ANCILLARY REVIEWS

Which ancillary reviews do I need and when do I need them? Refer to HRP-309 for more information about these ancillary reviews.			
Select yes or no	**Does your study…**	*If yes…*	***Impact on IRB Review***
☐ **Yes** ☒ **No**	Include Gillette resources, staff or locations	*Gillette Scientific review and Gillette Research Administration approval is required. Contact: research@gillettechildrens.com*	**Required prior to IRB submission**
☐ **Yes** ☒ **No**	Involve Epic, or Fairview patients, staff, locations, or resources?	*The Fairview ancillary review will be assigned to your study by IRB staff Contact:* ancillaryreview@Fairview.org	**Approval must be received prior to IRB committee / designated review.** **Consider seeking approval prior to IRB submission .**
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☐ **Yes** ☒ **No**	Include the use of radiation? (x-ray imaging, radiopharmaceuticals, external beam or brachytherapy)	*Complete the AURPC Human Use Application and follow instructions on the form for submission to the AURPC committee. Contact: barmstro@umn.edu*	**Approval from these committees must be received**

☒ **Yes** ☐ **No**	Use the Center for Magnetic Resonance Research (CMRR) as a study location?	*Complete the CMRR pre-IRB ancillary review* *Contact: ande2445@umn.edu*	**prior to IRB approval;** **These groups each have their own application process.**
☐ **Yes** ☒ **No**	Include the use of recombinant or synthetic nucleic acids, toxins, or infectious agents?	*Complete the IBC application via eprotocol.umn.edu* *Contact:*	
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☐ **Yes** ☒ **No**	Use data from the Information Exchange (IE)?	*The Information Exchange ancillary review will be assigned to your study by IRB staff* *Contact: ics@umn.edu*	**Approval must be received prior to IRB approval.** **These groups do not have a separate application process but additional information from the study team may be required.**
☒ **Yes** ☐ **No**	Use the Biorepository and Laboratory Services to collect tissue for research?	*The BLS ancillary review will be assigned to your study by IRB staff.* *Contact: cdrifka@umn.edu*	
☒ **Yes** ☐ **No**	Have a PI or study team member with a conflict of interest?	*The CoI ancillary review will be assigned to your study by IRB staff* *Contact: becca002@umn.edu*	
☒ **Yes** ☐ **No**	Need to be registered on clinicaltrials.gov?	*If you select "No" in ETHOS, the clinicaltrials.gov ancillary review will be assigned to your study by IRB staff* *Contact: kmmccorm@umn.edu*	
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Protocol Title	VISUAL SURROUND SUPPRESSION AND PERCEPTUAL EXPECTATION UNDER PSILOCYBIN
Principal Investigator/Faculty Advisor	Name: Jessica L. Nielson, PhD
	Department: Psychiatry & Behavioral Sciences
	Telephone Number: (612) 624-9469
	Email Address: jnielson@umn.edu
Student Investigator	Name: Link Swanson
	Current Academic Status (Student, Fellow, Resident): Student
	Department: Cognitive science
	Telephone Number: 612-625-8736
	Institutional Email Address: link@umn.edu
Scientific Assessment	HRPP facilitated scientific assessment
IND/IDE # (if applicable)	IND146989
IND/IDE Holder	Jessica L. Nielson, PhD
Investigational Drug Services # (if applicable)	5591
Version Number/Date:	Version 10: May 18, 2023

PROTOCOL COVER PAGE

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	8/28/2020	Changed UBACC to the use of the MacCAT-CR	No
2	10/02/2020	Adding language about video recording all study visits, adding inclusion criteria for wearing face masks/coverings at all times during study visits, description of mixed in-person and Zoom study visits, adding survey screening, and adding e-consenting.	Yes
3	12/09/2020	Adding information about required COVID testing prior to in-person visits, and adjusting visit schedules for enrolled participants that test positive for COVID prior to a visit to allow for quarantine and reschedule. Also applies to study staff who will also be asked to get tested prior to in-person visits, and adjusting scheduling of visits if quarantine is needed.	Yes
4	07/20/2021	Adding heart rate and respiratory rate data collection during MRI scans	No
5	10/29/2021	Adding a debriefing session for visits 3a and 5a over zoom (or in person) following each dosing session, adding a follow up EEG and psychophysics measurement during visit 6, updates to how MRI and EEG data will be stored and analyzed, updates to blood draws, and additional devices noted that will be used for data access and analysis, and updates to I/E criteria.	Yes
6	01/14/2022	Adding additional time for preparatory sessions totaling 8 hours;	Yes

		adding 4 additional measures for verbal and visual learning and memory, the adverse childhood experiences questionnaire, and the emotional breakthrough inventory; adding an adapted set of questions to the Matrix reasoning section of the WASI to assess divergent thinking; adjusting total hours in the study to reflect this, and adjusting the compensation to reflect the extra hours; updating the mask mandate for in person dosing visits; creating more structure around staff COVID testing requirements for in-person visits; adding that staff and participants be up-to-date on COVID vaccines, per CDC guidelines; updated language for CMRR MRI usage as updated by the facility.	
7	11/29/2022	Adding an administration of the subjective experience questionnaires at the end of the day on each dosing day; Collecting psychophysics and EEG starting at 2 hours into the dosing session, without taking a break between psychophysics and EEG; Extending the time frame for visits 1 and 2 to have some overlap; Participant facing materials for preparation/rapport building; extending the washout time between dosing sessions from 2 weeks to 1 month to account for carry-over effects; Add ECG recording for participants to exclude anyone with a QTc greater than 450 msec, based on the FDA Guidance of Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, collected at baseline, and at the end of the day on each dosing session (visits 2 and 4).	Yes

8	01/06/2023	Reverting to a 2-week washout between dosing sessions due to funders not approving this change. Clarification on hours for preparatory sessions for visits 2 and 4.	Yes
9	05/18/2023	Updating ICF to include language about potential repeated MRI risks/side effects. Also removing BMI as an exclusion criterion, removing language about COVID safety as the guidelines continue to evolve to reflect that we will adopt the current institutional guidelines to prevent the spread of COVID-19, and updating our phone screen to include more information to help determine ineligibility around mental health symptoms and substance abuse to help with enrollment failures.	Yes

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ABBREVIATIONS/DEFINITIONS

5D-ASC = 5 dimensional altered states of consciousness

5-HT = 5 hydroxytryptamine (AKA serotonin)

5HT1A = 5HT 1A receptor

5HT2A = 5HT 2A receptor

ACE = Adverse Childhood Experiences

AE = Adverse event

ARC = Ambulatory Research Center

BDNF = Brain Derived Neurotrophic Factor

BMI = Body mass index

BVMT = Brief Visual Memory Test

CMRR = Center for Magnetic Resonance Research

COVID = COVID-19, Coronavirus Disease 2019

CRF = Case report form

CRP = C-reactive Protein

CRU = Clinical research unit

C-SSRS = Columbia Suicide Severity Rating Scale

DEA = Drug Enforcement Agency

DSM = Diagnostic and Statistical Manual

EBI = Emotional Breakthrough Inventory

EDI = Ego dissolution inventory

EEG = Electroencephalogram

ECG/EKG = Electrocardiogram

ELISA = Enzyme-Linked Immunosorbent Assay

FDA = Food and Drug Administration

fMRI = Functional Magnetic Resonance Imaging

GFAP = Glial Fibrillary Acidic Protein

GPCR = G-protein coupled receptor

HPPD = Hallucinogen persisting perception disorder

HVLT = Hopkins Verbal Learning Test

IDS = Investigational Drug Services

I/E = Inclusion/Exclusion criteria

IL-1β = Interleukin 1 beta

IL-6 = Interleukin 6

IL-10 = Interleukin 10

IFN-γ = Interferon gamma

LGN = Lateral geniculate nucleus

MAOI = Monoamine oxidase inhibitor

MacCAT-CR = Macarthur Competence Assessment Tool For Clinical Research

MEG = Magnetoencephalography

MINI-7 = Mini international neuropsychiatric interview, English version 7.0.2 for DSM-5

