (per NIH SOP 25) there will be protocol-specific consent training. In general that involves demonstrated knowledge of protocol procedures and consent material, observing a minimum number of consents and being observed a minimum number of times by the MAI, PI, or other senior staff (as determined by PI or MAI). The MAI or PI will determine when an associate investigator has completed training and is deemed ready to obtain consent. The observation process is usually 3 – 5, but again, is determined by the MAI or PI.

Consent procedure

Written informed consent will be obtained from each subject at entry into the study and will be conducted in a private setting. The consent document will include details regarding all study procedures (e.g. TMS and fMRI). Informed consent is obtained by the following process: Subject reviews the study consent form; a designated investigator[3] then meets with the subject in a private area to review the consent, confirm subject understanding, and to answer any questions. This process will include reviewing the entire document with the participant in order to further ensure participant understanding. Once the subject verbally demonstrates understanding to the investigator and agrees to the process, a consent quiz is administered. Provided the participant answers at least 80% of the questions correctly, the participant is invited to sign the consent form. If the score on the consent quiz is less than 80% correct, the investigator reviews the incorrect answers and re-administers the consent quiz. Failure to obtain 80% correct on the second administration of the quiz excludes the subject from participating in the study. If the participant does score ≥ 80% on the consent quiz, they are asked to sign and date the consent form. Participants will be required to correctly answer questions #5 and #7 of the quiz in order to be in the study (#5 states "I cannot be in this study if I have certain types of metal in your body (**T**/F)" and #7 states "I cannot withdraw from the study once I sign the consent form (T/**F**)." The investigator co-signs the consent form and, the consent is also signed by a third-party witness to the subject's signature. Two copies are made of the consent. The original is attached to the participant's medical record, the participant is given a copy of the consent form for his/her own records and the second copy is stored with other protocol consents in a binder which is located in a locked filing cabinet. The consent quiz is attached to and stored with this latter copy. Once the signed consent has been obtained, the investigator will note the participant's enrollment in the study in the CDW database. Only after this last step has been completed will study procedures begin.

<u>Consent documents</u>
The consent form contains all required elements. The consent document for healthy volunteers is submitted with this protocol.

XIV. Evaluation of Risks/Discomforts and Benefits ratio

A) Anticipated Benefit

There is no prospect of direct health benefits to subjects in this study, but the study is likely to yield generalizable knowledge about the potential therapeutic use of TMS as a treatment in drug abuse. Moreover, the study may also yield generalizable knowledge about the local and brain circuit effects of rTMS delivered by the H-coil.

[3] Please see 'Investigator Qualifications' for details of investigators designated to obtain consent.

B) Risks and discomforts

1. Tasks completed inside and outside of the scanner:

Participants may find the tasks that they are asked to perform during, before and after scanning sessions boring, difficult, and/or frustrating.

> *Risk Minimization*. In order to reduce discomforts associated with performing the emotional and cognitive tasks, scanning sessions and task sessions outside of the scanner are organized in such a way that participants will not perform tasks for extended periods of time and will be given a chance to rest between tasks. In addition, the tasks are designed to make performance neither too difficult nor too easy. Ideally, individual adjustments of task difficulty enable participants to remain actively engaged in the task.

2. rTMS

Magnetic stimulation

TMS uses magnetic pulses, and could therefore interfere with the function of pacemakers, implanted pumps or stimulators. Moreover, the use of magnetic pulses over the head could affect metallic objects inside the eye or skull. The effects of magnetic stimulation on fetal development are unknown.

> *Risk minimization:* Subjects will undergo TMS safety screening and will be excluded from participation if they have pacemakers, implanted pumps or stimulators, and metal objects inside the eye or skull. If they have a question about any metal objects being present in their body, they will be prompted to inform the physician or approved covering clinician. In addition, all magnetic objects (for example, watches, coins, jewelry, and credit cards) must be removed. Women of childbearing potential will have a pregnancy test before each rTMS session and pregnant women will be excluded.

Seizure

The greatest concern with rTMS treatment is the possibility of inducing a seizure. The 1996 and 2008 International Consensus Safety Guidelines describe the maximum safe duration of an rTMS train based on intensity and frequency of the stimulation (Rossi et al., 2009; Wassermann, 1998). Since the issuance of these guidelines, the incidence of TMS-induced seizures worldwide is very low, estimated as "rare" with low-frequency ($\leq$ 1 Hz) rTMS and < 1% with high-frequency (> 1 Hz) rTMS (Rossi et al., 2009). There have been no reports of any subject developing epilepsy or repeated spontaneous seizures after rTMS. All rTMS-induced seizures to date have been transient and self-limiting, without long-term sequela (Loo, McFarquhar, & Mitchell, 2008; Rossi et al., 2009). Concurrent medication has been implicated as a risk factor in some of the seizures reported with rTMS. Some have suggested that certain medications, e.g. tricyclic antidepressants and neuroleptics, should be contraindicated in those receiving rTMS (Rossi et al., 2009; Wassermann, 1998).