MMN = Mismatch negativity

MSI = Minnesota Supercomputing Institute

PANAS = Positive and negative affect schedule

PI = Principal Investigator

QTc = QT corrected for heart rate (QTc) interval reflects ventricular repolarization

RMEQ-30 = Revised mystical experiences questionnaire

rsfMRI = Resting state functional magnetic resonance imaging

s100β = S100 calcium-binding protein beta

SAE = Serious adverse event

SNRI = Selective norepinephrine reuptake inhibitor

SSRI = Selective serotonin reuptake inhibitor

TGFβ-1 = Transforming growth factor beta 1

TNFα = Tumor necrosis factor alpha

TNF-R1 = Tumor necrosis factor receptor 1

TNF-R2 = Tumor necrosis factor receptor 2

UCHL-1 = Ubiquitin C-Terminal Hydrolase L1

UMN = University of Minnesota

vERP = Visual event related potentials

WASI-II = Wechsler Abbreviated Scale for Intelligence-II

1.0 Objectives

Purpose: The proposed study will address the critical need for more precise characterizations of the acute visual effects of the drug psilocybin by measuring the impact of acute psilocybin intoxication on a perceptual task known as visual surround suppression, compared to an active placebo control. The data collected in the proposed experiment will make important contributions to knowledge of how psilocybin impacts contextual processing in the brain. Moreover, this will in turn inform the neurobiology of visual surround suppression in general, providing the first investigation of links between surround suppression and serotonergic pathways in humans. Furthermore, the impact of psilocybin on surround suppression will complement recent discoveries of differences in surround suppression present in certain clinical populations. Taken together, these points suggest that our relatively simple and straightforward study could have significant payoff in its contribution to knowledge, not only of the effects of psilocybin but also of key brain processes underpinning human vision and context processing more broadly.

1.1 Specific Aims:

Aim 1a will test the acute impact of psilocybin on the strength of the psychophysical surround suppression effect. Healthy volunteers will complete a visual task at baseline (pre-drug administration) and again after either an oral dose (25mg) of psilocybin or Niacin (100mg) placebo control (baseline, 2 hours post-drug administration, 2 week followup). The psychophysical measurements are made via forced-choice binary (yes/no) responses to questions about participants' perceptions of visual stimuli. The data collected from this Aim will provide a psychophysical characterization of the impact of psilocybin on visual surround suppression.

Aim 1b will test the acute impact of psilocybin on the strength of known surround suppression-related vERPs measured with EEG. Neural data will be collected as participants complete the visual tasks in Aim 1a (baseline, 2 hours post-drug administration, 2 week followup). The data collected will provide a neurophysiological characterization of the effect of psilocybin on the target vERPs commonly associated with visual surround suppression.

2.0 Background

Significance of Research Question/Purpose:

Psilocybin, the perception-altering drug found in 'magic mushrooms', has recently gained accelerated scientific interest. Psilocybin reliably produces acute alterations in visual perception. However, the acute effects of psilocybin on the processing of visual information is largely unknown. This gap in current knowledge, combined with the rapidly increasing interest in psilocybin, has created a critical research need with three prongs. First, while the therapeutic mechanisms of psilocybin remain unknown, recent theories converge around the hypothesis that psilocybin changes how the brain applies contextual information to incoming stimuli

(Carhart-Harris, 2019; Swanson, 2018). Importantly, the visual surround suppression paradigm, widely used to study contextual processing in visual perception, has not been studied in humans under psilocybin. Furthermore, the role of the serotonergic system has not been previously investigated in the field of surround suppression.

To address this need, we will administer psilocybin to healthy volunteers and ask them to complete visual tasks. The visual tasks will use the surround suppression paradigm (Schallmo and Murray, 2016) to measure the degree to which surrounding stimuli can influence the perception of a target stimuli. The influence of surrounding stimuli is measured using two distinct methodologies: (1) a psychophysical (behavioral) measurement, and (2) a neurophysiological (EEG) measurement. EEG data will be analyzed for well-known event-related potentials (vERPs) commonly associated with visual surround suppression (Schallmo and Murray, 2016). Our hypothesis is that the psychophysical data will show weakened surround suppression effects under psilocybin and that the associated vERPs measured with EEG will also be attenuated. The feasibility of our design is supported by numerous previous studies in which various perceptual tasks have been administered to participants under psilocybin. Our team is well-qualified to execute the proposed experiment as it is composed of experts in visual perception with demonstrated expertise in surround suppression paradigms; experts on psychedelic drugs; previous experience with EEG measurements and data analysis; and licensed clinical psychiatrists. Our proposed experiment will make significant contributions to existing knowledge of the effects of psilocybin and to our understanding of the neurobiological mechanisms of visual surround suppression and contextual processing in the brain.

Psilocybin, like other serotonin 2A receptor (5-HT2AR) agonist psychedelic drugs, produces psychoactive effects that impact information processing across many modalities in the brain, including perception, emotion, cognition, and sense of self (Barrett et al., 2018; Muthukumaraswamy et al., 2013; Schartner et al., 2017; Studerus et al., 2011; Swanson, 2018). Recently, psilocybin has received increased attention due to preliminary evidence of its efficacy as a treatment for certain mental health disorders (Bogenschutz and Ross, 2018; Carhart-Harris and Goodwin, 2017). However, due to the lack of basic neuroscience on psychedelic drug effects, “large gaps in our knowledge” remain, including a “lack of understanding of the mechanism of action of psychedelic drugs” (Lieberman and Shalev, 2016, 1198–99).

We feel that investigating the visual effects of psilocybin is feasible with a high-yield scientific payoff that would directly address this knowledge gap. Why focus on the visual effects of psilocybin? The visual system is a (relatively) well-understood brain function compared with higher cognitive functions. Thus, if we can capture precise data on psilocybin’s impact on visual processes, we can leverage existing knowledge of the visual system to better understand the mechanisms of psilocybin’s effects. An additional but no less valuable payoff runs in the reverse direction, where a better understanding of the visual effects of psilocybin can advance our neuroscientific understanding of visual processes in the brain more generally (Carter et al., 2005a; Swanson, 2018).

Prior investigations into the visual effects of psilocybin have measured acute changes in motion processing (Carter et al., 2004), object completion (Kometer et al., 2011), and binocular

rivalry (Carter et al., 2005b, 2007). However, no previous study has attempted to measure *visual context processing* under psilocybin. This is a significant research gap, given the fact that a number of recent theories hypothesize that psilocybin disrupts context-driven expectation across the brain (Carhart-Harris and Friston, 2019; Swanson, 2018). The surround suppression paradigm enjoys widespread support as a technique for measuring context effects in human visual processes (Schallmo et al., 2018a, 2019; Schallmo and Murray, 2016). However, the neurochemical underpinnings of surround suppression remain unclear. Surround suppression has been investigated using pharmacological interventions, including drugs that activate GABAergic, cholinergic, dopaminergic, and noradrenergic pathways (Kosovicheva et al., 2012; Read et al., 2015; Schallmo et al., 2018a). Importantly, surround suppression has not been studied in human subjects using serotonergic activation, however it has recently been studied in mice (Michaiel et al., 2019). Thus, knowledge of psilocybin's effect on surround suppression will make significant contributions to questions that are of great interest to scientists working to discover the mechanisms of psychedelic drugs as well as those working to discover the neurochemistry of surround suppression. An investigation measuring surround suppression in humans under psilocybin is therefore of the utmost importance.

Our research question is "What is the impact of acute psilocybin intoxication on visual surround suppression in healthy human subjects?" The significance of our research question in the context of existing literature is explained in further detail in section 2.3 below.

2.1 Preliminary Data:

We have not collected preliminary data.

2.2 Existing Literature:

Surround suppression, a perceptual phenomenon which has been reliably measured in numerous human and animal studies, occurs when the response to a target stimulus becomes attenuated (suppressed) when that stimulus is embedded (surrounded) in the context of neighboring stimuli (Angelucci and Bressloff, 2006; Cavanaugh et al., 2002; Nurminen and Angelucci, 2014; Schallmo et al., 2018a, 2018b; Schallmo and Murray, 2016; Webb et al., 2005). This effect can be measured psychophysically, where a participant is asked to choose a binary (yes/no) answer to questions about their perception of the stimuli. In addition, surround suppression impacts neural responses to stimuli and this neural impact can be measured using neuroimaging techniques, including EEG, MEG, or fMRI. In summary, previous studies have shown that human visual processing is highly context-dependent, and surround suppression offers an experimental paradigm capable of measuring context effects using both psychophysical and neuroimaging techniques.

Importantly, the surround suppression paradigm has been leveraged to discover distinct perceptual abnormalities in clinical populations, including schizophrenia (Schallmo et al., 2015; Tadin et al., 2006; Tibber et al., 2013), bipolar disorder (Schallmo et al., 2015), major depressive

disorder (Golomb et al., 2009; Norton et al., 2016), autism spectrum disorder (Foss-Feig et al., 2013; Rosenberg et al., 2015; Sysoeva et al., 2017), epilepsy (Yazdani et al., 2017), Alzheimer's disease (Zhuang et al., 2016), and migraine (Battista et al., 2010). Our research question is directly relevant to this literature, as it will help to illuminate the relationship (if any) between psilocybin's perceptual effects and the perceptual abnormalities found in various clinical phenomena. Furthermore, our research may provide insights into the neurochemical underpinnings governing the differences in surround suppression found in clinical populations.

The neurochemical mechanisms of surround suppression remain unclear. A variety of reports have investigated the GABA system in human studies (Cook et al., 2016; Read et al., 2015; Song et al., 2017; van Loon et al., 2012; Yoon et al., 2010) and animal models (Adesnik et al., 2012; Haider et al., 2010; Ma et al., 2010; Nienborg et al., 2013; Ozeki et al., 2004, 2009; Sato et al., 2016; Shushruth et al., 2012). However, recent work has cast doubt on the hypothesis that surround suppression is directly mediated by GABA (Read et al., 2015; Schallmo et al., 2018a). Pharmacological agents are often used to investigate the role of neurochemicals in a given brain function. A small number of human studies have measured the impact of pharmacological agents on surround suppression. Previous investigations have targeted GABAergic pathways using the drugs ethanol (Read et al., 2015) and lorazepam (Schallmo et al., 2018a); cholinergic pathways using the drugs donepezil (Gratton et al., 2017; Kosovicheva et al., 2012) and caffeine (Nguyen et al., 2018); dopaminergic pathways using the drug bromocriptine (Gratton et al., 2017); and noradrenergic pathways using the drug guanfacine (Gratton et al., 2017).

Importantly, drugs that target serotonergic pathways have not been tested for their impact on human surround suppression. However, one recent animal study used the serotonergic psychedelic drug DOI to robustly induce weakened surround suppression measured in mouse V1 (Michaiel et al., 2019). Based on their findings, the authors argue that the serotonin 2A (5HT-2A) receptor "may be important for adjusting the influence of *context* in visual cortical processing" (Michaiel et al., 2019, 3481; emphasis added). Thus, the state of the current literature strongly warrants the use of serotonergic pharmacological agents paired with surround suppression tasks to probe for links between the serotonin system and visual context processing in the brain.

Psilocybin is a serotonin 2A receptor agonist psychedelic drug that can dose-dependently induce acute changes in perception, including alterations of object boundaries (Kometer and Vollenweider, 2016), illusions of perceived size or shape of objects (Carter et al., 2004; Isbell, 1959), alterations in motion perception (Carter et al., 2004), changes in the subjective meaning of percepts (Carbonaro et al., 2018; Muthukumaraswamy et al., 2013), and hallucinations (Carbonaro et al., 2018; Kometer and Vollenweider, 2016). Psilocybin was found to slow the switch rate and rhythm of the visual binocular rivalry phenomenon (Carter et al., 2005b, 2007). Psilocybin has been shown to acutely impair higher (global) levels of visual motion processing (Carter et al., 2004) and modal visual object completion (Kometer et al., 2011). However, low-level (local) motion processing (Carter et al., 2004), low-level line

orientation processing (Barrett et al., 2018), and early (preattentive) mismatch negativity (MMN) processing are not impacted by psilocybin (Bravermanová et al., 2018; Umbricht et al., 2003).

EEG (and MEG) studies consistently show reductions in oscillatory power across a broad frequency range under psilocybin (Kometer et al., 2011, 2013, 2015; Muthukumaraswamy et al., 2013; Schartner et al., 2017; Tyls et al., 2016). Reductions in the power of alpha-band oscillations, localized mainly to parietal and occipital cortex, have been correlated with intensity of subjective visual effects (Kometer et al., 2013; Muthukumaraswamy et al., 2013; Schartner et al., 2017). Reductions in alpha power localized to anterior and posterior cingulate cortices and the parahippocampal regions have been correlated with ego-dissolution effects and mystical-type experiences (Kometer et al., 2015; Muthukumaraswamy et al., 2013). Although oscillatory power decreases, overall whole-brain signal diversity actually increases and the increase in signal diversity correlates with the intensity of subjective effects (Schartner et al., 2017).

In conclusion, our research question is of great interest to scientists from a diversity of fields, including perceptual neuroscience, neuropsychopharmacology, and clinical psychopathology. Given that psilocybin can reliably produce robust psychophysical and neurophysiological changes, we expect that our surround suppression measurements will be significant. Based on the above considerations of existing literature, we strongly feel that our research has the potential to close existing knowledge gaps and address multiple critical research needs.

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome:

We will obtain a psychophysical (behavioral) measurement of the impact of acute psilocybin intoxication on visual surround suppression in healthy human volunteers. Baseline data will be collected as participants complete the perceptual tasks pre-drug administration. Participants will repeat the tasks again 2 hours after an oral dose of psilocybin, and at 2 week followup.

3.2 Secondary Endpoint(s)/Event(s)/Outcome(s):

We will obtain a neurophysiological (EEG) measurement of the impact of acute psilocybin intoxication on the vERPs commonly associated with visual surround suppression. Prior to the start of the dosing session, we will collect baseline EEG data for each participant. After the dosing session has begun, EEG data will be recorded again during both task completion time points (2 hours after an oral dose of psilocybin or placebo control), as well as at 2 week followup, as described in the Primary Endpoint above.

4.0 Study Intervention(s)/Investigational Agent(s)

4.1 Description:

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is a naturally-occurring tryptamine compound found in an estimated 144 different species of mushrooms worldwide (Guzmán, 2005; Guzmán et al., 1998). Humans have intentionally consumed psilocybin-containing fungi for ritual and medicinal purposes for more than 3,000 years in Mesoamerican cultures (Carod-Artal, 2015) and possibly also in prehistoric European cultures (Akers et al., 2011; Schultes et al., 2006; Wasson and Wasson, 1957). Today, psilocybin-containing mushrooms remain one of the most widely-used hallucinogens worldwide (Johnson et al., 2018b). When administered orally, psilocybin undergoes rapid first-pass dephosphorylation into the drug psilocin (4-Hydroxy-N,N-dimethyltryptamine) (Brown et al., 2017; Horita and Weber, 1961). Psilocin activates a number of G protein-coupled receptors (GPCRs) several of which likely contribute to its overall profile of subjective effects (Ray, 2010). However, the subjective psychoactive effects of psilocybin critically depend on the drug's ability to activate the 5-HT2A (Glennon et al., 1984; Kometer et al., 2013) and 5HT1A (Pokorny et al., 2016) receptors.