Risk Minimization: There is a small risk of seizures from rTMS which is usually associated with high frequency stimulation (20 Hz) and in the context of subjects taking medications that can affect seizure threshold. Neither will be the case in this study. Subjects will undergo TMS screening which will exclude subjects with a family history of epilepsy, subjects who take medication that can affect the seizure threshold, and subjects with recurring fainting spells. Psychotropic medications and use of illicit drugs associated with a reduction in the seizure threshold will also be exclusionary in this study. All staff administering TMS will be trained in BLS. An ACLS certified physician or approved covering clinician will be available in the building while TMS sessions are in progress and will be called in the event of any medical issue.

Vasovagal syncope

A small number of vasovagal syncopes have been reported following rTMS stimulation. In a number of the reports on TMS-induced seizures, it is unclear whether the event was a seizure or a syncope (Rossi et al., 2009).

Risk minimization: Subjects undergo screening and are not admitted to the protocol if they have a history of fainting from an unknown cause. All staff administering TMS will be trained in BLS. An ACLS certified physician or approved covering clinician will be available in the building while TMS sessions are in progress and will be called in the event of any medical issue.

Scalp pain, headache and other minor symptoms

Mild headache responding readily to non-opioid analgesics is the most common side-effect of rTMS reported in depression treatment trials. It may result from direct stimulation of superficial facial muscles or nerves, as rTMS may cause an uncomfortable facial twitch (Loo et al., 2003). However, discomfort levels are quickly habituated to and painful sensations over the scalp decrease over sessions (Anderson et al., 2009; George et al., 2010; O'Reardon et al., 2007). In sham-controlled studies that reported rates of side-effects, about 28% of subjects experienced headache and 39% experienced pain or discomfort during stimulation with active rTMS, compared with rates of 16% and 15%, respectively, after sham rTMS (Loo et al., 2008). There is one report of nausea in two subjects from rTMS over the cerebellum at an intensity of 90% of MT with a frequency of 0.9 Hz for 15 min (Satow et al., 2002). A small number of reports described focal pain, discomfort, and other minor symptoms.

The rTMS coil may heat up with prolonged use, raising the risk of scalp burns (Pascual-Leone et al., 1991).

In a single case report, a 57-year-old women being treated for major depressive disorder reported a pulsating, localized dental twinge in the region of the upper left jaw associated with the rTMS treatment (Ropohl, Hiller, Elstner, Sperling, & Kornhuber, 2004). The pain disappeared during the inter-train interval but emerged again during the next train of stimuli. The pain was dependent on the stimulus intensity and remained despite repositioning of the coil. The cause of the pain is unclear, but may be due to stimulation of the trigeminal nerve by the rTMS magnetic field (Ropohl et al., 2004).

Risk Minimization: The sensation of TMS over the scalp becomes better tolerated with experience, and habituation procedures can exploit this effect to minimize scalp pain. We will therefore include brief habituation procedures during the orientation visit and during rTMS visits. Similar procedures have been used in medial prefrontal cortex stimulation paradigms (Downar et al., 2013b). Headaches and scalp pain usually go away promptly with nonprescription medication, such as acetaminophen, which will be offered to subjects as needed.
Coil heating will be avoided in the present study by using an air-cooled coil and by allowing the coil to cool off between treatment sessions. Moreover, the HAC coil is designed to shut down immediately if the coil temperature exceeds 38° C (100.4° F).
If a participant reports dental pain, rTMS will be stopped. Acetaminophen or other medications may be provided for treatment of pain, if necessary.

Acoustic noise:

Rapid excitation of the stimulation coil produces clicks that have resulted in transient increase in the auditory threshold of human subjects (Wassermann, 1998). This should not occur if earplugs are used. Loo et al., (2001) assessed the auditory threshold before and after 30 sessions of rTMS given over 6 weeks in a depression treatment trial. All subjects wore earplugs during stimulation. No significant mean changes in hearing threshold were detected. Two subjects showed small bilateral increases in threshold at mid to high frequencies, which returned to previous levels when retested 1 month later. Personnel in the rTMS room will also wear hearing protection during the delivery of stimulation. FDA guidelines require testing of auditory threshold only if subjects receive rTMS at a frequency higher than 1 Hz for four or more weeks. Auditory threshold will not be monitored in the current proposed study.

Risk Minimization: The subjects will be fitted with earplugs to wear during the study to protect their hearing from the noise of the magnet. Subjects with known hearing loss will be excluded. Investigators will ask each subject to report immediately any loosening or detachment of a subject's earplug during application of rTMS. If a subject reports or if an investigator observes that a subject's earplug has loosened or fallen out, investigators will immediately stop applying rTMS.

rTMS-Induced Manic Effects and other psychiatric complications

rTMS over dorsolateral prefrontal cortex has induced manic and hypomanic symptoms in a very small number of healthy and depressed subjects.

Nedjat and Folkerts (1999) reported hypomanic symptoms after a single session of rTMS in three female subjects without a prior history of mood disorder. Stimulation parameters were comparable to those used in depression treatment studies and studies of mood changes in healthy subjects.

Two subjects with unipolar depression have shown manic changes with rTMS treatment. George et al. (1995) reported mild hypomania in a patient with refractory recurrent unipolar depression. This female patient had responded well to previous shorter courses of rTMS, but became hypomanic after nine treatment sessions in the third course. The hypomanic symptoms resolved when rTMS was reduced to treatment every second day. Sakkas et al. (2003) reported on a 55-yr-old depressed male who became hypomanic for the first time after 3 weeks of twice daily rTMS to the left dorsolateral prefrontal cortex and concomitant citalopram. Over the following week, medication was stopped, but rTMS continued. His symptoms deteriorated into mania and rTMS was also stopped. The patient gradually became depressed again and five months later, a second course of 2 weeks of twice-daily rTMS also resulted in hypomania. Treatment intensity was decreased to once-a-day TMS treatment, and the patient returned to a normothymic state. rTMS may also have a therapeutic effect in mania, with high-frequency application to the right prefrontal cortex (Praharaj, Ram, & Arora, 2009)

We are aware of six reports of mania induced by rTMS in patients with bipolar disorder (Dolberg, Schreiber, & Grunhaus, 2001; Garcia-Toro, 1999; Hausmann et al., 2001; Huang, Su, & Shan, 2004; Sakkas et al., 2003), in some cases while taking mood-stabilizing medications. In a trial of right prefrontal rTMS for post-traumatic stress disorder, two patients developed a manic episode after the third session (Cohen et al., 2004). One patient was randomized to 1 Hz rTMS and one to 10 Hz. Another subject in this trial developed a ‘mild rage attack, probably related to the stimulation’. Apart from manic symptoms, there is a single case report of high-frequency left prefrontal rTMS inducing transient persecutory delusions in a depressed, non-psychotic subject (Zwanzger et al., 2002).

In all the above cases, the psychiatric side-effects induced by rTMS were transient, resolving with the cessation of rTMS or rapidly responding to pharmacological treatment.

> *Risk Minimization*: Reports of manic symptoms occurred exclusively after unilateral or bilateral DLPFC stimulation, whereas the site stimulated in this section is medial PFC (ACC). The risk of side-effects associated with DLPFC stimulation is therefore minimal. Moreover, the risk for psychiatric complications appears to exist predominantly in subjects with pre-existing psychiatric morbidity (all except one report), and in patients who are on antidepressants or antipsychotics. An important means of minimizing risk in the current proposed study is therefore to exclude this population. In addition, rTMS sessions will not occur on more than 3 consecutive days of which 1 or 2 will be sham sessions. Finally, subjects will be informed of the small risk of transient mania or hypomania, informed of early symptoms to look out for, and instructed to contact the study physician if they believe they are experiencing any such symptoms.

3. MRI scanning

Magnetic field

When used on appropriately qualified individuals, MRI presents virtually no risk as long as technical scan parameters remain within FDA guidelines. There is no exposure to x-rays or radioactivity. The radio waves used have produced burns (most of these minor) in about one in a million exams. The field of the 3T scanner is higher than that of most clinical magnets and there is a remote chance of other risks associated with the stronger magnetic field that might include temporary dizziness with nausea and flickering light sensations. The magnet may move metal implants in the body, the motion of which could be painful and harmful. Metal implants may also cause burns from the radio frequency energy used. While inside the magnet, subjects may experience an acute panic attack due to claustrophobia. Subjects may also experience mild, remittable discomfort from lying in the scanner.

Risk Minimization. To ensure adherence to FDA guidelines for MRI, a trained MRI operator who has been instructed in these guidelines performs all machine manipulations. Other preventative measures include assuring that all equipment to be used during imaging sessions is MR compatible, that participants are familiar with the MRI environment (using the mock scanner), and that participants are aware of how to signal the MR operator if they need to do so during the session. Furthermore, participants are screened prior to each MRI session for any MR contraindications, including metal implants, pregnancy, fear of small, enclosed spaces, and inability to lie still for prolonged periods of time.

Acoustic Noise

The sound generated by an MR system usually consists of a series of repetitive pulses. Acoustic noise is a result of the mechanical vibration produced by the gradient coils when the large currents are applied to them to create time varying imaging gradient fields. Some subjects may experience temporary, reversible shifts in hearing threshold after MRI.

Risk Minimization: MRI compatible headphones and earplugs will be used for hearing protection. The use of these two devices in combination reduces the noise level to levels much lower than those required by the Occupational Safety and Health Administration (OSHA) regulations (Occupational Noise Exposure – 1910.95, www.osha.gov) regulations for lifetime exposure, and provides effective hearing protection for the participants. Nevertheless, some subjects may experience temporary, reversible shifts in hearing threshold after MRI.

4. Mock Scanner

Potential side effects associated with the mock scanner include mild backache from having to lie still for a prolonged period of time, temporary difficulty hearing soft sounds after the exam, and being uncomfortable being in a small enclosed space.