In controlled settings, psilocybin has a robustly established physical and psychological safety profile (Brown et al., 2017; Hasler et al., 2004; Johnson et al., 2008; Johnson and Griffiths, 2017). Psilocybin has been generally well-tolerated by subjects in experimental studies (Dos Santos et al., 2018), both in clinical populations (Carhart-Harris et al., 2017a, 2018; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016) and in healthy volunteers (Barrett et al., 2018; Bravermanová et al., 2018; Carhart-Harris et al., 2012, 2013; Carter et al., 2005b; Gouzoulis-Mayfrank et al., 2002; Griffiths et al., 2011; Grimm et al., 2018; Hasler et al., 1997; Kometer et al., 2015; Kraehenmann et al., 2015; Muthukumaraswamy et al., 2013; Nicholas et al., 2018; Quednow et al., 2012; Schartner et al., 2017; Turton et al., 2014; Umbricht et al., 2003; Vollenweider et al., 2007; Wittmann et al., 2007). The most common acute physiological effects include a moderate increase in pulse and blood pressure (Gouzoulis-Mayfrank et al., 1999; Griffiths et al., 2006; Johnson et al., 2008) and delayed, transient, dose-dependent headaches (Johnson et al., 2012).

Risk of adverse psychological reactions collectively known as "bad trips" involve acute states of distress characterized by fear, panic, anxiety, disturbing feelings, and troubling thoughts (Johnson et al., 2008). These reactions can be minimized and mitigated in a controlled experimental session using a variety of well-established techniques that include careful screening of subjects, training of study personnel, holding the dosing session in a secure and comfortable physical environment, careful preparation of participants, and following established pre-session, session, and post-session protocols (Johnson et al., 2008).

Long-range risks, while very unlikely, include the possibility of triggering substance abuse, prolonged psychotic episodes, and lasting perceptual abnormalities (Johnson et al., 2008). Psilocybin has an extremely low abuse potential (Johnson et al., 2018a), does not induce cravings or withdrawal (Johnson et al., 2018a), and does not activate dopaminergic reward circuits critical to substance use disorders (Nichols, 2004). Psilocybin is thus generally regarded as safe to introduce to drug-naive subjects without risk of initiating abuse or habitual use (Johnson et al., 2008, 2018a). Lasting perceptual abnormalities can occur, especially in naive

users, although their occurrence is rare and in most cases are very brief, not regarded as detrimental, and sometimes even regarded as pleasurable (Johnson et al., 2008). Hallucinogen persisting perception disorder (HPPD), a condition in which the acute perceptual effects of the drug persist for prolonged periods after the peak effects have subsided, is extremely rare, mostly associated with LSD use in combination with cannabis, and has not been reported as having occurred in participants in any modern studies with psychedelic drugs (Martinotti et al., 2018). Nonetheless, careful follow-up on perceptual abnormalities is recommended (Johnson et al., 2008).

The relative safety of psilocybin extends beyond controlled clinical settings, as epidemiological data on illicit and ritual use shows that adverse reactions leading to hospitalization are relatively rare (Johnson et al., 2018b; Leonard et al., 2018). Since there is little to no risk of physical overdose (Brown et al., 2017; Johnson et al., 2008), most hospitalizations resulting from illicit use in the general population are due to emotional distress and unstable mental states (Leonard et al., 2018) and subside within 48 hours (Johnson et al., 2018b; Tylš et al., 2014).

In summary, psilocybin has a proven track record of safety when administered in controlled experimental settings that follow established protocols (Brown et al., 2017; Dos Santos et al., 2018; Hasler et al., 2004; Johnson et al., 2008; Johnson and Griffiths, 2017). Although not completely without risks, psilocybin does not impose unusual danger compared with other standard experimental treatments and interventions.

4.2 Drug/Device Handling:

Psilocybin is a tryptamine derivative presenting as a white crystalline solid with a melting point of 220-228°C. It is stable over extended periods in dark storage at controlled room temperature. Psilocybin is soluble in 20 parts boiling water or 120 parts boiling methanol. For use in clinical studies, psilocybin is provided as 25 mg capsules (white opaque, Capsugel Vcaps Plus HPMC size 2). Psilocybin will be obtained from Usona Institute in Madison, WI and stored in the Investigational Drug Service (IDS) Pharmacy at UMN. UMN IDS will handle all psilocybin allocation and storage, and will provide the compound as needed for each testing session. We will create a system which will allow the IDS staff to enter variables necessary for our minimization randomization procedure as described which will allow the IDS staff to determine the participant's group to ensure the double blind. All participants, family members, and the entire research team will be blinded to testing group and order.

The active placebo niacin, also known as vitamin B3, is provided as 100 mg capsules (white opaque, Capsugel Vcaps Plus HPMC size 2). Niacin is United States Pharmacopeia (USP)-grade and also provided by Usona in the same capsules to maintain the blind.

Within the week of the dosing/testing session at the CRU, one of the MD psychiatrists will formally request the study drug using the IDS calendar system. One person from the study team that will be running the testing session, plus one member of the CRU clinical staff, will

walk over to IDS together to receive the study drug and bring it to the participant. Any unused product will be immediately returned to IDS.

4.3 Biosafety: N/A
4.4 Stem Cells: N/A
4.5 Fetal Tissue: N/A

5.0 Procedures Involved

5.1 Study Design:

The study involves a randomized, double blind, placebo controlled, crossover design with two different groups pairing the psychoactive drug psilocybin, or the active placebo Niacin, with a combination of perceptual tasks.

Randomization and Double-Blind: Participants who meet criteria for entry into the study (based on the telephone screen and the clinical interview) and consent to participate will be randomized to *psilocybin first (group A) or niacin first (group B), using an adaptive minimization randomization method.* The purpose of the procedure is to ensure that the 2 groups are similar with respect to *age and gender*. Specifically, the minimization procedure will balance age groups *(45 years or below/above 45 years)* and gender. Following the evaluation, the study coordinator will share numerical values for these variables along with the subject ID number through a secure system (Box Secure Storage) with the study statistician who will use participant information to assign a blinded randomization group (A or B) using the minimization procedure.

The study statistician will then pass the blinded group assignment to IDS. Before the first participant is randomized, IDS will randomly assign “psilocybin first” “niacin first” to the letters A, and B; this assignment (of group to treatment letter) will not be communicated to anyone outside of IDS until the study is complete and the study team is ready to break the blind. Randomization will occur after Visit 1 (Day 0), when it is confirmed all eligibility criteria are met and before Visit 2, with a maximum 30-day window between them.

Participants will have one training/baseline session, followed by 2 experimental sessions in randomized order for each of the drug conditions (psilocybin or niacin placebo). We will test subjects under the influence of 25mg of psilocybin (**condition 1**) or 100mg of active placebo control (niacin or, **condition 2**).

We will test two groups for each of these conditions. Group A will be given psilocybin first, and active placebo Niacin second (N=20) and tested on surround suppression and EEG recording starting at 2 hours after ingestion of the experimental compound. Group B will be given niacin on their first dosing day and psilocybin on their second dosing day (N=20) and tested on surround suppression and EEG recording starting at 2 hours after ingestion of the experimental compound.

Furthermore, this study will be conducted in two phases. A pilot phase (n=6) will be completed before full study. For this phase, we will enroll an initial 6 subjects to work through the feasibility of implementing the study design, and to determine if any modifications need to be made for the full study design. We will start off slow and only enroll a single participant for the first 1-2 participants to test out the full protocol and closely monitor any potential problems that may arise that would need to be modified or removed from the design. See section 5.3 for more information on this pilot phase. Once this phase is complete, we will commence with the full study. See Figure 1.