Risk Minimization. Pre-study screening for history of back problems or claustrophobia will minimize the likelihood of side effect from mock scanning. In addition, participants will be given adequate hearing protection to minimize hearing difficulties resulting from Classification of risk (for the study as a whole)

C) Overall Risk Determination

More than Minimal Risk: Overall risk and discomfort in this study are more than minimal due to the use of rTMS. This level of risk is justified because it may facilitate understanding of the therapeutic uses of TMS in addiction, thereby addressing unmet medical needs.

XV. Protection of participants' Privacy and Confidentiality

Great care is taken to protect participants' privacy and strict participant confidentiality will be maintained throughout. Participants will be consented in a private setting. Participants will be assigned a code number without personally-identifying information following their first contact in the protocol. This number will be used throughout the experiment and will be the only identifier on specimen samples, behavioral and physiological archival data, fMRI/MRI and TMS data. The identity of participants will not be revealed at scientific meetings, in publications or other vehicles of public communication. The PI and co-investigators will have access to the ID code, which will be maintained in a separate electronic file from the study data. Medical and questionnaire data will be gathered in a secure database on a closed network. Access to records is protected by a system of password-protected accounts and monitored by the Clinical Director (CD). Data downloaded for analysis will be identified only by participant number. A Certificate of Confidentiality will be obtained for this protocol.

A) Medical records:

All medical history information is stored in the CDW database, which is password protected and has limited access. In addition, each participant is assigned a medical records folder during the screening process, which is used to store source documents collected on paper rather than electronically. This record is kept in locked cabinet and access to these files is limited to study personnel, including study investigators, nursing staff and clinicians.

B) Research Records/Data.

Participant records will be kept in a research record folder upon entry to the first NRB study that they enroll in. This folder is kept in a locked cabinet, in a locked room, which has limited access. Participant folders remain in this room at all times, apart from when required for study sessions. At the completion of each session the folder will be returned to the locked cabinet by the investigator or research associate responsible for the experimental session.

C) Stored Samples.

No biological samples will be stored for future use.

XVI. Study Agents/Interventions

This protocol uses a TMS intervention. We will use an HAC coil from Brainsway Inc., (Jerusalem, Israel). This protocol does not intend to determine the safety or efficacy of the HAC coil and should therefore be exempt from CRF Title 21, part 812. An IDE is not necessary for this protocol. A previously approved protocol (Protocol 10-DA-N479) also uses the HAC coil and has received an exemption from CRF Title 21, part 812, for the same reason.

XVII. Event Characterization and reporting to the IRB, Clinical Director (CD) and Sponsor

Adverse events, protocol deviations, unanticipated problems (UP), Unanticipated Adverse Device Effects (UADEs), serious adverse events, sponsor and serious, are defined as described in NIH HRPP SOP 16 ("Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations."). All adverse events occurring during the study, including those observed by or reported to the research team, will be recorded. Serious unanticipated problems, Unanticipated Adverse Device Effects and serious protocol deviations will be reported to the IRB and CD as soon as possible but not more than 7 days after the PI first learns of the event. Not serious unanticipated problems will be reported to the IRB and CD as soon as possible but not more than 14 days after the PI first learns of the event. Not serious protocol deviations will be reported to the IRB as soon as possible but not more than 14 days after the PI first learns of the event. Deaths and other serious events will be reported to the Clinical Director and IRB within 7 days after the PI first learns of the event.

XVIII. Data and Safety monitoring Plan

a. Selection of a Data and Safety Monitoring Mechanism -

1. Daily Study Monitoring: Data and safety for this protocol will be monitored by the Principal Investigator and MAI.
2. Overall Study Monitoring: Data and safety will be monitored by an Independent Safety Monitor, Dr. Mark Hallett, M.D., a neurologist and TMS expert.

b. Frequency of the monitoring – Dr. Mark Hallett will review data every 10 participants who complete the protocol.

c. Stop or change rules - The study will be put on hold pending investigation to determine appropriate adjustments to the stimulus parameters by the Principal Investigator if repeated (more than 2) serious adverse events that are related to the protocol interventions are encountered.

d. Advanced plans for any interim analyses and/or futility analyses - There are no current plans for interim analyses and/or futility analyses.

e. Information to be monitored -

1. Progress of the study, including assessment of participant recruitment and accrual and adverse events will be reviewed to determine whether there is any change to the risk/benefit ratio of the study. This information will be reported to the IRB at the time of continuing review.
2. Subjects will be monitored for adverse events by study staff. Significant as well as mild adverse effects of rTMS stimulation will be monitored through questionnaires (see Appendix 6; TMS monitoring questionnaire) before and after each rTMS session. At the start of the first session, the baseline occurrence of the events in the checklist will be asked for (i.e. how often do you experience these symptoms per week, per month?) Moreover, participants will be contacted telephonically two to three weeks after the rTMS session and will again be asked the questions from the TMS monitoring questionnaire. The ISM will review unblinded data for all participants, confirm that AE's have been appropriately reported, and determine whether the risk to benefit ratio has changed.
3. There are no external factors (e.g., developments in the literature, results of related studies, etc.) that may have an impact on the safety of participants or on the ethics of the research study.

f. Communication - Adverse events will be recorded by staff in the subjects' medical record and reported to the Clinical Director and NIDA IRB in accordance with all NIH and NIDA requirements for adverse event reporting. Additionally, a summary of study progress, including assessment of participant recruitment and accrual and adverse events will be reported to the IRB at the time of continuing review. If any of the responses to the TMS monitoring questionnaire are positive, the MAI will evaluate the responses and contact the participant further as necessary. The NIDA PI will report adverse events according to established NIH IRB guidelines. ISM reports will be forwarded to the IRB at the time of continuing review or within a separate submission.

XIX. Data/Records Management

Medical and questionnaire data will be gathered in the CDW, a secure database on a closed network. Access to records in the CDW is protected by a system of password-protected accounts and monitored by the Clinical Director (CD). Data downloaded from the CDW for analysis will be identified only by participant number.

Data (physiological, behavioral) obtained during experimental sessions is stored on password protected, network drives, which have limited access. Data stored on these drives is identified by study number, participant code number and/or task. Some files may also include age, race and gender. No personal identifiers are stored with the data. Imaging data is stored on a password-protected LINUX computer with limited access. Data on this server is identified by participant number only with no other identifying information. These data are backed up nightly to a second secure server.

XX. Compensation

All participants will be compensated for their participation following the NIDA-IRP remuneration guidelines. Participants will be compensated for those parts of the study completed. Remuneration rates are summarized in *Table 1*. In addition to the hourly rate ($20/hr), subjects will receive the following remuneration: $15 per TMS session will be given as compensation for inconvenience. $15 will be given per visit that includes MRI scanning. A completion incentive of $25 will be given at the end of each set of rTMS visits, since the within-subject comparison between several conditions on different days is critical for this protocol.
Remuneration rates will vary according to the phase of the protocol (Phase A does not include MRI scanning), and the amount of times the subjects is invited back (3 to 10 rTMS sessions).

Table 2. Remuneration rates.

	Rate	**Time/frequency**
Hourly rate	$20/hour	3-4 hours per visit
Compensation in addition to hourly rate:		
TMS	$15/visit	Up to 11 visits (10 rTMS)
MRI scan (if appropriate)	$15/visit	up to 10 visits
Travel	$15/visit	Up to 11 visits
Compliance Incentive	$25/set of visits	Up to 4 sets of rTMS visits
Total (max) per visit	$125	
Total (min) per visit	$90	
Total (max) overall	$1,465	

XXI. Quality Assurance

A) Quality Assurance Monitor:

The Principal Investigator and the MAI will be monitoring data collection and the study on an ongoing basis. Quality assurance will monitored by the NIDA Quality-Assurance Team on a schedule to be determined by the Clinical Director.

B) Quality Assurance Plan

We will use the quality-assurance plan that is being developed by the NIDA IRP Clinical Director.

XXII. Alternatives to participation or Alternative therapies

Participants do not receive any treatment in this study or forgo any treatment in order to join it. The alternative, therefore, is simply not to participate.

XXIII. Conflict of Interest

A) Distribution of NIH Guidelines

NIH guidelines on conflict of interest have been distributed to all investigators. There are no conflicts of interest to report.

B) Conflict of interest

There are no conflicts of interest to report.

C) Role of a commercial company or sponsor

This study is investigator-initiated and investigator-sponsored.

XXIV. Technology Transfer

There are no confidential disclosure agreements necessary for this protocol. There is a Data Transfer Agreement (DTA) in place with the University of Illinois at Urbana-Champaign (UIUC) to analyze the MRS data. Specifically, Drs. Zhi-Pei Liang and Fan Lam will receive de-identified magnetic resonance imaging data to conduct data analyses specific to measuring glutamate levels using MRS. UIUC will set up a secured ftp server for NIDA to upload the de-identified data. The code to the data will not be shared with investigators at UIUC.

XXV. References

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XXVI. Appendices

A) Appendix 1: Eligibility checklist

186 Inclusion/Exclusion Criteria for CDW

To be considered for participation, individuals must meet the following eligibility criteria:

Note: There may be stricter medical and screening criteria depending on the task or experiment.