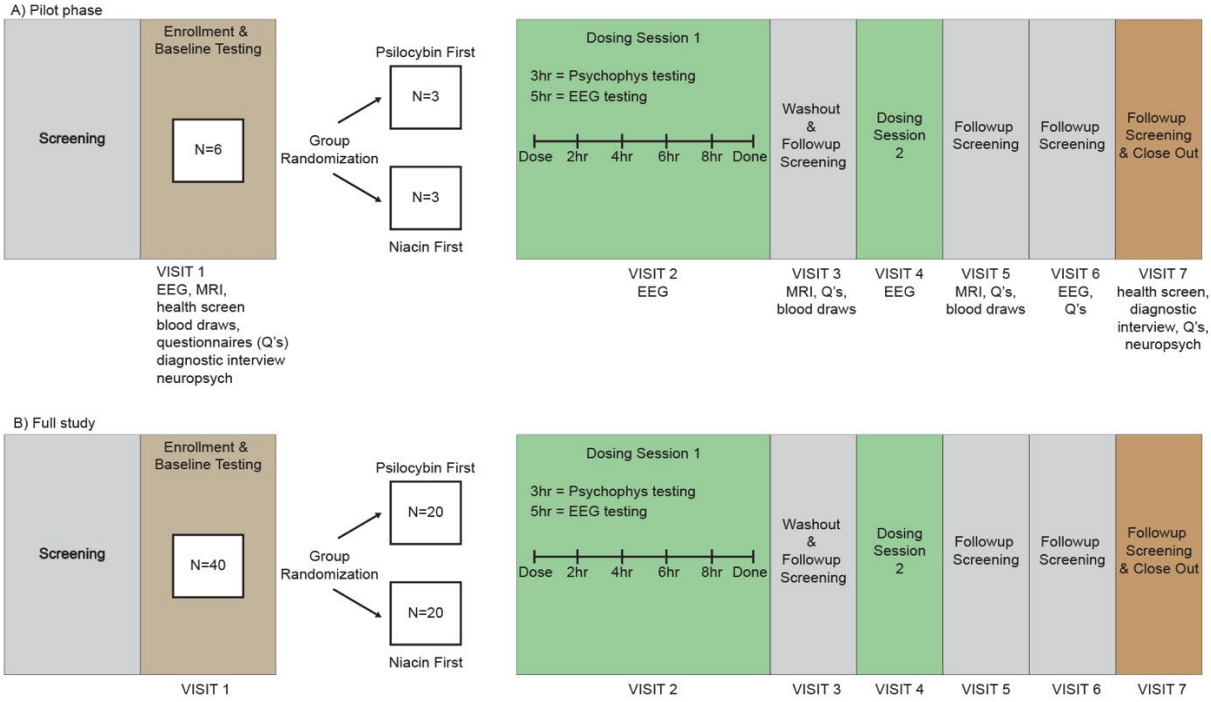

Figure 1. Timeline of study design for the A) pilot phase to test the feasibility of the protocol prior to initiating the B) full study design in our cohort.

5.2 Study Procedures:

Additional Procedures for COVID Screening. Participants and study personnel (e.g. staff, students, volunteers, or anyone with direct participant contact) will adhere to institutional guidelines around COVID-19 risk and safety and adjust our precautions accordingly as they evolve. These guidelines will be communicated to the participants at the time they are in effect, and implemented accordingly.

Initial Survey and Phone Screening. Interested candidates will be contacted through a survey in REDCap to gather preliminary eligibility criteria and contact information (see Appendix A), and

interested participants that meet our basic inclusion criteria will be contacted via phone or Zoom to determine if they meet additional criteria for scheduling an in-person interview to determine final eligibility and enrollment. Phone screens will be conducted by the study coordinator and will adhere to an approved phone script (see Appendix B). All study visits and assessments performed remotely over the phone or Zoom will have both audio and video recordings (when applicable) of each visit.

VISIT 1:

In-person consent/interview screening. Participants that pass the survey and telephone screens will be invited to the ARC to be consented and interviewed by the research coordinator, to be consented and tested. Participants will be screened on the assessments outlined below to determine final eligibility for enrollment into the study. Participants will receive a physical exam to assess overall health, urine for pregnancy testing, as well as blood draws to screen for blood-based biomarkers of major health problems and for baseline cytokine levels, a diagnostic interview with the MINI-7 to assess presence or history of mental illness and substance abuse, and a review of their personal and family medical history, and measure weight and vitals. Blood draws for health screening at baseline will be collected in green top tubes containing lithium heparin as an anticoagulant, and 2.5mL of blood will be collected and analyzed at the UMMC West Bank Children's Hospital lab. Blood draws for cytokine testing will be collected in red top serum separator tubes that contain a clot activator but no anticoagulants, preservatives, or separator material, and we'll collect 6mL of whole blood per participant. Participants will be screened for uncontrolled hypertension with two separate measurements of blood pressure using a blood pressure cuff during their visit. They will be brought in for a second visit (visit 1b) within 1 week of visit 1a to obtain two additional blood pressure measurements to assess whether they have uncontrolled hypertension, which will be determined if their average blood pressure across the 2 days and 4 measurements is greater than 140/90mmHg. We will also collected ECG data to test whether they have a QTc greater than 450 msec, based on the FDA Guidance of Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. Those that do have a QTc greater than 450 msec will be excluded from the study.

Candidates who do not meet all of the inclusion and/or one or more of the exclusion criteria will not be enrolled into the study.

Clinical Assessment. Assessment interviews will be conducted by trained research team members, directly after the consent process.

Assessment of General Psychopathology and Demographic Information (Zoom option). To describe our sample and to determine criteria for ineligibility, we will screen for the presence of Diagnostic and Statistical Manual of Mental Disorders-5th edition (DSM-5) (American Psychiatric Association, 2013a) psychiatric diagnoses (American Psychiatric Association, 2013b) using the MINI-7 (Sheehan et al., 1998). We will also administer the Adverse Childhood

Experience (ACE) questionnaire, which is a 10-item assessment of childhood abuse that predicts health concerns in adults (Feliti et al., 1998). Clinicians formulate the diagnosis combining all clinical information. Following the clinical evaluation, the study team will review all clinical information and determine final eligibility to decide whether the participant will move forward to randomization.

Neurocognitive assessments.

- The Wechsler Abbreviated Scale for Intelligence-II will be used to estimate intellectual functioning *(in person)*. An add-on will be used during the Matrix Reasoning subtest to test for divergent thinking, a form of creative thinking and cognitive flexibility used in other psychedelic research studies (Kiraga et al., 2021). In addition to the standard response about which answer is correct, participants will be asked to provide alternative answers they think also might be correct.
- The 5D-ASC *(Zoom option)* is a 94-item questionnaire that measures altered states of consciousness, and consists of 5 dimensions/subscales (Dittrich, 1998), including "Oceanic Boundlessness" (27 items), "Anxious Ego Dissolution" (21 items), "Visionary Restructuralization" (18 items) "Auditory Alterations" (15 items) and "Reduction of Vigilance" (12 items). This validated scale has been used in multiple research studies aiming to understand the subject experience of psychedelic drugs (Carhart-Harris et al., 2016; Hasler et al., 2004; Hysek and Liechti, 2012; Liechti et al., 2017; Schmid et al., 2014; Vollenweider et al., 2007; Vollenweider and Kometer, 2010).
- The RMEQ-30 *(Zoom option)* is a 30-item measure that consists of 4 orthogonal dimensions that represent different aspects of a mystical experience, including mystical experiences, positive mood, transcendence of space and time, and ineffability (Barrett et al., 2015; Maclean et al., 2012). Previous work has linked certain domains of the mystical experience with positive outcomes (Garcia-Romeu et al., 2014; Griffiths et al., 2018; MacLean et al., 2011).
- The PANAS *(Zoom option)* is a self-report of positive and negative affect and has been used in both clinical and nonclinical populations to measure mood affect (Crawford and Henry, 2004; Watson et al., 1988).
- The 5-factor personality inventory (NEO-FFI) (Costa and McCrae, 2008) *(Zoom option)* will be administered at baseline testing, as well as at the final follow up session. Previous research with psilocybin in healthy volunteers has shown that mystical experiences occasioned by psilocybin in the appropriate set and setting leads to increases in the openness domain of the NEO-FFI (MacLean et al., 2011), and that those who score higher on the neuroticism domain may be more prone to difficult experiences on psilocybin (Barrett et al., 2017) and may require more attention during parts of the dosing session.
- We will also administer the Ego-Dissolution Inventory (EDI) to participants *(Zoom option)*, which is a validated assessment of both ego dissolution (ED) and ego-inflation (EI) applied in previous psilocybin research (Nour et al., 2016). Ego dissolution has been

correlated to improved mental health outcomes associated with psilocybin-occasioned experiences.