Screening

General Participants

	Yes	No	N/A	MAI
1. Age 18 – 55 years	☒	☐		☐
2. Right-handed.	☒	☐		☐
3. Estimated IQ ≥ 85	☒	☐		☐
4. Free from learning disability or current ADHD	☒	☐		☐
5. Free from present or past moderate to severe substance use disorder (as defined by DSM-V) for alcohol or cannabis in the last 5 years	☒	☐		☐
6. Free from present or past moderate to severe substance use disorder (as defined by DSM-V) for any other substance except nicotine.	☒	☐		☐
7. Free from any past or current DSM-V axis I disorder	☒	☐		☐
8. Two weeks or more since last rTMS session, or no previous TMS	☒	☐		☐
9. Free from daily smoking	☒	☐		☐

Medical

General Participants

	Yes	No	N/A	MAI
10. MRI compatible	☒	☐		☐
11. TMS compatible	☒	☐		☐
12. Free of medication that may alter seizure threshold	☒	☐		☐
13. Free of current or history of any heart condition.	☒	☐		☐
14. Free from personal history of any neurological disorder, stroke, brain lesions, previous neurosurgery, any personal history of seizure or fainting episode of unknown cause, or head trauma resulting in loss of consciousness, lasting over 30 minutes or with sequela	☒	☐		☐

lasting longer than two days.				
15. Pregnancy/breastfeeding-free and not planning to become pregnant.	☒	☐	☐	☐
16. Generally healthy (based on physical exam, vital signs, EKG, height/weight, blood work, urinalysis, HIV and Syphilis screen)	☒	☐		☐
HIV negative	☒	☐		☐
Syphilis-free	☒	☐		☐
Cholesterol < 251 mg/dl	☒	☐		☐
Hemoglobin > 10.4 g/dl	☒	☐		☐
WBC > 2399/µl	☒	☐		☐
LFTs < 3Xnormal	☒	☐		☐
Casual serum glucose < 201 mg/dl	☒	☐		☐
Urine protein < 2+	☒	☐		☐
17. Free from first-degree family history of any neurological disorder with a potentially hereditary basis, including migraines, epilepsy, or multiple sclerosis.	☒	☐		☐

B) Appendix 2: Recruitment materials

PTMS	Status	Material	Participant Type	Uses
12-DA-N888 Amend (FF)	In use	  	Healthy volunteers	Print Ad Bus Ad Flyer

PTMS	Status	Material	Participant Type	Uses
10-DA-999 **Amend (YY)**	**In use**		**All participants**	**Card**

<table>
<tr><th>PTMS</th><th>Status</th><th>Material</th><th>Participant Type</th><th>Uses</th></tr>
<tr><td>10-DA-999

Amend (X)</td><td>In use</td><td>


</td><td>All participants</td><td>Website</td></tr>
</table>

<table>
<tr><th>PTMS</th><th>Status</th><th>Material</th><th>Participant Type</th><th>Uses</th></tr>
<tr><td>12-DA-N888

Amend (W)</td><td>In use</td><td>
</td><td>All participants</td><td>Flyer.</td></tr>
</table>

PTMS	Status	Material	Participant Type
On line Posting Healthy Volunteer	In use	888(I)	**Research opportunities available for volunteers who DO NOT smoke cigarettes or use drugs of any kind.** The National Institute on Drug Abuse (NIDA) conducts research studies to find out how various drugs, including nicotine, affect the body, the brain, and behavior. Your part in a NIDA research study could help us better understand how the healthy brain works and how to prevent and treat drug abuse and addiction. The studies take place in East Baltimore area. All volunteers will receive money for their participation in a study.

			If you are interested in being a healthy control in a NIDA research study, please call 1-800-535-8254 or 443-740-2295 or visit www.ResearchStudies.DrugAbuse.gov for a confidential screening.
Craigslist Posting w/titles **Healthy Volunteer**	In use	888 (B)	**1. Are You Drug Free? Join a Research Study at NIDA** **2. Healthy Participants: We Need You for a Research Study!** **3. Healthy Volunteers Needed to Help Scientists Learn About the Body and Brain** **4. Don’t Smoke or Use Drugs? Participate in a Confidential Research Study** **5. Don’t Smoke or Use Drugs? Join a Research Study as a Healthy Volunteer** **6. NIDA Seeks Healthy Participants for a Research Study** **7. Help Advance Science — Join a Research Study** **Research opportunities available for volunteers who DO NOT smoke cigarettes or use drugs of any kind.** **The National Institute on Drug Abuse (NIDA) conducts research studies to find out how various drugs, including nicotine, affect the body, the brain, and behavior.** **Your part in a NIDA research study could help us better understand how the healthy brain works and how to prevent and treat drug abuse and addiction.** **The studies take place in East Baltimore area. All volunteers will receive money for their participation in a study.** If you are interested in being a healthy control in a NIDA research study, please call 1-800-535-8254 or visit www.ResearchStudies.DrugAbuse.gov for a confidential screening.

C) Appendix 3: Fact Sheet

STUDY T-DA-1042 FACT SHEET

T-DA-1042: "rTMS equipment testing and pilot"

All visits will take place at the NIH/NIDA research facility on the Johns Hopkins Bayview Medical Campus. This study will use a type of brain stimulation called "repetitive transcranial magnetic stimulation" (rTMS) to stimulate a part of the brain that is thought to play a role in decision making and in addiction. This study is looking at how stimulating this area affects brain function, thinking and decision making.

rTMS stimulation:

TMS uses a magnet to stimulate parts of the brain and is not an invasive procedure. We place a coil on the scalp and deliver magnetic pulses. Similar types of brain stimulation are used to understand brain function in healthy participants, and this type of brain stimulation is also used to treat depression. It is now being studied for other mental problems. We will measure brain function after rTMS stimulation using a cognitive task and/or magnetic resonance imaging (MRI). MRI uses a magnet and radio waves to measure brain function. The procedures conducted in this study will help us design future studies in people who are suffering from addiction. Participation in this study will consist of 4 to 11 visits. At each visit (except the first) you will have an rTMS session. During some of the visits you may also have two MRI scans.

rTMS has been used on thousands of people throughout the world. Most people do not find the stimulation painful. Common side effects can include contractions of scalp muscles, headache and hearing disturbance. These usually go away promptly without treatment. Rare side effects include seizures but this has occurred largely in persons taking certain medications and in people with past seizure disorders. Persons on such medications or those that have past or family history of seizures will not be able to participate.

Study commitment:

- 4 to 11 total sessions
- First visit includes consent, orientation, and a baseline assessment, and can take up to 5 hours. This session will include a TMS session and may also include an MRI scan.
- Visits 2-11 will take 3-4 hours.
    - There will be a brief medical assessment at each visit
    - There will be an rTMS session at each visit.
    - Most visits will include two or three thinking tasks.
    - Some or all visits can include two short MRI scans (30-45 min). During these scans you may be asked to perform a thinking task, or just to relax. The MRI scans will take 30-45 minutes each.

Compensation:

Compensation will be $20 per hour during each study visit which will last from 3-4 hours; $15 per visit if this visit has MRI scans, and an additional $15 for each TMS session. Fifteen dollars compensation for travel costs will also be given per visit, and $25 per set of studies will be given as a completion incentive.

D) Appendix 4: TMS information sheet

TMS INFORMATION SHEET

What is TMS?

TMS (transcranial magnetic stimulation) is a method to non-invasively stimulate regions of the brain. To deliver TMS, a wire coil is placed on the head. A brief electrical current is passed through the coil to create a magnetic pulse that stimulates the brain. When a long series of pulses is delivered in short succession, this is called repetitive TMS or rTMS. The effects of rTMS depend on what part of the brain the coil is placed over. The duration of the effect depends on how long the part of the brain was stimulated for. For example, if the rTMS is delivered for 30 minutes, the effects will last about 30 minutes after the stimulation is over. In this study we will deliver no more than 30 minutes of rTMS. Therefore, the effects are expected to wear off by the time you leave NIDA.

This is the TMS helmet that will be used in this study. You will also be fitted with a cap like the one displayed.

What does TMS feel like?

Scalp sensation and muscle twitches: Your brain does not actually feel the TMS pulses, because there are no pain receptors or other sensory receptors in the brain. What you feel during TMS is stimulation of the muscles and nerves around your head and scalp. We will use different types of TMS and these are likely to differ in the way they stimulate the overlying nerves and muscles and in how they feel. Many people describe the sensation of these muscle contractions as a series of taps on the head. Depending on which muscles and nerves get stimulated, these taps can feel quite hard and uncomfortable, but usually the discomfort decreases as you get used to the sensation. In addition to the tapping sensation, it is possible that you will blink involuntarily and it as also possible that you will feel a twitching or ticklish sensation on other parts of the head (for example a tickling sensation over the nose). These side effects stop after the rTMS pulses stop. Any remaining scalp pain from TMS is easily treated with over-the-counter pain medication, which we will provide to you if requested.

During the first visit, you will receive TMS pulses at a number of different strengths. During this procedure, we will we slowly increase the strength of the pulses, to allow you to get used to the sensation. We will ask you how uncomfortable the stimulation is and will only increase the strength of the stimulation if you agree to this. Before every rTMS session, we will repeat this procedure briefly.

Sound: TMS makes a clicking sound, which can be rather loud. You be fitted with earplugs during the rTMS stimulation session.

Screening precautions:

Metal: TMS works with magnetic pulses and can therefore have an impact on metal. All metal around the head must be removed before the stimulation. If you have metal objects inside the eye or skull you cannot participate in this study. You will be screened for the presence of metal and if you have any, you will not receive TMS.

Implanted medical devices: Because of the magnetic pulses, TMS can interfere with implanted medical devices and will not be done in people who have pacemakers, implanted pumps or stimulators (like cochlear implants). You will be screened for implanted devices and if you have any, you will not receive TMS.

Noise: TMS makes a clicking sound, which can be rather loud and can lead to hearing damage if no ear protection is worn. You be fitted with earplugs during the rTMS session. If you already have some hearing loss or a persistent ringing in your ear (tinnitus), you may be particularly vulnerable to hearing damage from the sounds. You will be screened for these conditions and if you have any, you will not receive TMS.

SIDE-EFFECTS

Common side-effects

Most people who receive TMS do not report any side-effects. However, it is estimated that about 5 out of every 100 people who receive TMS report mild, transient side-effects after the stimulation.

Headache: In about 2 out of every 100 sessions, individuals develop a headache after the stimulation. These headaches can be treated with over-the-counter pain-killers, which will be provided to you if necessary.