- BVMT-R™, which has been used to measure changes in cognitive function linked to neuroplasticity in schizophrenia patients undergoing targeted cognitive training (Fisher et al., 2009; https://www.parinc.com/Products/Pkey/30). BVMT-R measures visuospatial memory where participants are shown a stimulus page and asked to draw as many of the figures as possible in their correct location on their own page, and then retested 25 minutes later for memory recall, followed by a recognition trial where they are asked which of the figures were included in the original stimulus.
- HVLT-R™ has also been used to measure changes in cognitive function linked to neuroplasticity in schizophrenia patients undergoing targeted cognitive training (Fisher et al., 2009; https://www.parinc.com/Products/Pkey/130). HVLT-R is a word-list learning and memory test.
- EBI has been developed and used in psilocybin clinical trials to measure emotional breakthrough, which has been linked to longer term changes in psychology function (Roseman et al., 2019).

Neuroimaging Procedures. All brain imaging will be completed at the CMRR on a 3T whole body Siemens MAGNETOM scanner (Siemens Medical Solutions, Erlangen, Germany) using a standard Nova coil. We will take a series of scans during a single session to collect structural and functional fMRI data. Data will be collected from participants during baseline assessment and within 24 hours following each dosing day, and again at 3-4 days and 7 days after each dosing session for a total of 7 scans per participant. After an initial structural scan, we will collect resting state fMRI to test changes in BOLD signal in brain networks known to be impacted by psilocybin and other 5HT2A receptor mediated psychedelics, including the default mode network (Carhart-Harris et al., 2014). Heart rate and respiratory rate data will also be collected during the scan to account for artifacts that may confound results during resting state scan. We will then perform a series of task-based scans using the same visual tasks tested during the EEG dosing session (*SEE Psychophysics section under Visits 2 and 4*). We will then perform a diffusion-weighted MRI (dMRI) scan to look for changes in structural connections in white matter, which has been shown previously in animal models with serotonergic psychedelics (Ly et al., 2018). Data will be processed using standard software packages (e.g., the FMRIB Software Library (FSL - FslWiki)), which is an open-source software library that contains tools for statistical analysis and image processing for MRI brain imaging data).

The same study procedures, except consent, demographics and medical history will be performed at Visits 3, 5, 6 and 7. Pregnancy test will be collected on Visit 1, 2, 3, 4, and 5. EEG and psychophysics will be collected on visits 2, 4, and 6, and fMRI will be collected on Visits 1, 3, and 5. Regarding blood draws, two separate tubes of blood will be collected at Visits 1, 3, and 5 for serum chemistry and cytokine assays.

VISITS 2 and 4

Dosing Session. Dosing sessions will involve 8 hours of preparatory visits (2a-d) before the day of the first dosing session, and one hour before the second dosing session (4a), which will occur either in person in the dosing room in CRU or over Zoom if preferred, and will be recorded for both audio and video. During these 4 preparatory visits, which will last approximately 2 hours each prior to the first dosing session, and 1 hour prior to the second dosing, for a total of 9 hours, participants will meet with at least one of their dosing session monitors that will be sitting with them, and discuss what to expect during the dosing session, and what food preferences they have for two meals they will be offered during their time in the CRU. This visit also serves to help build rapport and common understanding between the two monitors and the participants prior to the dosing session, to review the participants personal history and anything that might come up during the dosing sessions (see visual aid that will be used for this in Appendix H), as well as an opportunity to educate the participants more on the procedures that will occur during the day, and the purpose of the study and the characteristics of the study drug. Participants will be asked to get at least 6-8 hours of sleep, and get dropped off in the morning by a trusted familiar individual. Once checked and settled into the room, participants will be allowed the option to remove their mask during the day, if that feels more comfortable for them. Prior to the administration of psilocybin or placebo, the participants will be given a brief physical exam, including a pregnancy test, breathalyzer for alcohol content, and measuring weight and vital signs. Participants will then be asked to answer a few questions on a checklist about their substance use since being enrolled in the study to assess whether they have engaged in activities that would make them ineligible and withdrawn from the study (see Appendix C). If they pass, we will proceed to the dosing session after a team member from the CRU and one of the study team members will walk over to IDS to receive the study compound, and escort it back to the testing room. The dosing sessions will be recorded using video equipment in the room for the duration of the visit.

Participants will undergo baseline testing for outcome measures and preparatory interviews with the co-facilitators of the dosing sessions. On each of the testing day sessions (approximately 8 hours each), a hospital room in the CRU will be set up to create the optimal setting for a psychedelic experience, per the guidance and recommendations of other researchers performing work with these compounds in controlled clinical settings (Johnson et al., 2008). The room will not have windows, and will be equipped with a private bathroom in the room for when participants need to excrete urine, feces or vomit. The hospital bed will be set up with blankets and pillows to keep participants comfortable. We will place decorations around the room with neutral art/photographs of nature, and will have the participants bring some personal item with them that they find helpful for their own well-being (this may vary, but could include a stuffed animal, a sacred item or other totem that they use to help in their past experiences in altered states of consciousness).

Participants will receive a 25mg/70kg dose of psilocybin, or 100mg dose of the niacin placebo, in a private, quiet space and encouraged to focus their attention inward for the majority of the experience, using eye shades and headphones with instrumental music. Participants will be lying on a comfortable surface. At least two monitors will be present for the duration of the participants stay in the research unit to monitor them. One of those monitors

will have either an RN (Clinical Research Unit staff) or MD degree, with experience managing behavioral emergencies, including de-escalation, calming and preventing elopement. The other monitors that do not have an RN or MD have extensive field experience providing support for psychedelic crisis situations at festivals and other events where people take recreational psychedelics and come to the facility designated for people seeking out psychological support during a psychedelic-induced crisis. Other monitors that will serve as the second person will be trained accordingly. We will call these monitors "sitters" and they will be positioned near the participant during the portion of the session where they are laying down with eye shades and listening to music. Sitters will be trained in fundamental guidelines for helping people navigate a psychedelic experience, adapted from models of harm reduction services offered at festivals for people having a difficult experience. Examples include instances where the participant arises from their headphones and eyeshades, and the sitters will engage with the participant using a supportive and non-directive approach, maintaining an empathic presence, while encouraging them to maintain their focus inward in between testing sessions for the duration of the experience. At least one sitter will be present at all times to be able to respond to verbal and non-verbal behavior with communication or supportive touch. Supportive touch will be discussed during the consent and enrollment process. We will ask the participants what their comfort level is for supportive touch, while ensuring that extensive touch, such as hugging or cuddling will not be allowed, even if requested. We will simply, if they consent before the dosing session, provide a hand on the back, arm, or hold their hand during challenging or stressful parts of the experience. We will ask for their permission anytime a supportive touch seems warranted, and will only touch if they have agreed beforehand during the consent process, and with a verbal confirmation during the dosing experience. The consent and extent of supportive touch will be assessed and agreed upon with the participant during enrollment, and confirmed on the day of testing. We will ensure that we have an MD physician present in a nearby room in the CRU for the duration of each dosing session to monitor safety and guide/provide interventions should medical situations arise that require the physicians care.