Nausea: In about 1 out of every 100 sessions, participants report nausea after the stimulation. This has only been reported after stimulation of a different part of the brain than the one we stimulate, so it is unlikely that it will happen in this study. However, there will be medically trained staff available to respond appropriately if this should happen.

Muscle pain: About 1 in 200 people report muscle aches after TMS, and these tend to be muscles around the area stimulated. Muscle pains tend to occur after stimulation of areas different than the one we stimulate in this study.

Uncommon side-effects

Seizure: There have been a very small number of reports of people getting a seizure during or after TMS stimulation. These seizures were single, non-recurring events, which did not lead to the development of a seizure disorder. In most cases, seizures have happened with people who already had an elevated risk of seizures or after they received TMS with a very high stimulation rate. The stimulation rates in this experiment are much lower. If you have higher risk of seizure, you cannot participate in this study. For example, if you have a family history of epilepsy, or if you are on any medication that makes you more vulnerable to seizures. You will be screened for these conditions and if you have any, you will not receive TMS. It is therefore extremely unlikely a seizure will be induced. However, we will have medically trained staff available to respond appropriately if this should happen.

Vasovagal syncope (fainting): There have been a small number of reports of people fainting during or immediately after TMS. It is very unlikely that this would happen. However, medically trained staff will be available to respond appropriately if this should happen.

Manic symptoms: There have been a very small number of reports of people developing manic symptoms (excited or euphoric mood) after TMS stimulation. This has only happened after stimulation of a part of the brain that will not be stimulated in this study. In addition, most of the people who showed manic symptoms already had a psychiatric disorder like bipolar disorder or post-traumatic stress disorder. This is a why if you have ever been diagnosed with a psychiatric disorder you cannot participate in this study.

Feelings of detachment: There have been a very small number of reports of people feeling “detached” after TMS stimulation. This has only ever happened after the use of a piece of equipment that we will not use in this study and after stimulation of a different part of the brain than the area we will stimulate in this study. In cases where it this has been reported, it was gone in the first hours or days following stimulation.

MONITORING OF SIDE-EFECTS

To monitor possible side effects of stimulation, we will use questionnaires at each visit. Please fill these in truthfully. Two to three weeks after your participation, we will also contact you telephonically to ask you whether you have had any side-effects of the rTMS. Like all information gathered during the study, your answers are always confidential.

E) Appendix 5: rTMS questionnaires

TRANSCRANIAL MAGNETIC STIMULATION (TMS) MONITORING QUESTIONNAIRE

Please answer the questions listed below. The information you provide will be treated as confidential and will be held in secure conditions. Group results of this survey may be published, but no information will be disclosed that can identify any individual person. If you have any questions, please ask the researcher who gave you this form.

Please tell us if you experienced any of the following symptoms following your most recent TMS session.

Seizure

☐ Yes ☐ No **Details:**

Fainting or Collapse

☐ Yes ☐ No **Details:**

Dizziness

☐ Yes ☐ No **Details:**

Nausea or vomiting

☐ Yes ☐ No **Details:**

Headache

☐ Yes ☐ No **Details:**

Muscular aches

☐ Yes ☐ No **Details:**

Muscle spasm or twitch

☐ Yes ☐ No **Details:**

Insomnia

☐ Yes ☐ No **Details:**

Sensory Problems

☐ Yes ☐ No **Details:**

Difficulties speaking or understanding speech

☐ Yes ☐ No **Details:**

Lack of coordination

☐ Yes ☐ No **Details:**

Slowness or impairment of thought

☐ Yes ☐ No **Details:**

Other (please specify)

☐ Yes ☐ No **Details:**

Any other comments

Do not write below this line (for staff use only)

Details of protocol undertaken TODAY: to be completed by researcher following session

Researcher	Participant ARC	Sham/Active (cardno)	TMS Frequency	TMS Intensity	No. Pulses

POSITIVE AND NEGATIVE AFFECT SCALE (PANAS)

This scale consists of a number of words that describe different feelings and emotions. Read each item and then list the number from the scale below next to each word. Indicate to what extent you feel this way right now.

Right now I feel…	very slightly or not at all	a little	moderately	quite a bit	extremely
interested	1	2	3	4	5
excited	1	2	3	4	5
upset	1	2	3	4	5
strong	1	2	3	4	5
guilty	1	2	3	4	5
scared	1	2	3	4	5
scared	1	2	3	4	5
hostile	1	2	3	4	5
enthusiastic	1	2	3	4	5
proud	1	2	3	4	5
irritable	1	2	3	4	5
alert	1	2	3	4	5
detached	1	2	3	4	5
inspired	1	2	3	4	5
nervous	1	2	3	4	5

Right now I feel…	very slightly or not at all	a little	moderately	quite a bit	extremely
determined	1	2	3	4	5
attentive	1	2	3	4	5
jittery	1	2	3	4	5
active	1	2	3	4	5
afraid	1	2	3	4	5
ashamed	1	2	3	4	5