Schedule for checking vital signs. In order to monitor participant safety during the dosing sessions, we will monitor their heart rate and blood pressure throughout the session. Heart rate will be measured with a pulse oximeter and blood pressure will be measured with a pressure cuff. We will measure vital signs 15 minutes before dosing, and then again at 15, 30, 45, 60, 90, 120 minutes and three, four, six and eight hours after dosing, with an allowable time deviation of +/- 5 minutes to account for any delays during the day for checking vitals. In the event of a hypertensive emergency where blood pressure rises above 180/120mmHg (systolic/diastolic), and they are experiencing other associated symptoms of potential organ damage, including chest pain, shortness of breath, back pain, numbness/weakness or difficulty speaking, then we will stop the session and call a code 21, per our crisis communication plan (see appendix D). In the unexpected event that we do have a participant with a hypertensive emergency (Johnson et al 2008), we will immediately administer sublingual clonidine while we wait for emergency personnel to arrive. Our physicians do not feel administering an IV injection would be wise, as in the altered state of consciousness, this may exacerbate their symptoms, as would having an

IV catheter placed for the duration of the dosing session. The emergency room is in the building adjacent to the Clinical Research Unit, accessible via underground tunnels, and calling a code 21 will alert emergency personnel to come to our dosing room to treat the participant and transfer them to the emergency department.

Participants experience will be interrupted in order to conduct the EEG and behavioral testing during the peak of the experience (starting 2 hours after ingestion of study drug). EEG will be administered by trained study staff using a dry-electrode wireless headset paired to a computer and monitor that will be used to administer the surround suppression task.

EEG. We will use an EEG paradigm to measure responses to the presentation of simple visual stimuli (e.g., black and white stripes) presented on a computer. Subjects will be asked to respond to the appearance of the visual stimuli via button press (Figure 2). We will record EEG signals from multiple scalp sites (electrodes) using a 21-channel dry electrode EEG system. Subjects will be asked to keep their eyes focused on the screen during the task, and to remain as still as possible to ensure higher data quality. Subjects will be monitored by study staff (in the testing room) during the experiment. EEG data using a dry electrode system will be collected in the CRU testing room during baseline and on dosing session days for consistency of environment/setting. EEG sessions will be conducted by study staff that are trained to collect EEG data.

Psychophysics behavioral task. We will use visual behavioral tasks to assess perceptual functioning and learning in human subjects. Subjects will see a series of simple images (e.g., gray stripes) presented on a computer screen and will be asked to make basic judgments about their appearance (e.g., report which of the two images appears stronger). Subjects will make responses by pressing buttons on a response device (e.g., keyboard). Subjects will be asked to keep their head position stable on a chin rest and to focus their eyes at the center of the screen during the task. Behavioral data will be collected in subject testing space located in the CRU.

Subjective experience questionaires at end of dosing session. Once the subjective effects of the study drug have subsided, prior to being discharged from the CRU, we will administer subjective experience questionnaires (5D-ASC, RMEQ-30, EDI, EBI) related to how their experience was during the day on the study drug.

Assessment of participant before discharge from dosing session. Prior to being released to a trusted family member or friend at the end of the session, we will assess the participant to make sure they are safe to leave. We will do a physical and mental health assessment, including measuring vital signs, ECG, mental health status and responses to questions about thought processes, such as suicidal ideation with the CSSRS or other concerning symptoms (see appendix E). If the participant is displaying symptoms that need to be continually monitored, we will discuss with the clinical staff whether to admit them for follow-up care. Additional follow-up care that is needed will be billed to the participants health insurance.

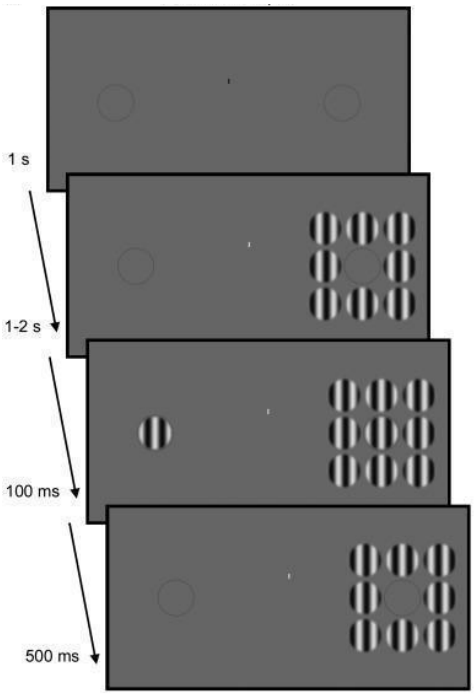

Figure 2. Schematic of surround suppression task (Schallmo and Murray, 2016)

Safety. Participants will be instructed to immediately inform the study team if any serious concerns arise with their health during the study. The team will assess all adverse effects, including frequency, severity and relationship to study drug. For participants that experience adverse psychological effects, including, but not limited to suicidal ideation, likely or probably related to study drug, the participant will be instructed to speak with a mental health professional to assess their status, either by Drs. Kathryn Cullen or Ranji Varghese (clinical Co-Investigators). Participants will be given a list of phone numbers to call in the event that they are experiencing distress, such as suicidal ideation, including the study investigator at the telephone number listed on the first page of the consent forms, and instructed that if they feel they are crisis, that they can call 911 and/or a Nationwide Suicide Hotline that is answered 24 hours a day with a skilled, trained counselor. One example is the National Suicide Prevention Lifeline at 1-800-273-TALK (8255).

Participants will be pre-prescribed antipsychotics and antianxiety medications in case the participants or the study staff want to stop the psilocybin experience with these pharmacological interventions. These costs will be paid for by the study funding. Some antipsychotics, like Risperidone, are able to bind to 5HT2A to block the activation of this receptor in the presence of psilocybin, whereas anti-anxiety medications, such as benzodiazepines, will help calm down the participants should they become agitated or too

anxious during the testing session. See Appendix D for more information on the crisis commination plan.

At the end of each experimental session (8 hours post-drug administration), participants will be released into the care of a trusted friend or family member to drive them home. (Prior to dosing on the day of each experimental session, participants will be required to confirm that they have arranged for reliable transportation).

Visits 3 and 5

Digital Journal. Throughout the study, participants will also be asked to keep a digital journal that will be submitted after each dosing session (**Visit 3 and Visit 5**), and at the end of the study (**Visit 7**) to document their qualitative and subjective experience for content analysis. Within 1 week after their dosing session, participants will be asked to write for 30-60 minutes to describe the content of their experience, and any reflections or interpretations they derived from the experience to help determine the subjective information of their drug experience. These will be collected in a REDCap form (see Appendix F) and sent out to participants via email or text after completion of the dosing session, and a follow-up email or text towards the end of the week if they have not completed the form.

Debriefing session. One day following each dosing session (Visits 3a and 5a), study staff will meet with the participant for about 60 minutes (either in person at CMRR prior to MRI, or remotely over Zoom) to discuss the dosing session the previous day, and debrief on anything they want to discuss or process with the study staff.

Blood Draws. All blood draws will be performed by the clinical staff onsite, and blood samples will be stored at the Cytokine Reference Lab on campus for cytokine assays, and serum chemistry will be processed by Fairview. Samples will be collected at baseline (**Visit 1**) and again at **Visit 3 (a,b,c)** and **Visit 5 (a,b,c)**.

MRI. See CMRR section below (5.5).

All neuropsychiatric, baseline and follow up testing will be conducted in the ARC (or Zoom, if appropriate), and all fMRI sessions will be collected at CMRR. All dosing sessions and EEG data collection will be performed in the CRU. The study coordinator will greet each participant upon arrival, and escort them to the different locations for data collection and testing.

Participants will be monitored at each visit for adverse events *(Zoom option)*, including for suicidal thoughts, and given at least 2 weeks between dosing/testing sessions for drug washout. After completion of final dosing sessions, participants will undergo follow up assessments at 2 weeks (**Visit 6**) and 2 months after the final dosing session for study closeout (**Visit 7**).

Schedule of Events

	Enrollment and Baseline Testing Visit 1*	**Dosing Session Study Visit 2^ (Condition 1)**	**Study Visit 3# (Follow up and Washout)**	**Dosing Session Study Visit 4^ (Condition 2)**	**Study Visit 5# (Follow up and Washout)**	**Study Visit 6 (Follow up)**	**Study Visit 7 (follow up and close out)**
COVID+ and other time deviations for Visit Window Adjustment	+/- 7-14 days$	+/- 7-14 days$	+/- 7-14 days$	+/- 7-14 days$	+/- 7-14 days$	+/- 7-14 days$	+/- 7-14 days$
Time Point	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 12
Informed consent	X						
Demographics	X						
Medical history	X						
Psilocybin or Placebo		X		X			
Concomitant medication review	X	X	X	X	X	X	X
Physical exam (including height and weight)	X	X	X	X	X	X	X

	Enrollment and Baseline Testing Visit 1*	**Dosing Session Study Visit 2^ (Condition 1)**	**Study Visit 3 (Follow up and Washout)**	**Dosing Session Study Visit 4^ (Condition 2)**	**Study Visit 5 (Follow up and Washout)**	**Study Visit 6 (Follow up)**	**Study Visit 7 (follow up and close out)**
COVID+ Visit Window Adjustment	+/- 7-14 days[$]	+/- 7-14 days[$]	+/- 7-14 days[$]	+/- 7-14 days[$]	+/- 7-14 days[$]	+/- 7-14 days[$]	+/- 7-14 days[$]
Vital signs (including heart rate and blood pressure)	X	X[#]	X	X[#]	X	X	X
ECG	X	X		X			
Serum Chemistry and cytokine testing [a]	X		X		X		
Pregnancy test [b]	X	X	X	X	X		
Alcohol intoxication screen[c]		X		X			
Adverse event review and evaluation	X	X	X	X	X	X	X
Neurophysiology/EEG	X	X		X		X	
MRI	X		X		X		

	Enrollment and Baseline Testing Visit 1*	**Dosing Session Study Visit 2^ (Condition 1)**	**Study Visit 3 (Follow up and Washout)**	**Dosing Session Study Visit 4^ (Condition 2)**	**Study Visit 5 (Follow up and Washout)**	**Study Visit 6 (Follow up)**	**Study Visit 7 (follow up and close out)**
COVID+ Visit Window Adjustment	+/- 7-14 days[$]	+/- 7-14 days[$]	+/- 7-14 days[$]	+/- 7-14 days[$]	+/- 7-14 days[$]	+/- 7-14 days[$]	+/- 7-14 days[$]
MINI-7	X						X
WASI-II Intelligence Assessment[d]	X		X		X	X	X
5-D Altered States of Consciousness Rating Scale (5D-ASC)	X	**X**	X	**X**	X	X	X
Digital Journal			X		X		X
Revised Mystical Experiences Questionnaire (RMEQ-30)	X	X	X	X	X	X	X
Ego Dissolution Inventory (EDI)	X	X	X	X	X	X	X

	Enrollment and Baseline Testing Visit 1*	**Dosing Session Study Visit 2^ (Condition 1)**	**Study Visit 3 (Follow up and Washout)**	**Dosing Session Study Visit 4^ (Condition 2)**	**Study Visit 5 (Follow up and Washout)**	**Study Visit 6 (Follow up)**	**Study Visit 7 (follow up and close out)**
COVID+ Visit Window Adjustment	+/- 7-14 days[$]	+/- 7-14 days[$]	+/- 7-14 days[$]	+/- 7-14 days[$]	+/- 7-14 days[$]	+/- 7-14 days[$]	+/- 7-14 days[$]
Positive and Negative Affect Schedule' (PANAS)	X		X		X	X	X
NEO-FFI Personality Questionnaire	X						X
ACE	X						
BVMT-R	X		X		X	X	X
HVLT-R	X		X		X	X	X
EBI	X	X	X	X	X	X	X
COLUMBIA-SUICIDE SEVERITY RATING SCALE (CSSRS)	X	X	X	X	X	X	X

	Enrollment and Baseline Testing Visit 1*	**Dosing Session Study Visit 2^ (Condition 1)**	**Study Visit 3 (Follow up and Washout)**	**Dosing Session Study Visit 4^ (Condition 2)**	**Study Visit 5 (Follow up and Washout)**	**Study Visit 6 (Follow up)**	**Study Visit 7 (follow up and close out)**
Debrief/Integration@			X		X		
Complete Case Report Forms (CRFs)	X	X	X	X	X	X	X

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, AST, ALT, sodium. For cytokine testing: Blood draws will be collected and stored for analysis by the cytokine reference library, and will include ELISA analyses for total BDNF, CRP, TGFβ-1, and GFAP; High Sensitivity Luminex Panel for TNFα, IL-1β, IL-6, IL-10, IFN-γ; and a 4 plex Luminex Panel for TNF-R1, TNF-R2, s100β, UCHL-1.

b: Urine pregnancy test (people of childbearing potential).

c: Breathalyzer on dosing session days for presence of alcohol

d: An additional modification will be added to the matrix reasoning subtest to assess divergent/creative thinking.

* Visit 1 will be conducted over 2 separate days to obtain 4 independent blood pressure measurements to test for uncontrolled hypertension, determined as an average blood pressure greater than 140/90mmHg.

Blood pressure monitoring during dosing sessions will be performed with a blood pressure cuff and will be taken 15 minutes before dosing, and then again at 15, 30, 45, 60, 90, 120 minutes and three, four, six and eight hours after dosing to monitor potential hypertensive emergencies, allowing for +/- 5 minutes to account for any delays.

^ Visits 2 will be conducted over 5 separate days, where participants will spend 8 hours total doing preparatory sessions with their

session monitors before the dosing session (4 x 2 hour sessions) to prepare them for the dosing session and help develop and maintain rapport between the participant and the session monitors. Only one hour of preparation before the second dosing session on visit 4 will be needed to check-in with participants on any new developments or concerns.
[#] Visits 3 and 5 each will be conducted over 3 separate days to conduct a follow up assessment, as well as to get repeated measures for fMRI data and blood draws in the days immediately following the dosing sessions (visits 2 and 4, respectively).
[$] Based on evolving guidance adjustments for quarantine times from the Centers for Disease Control and Prevention (CDC). This will not compromise the integrity or quality of the data, and to account for scheduling logistics that may require overlap between visit 1 and visit 2 for baseline testing and the preparatory sessions. https://www.cdc.gov/media/releases/2021/s1227-isolation-quarantine-guidance.html
[@] Participants will meet with the study staff the day after each dosing session and have a 60-minute debrief to discuss and process their experience with the dosing session with the study stuff. This will be done prior to initiating any follow up questionnaires, blood draws or MRI scans for visits 3 and 5.

5.3 Study Duration:

It will take approximately 12 weeks for a single participant to be enrolled and complete the study. For the pilot phase of the study, we will enroll an initial 6 subjects to work through the feasibility of implementing the study design, and to determine if any modifications need to be made for the full study design. For the pilot phase, we will start off slow and only enroll a single participant for the first 1-2 participants to test out the full protocol and closely monitor any potential problems that may arise that would need to be modified or removed from the design. We will assess the results from participant #1 after the 1-week follow up after the second dosing session, and then we will begin enrolling the second participant. After these first 2 subjects have completed the full protocol (about 17 weeks from start date), the team will get together and discuss the results and any issues that arose that may need to be considered and modified for additional participants. If the protocol implementation for the first 2 subjects goes well without needing to modify anything, we will then stagger enrollment and anticipate completing the pilot phase in the first year of the study. For the full study design with N=40 participants, we will run 2 participants per week, and stagger the enrollment of each additional participant after the previous participant has completed the follow up after the first dosing session, and anticipate the implementation of the full study design across all participants to take approximately 3.5 years, or 5 years total for the pilot and full study design.

5.4 Use of radiation*:* N/A

5.5 Use of Center for Magnetic Resonance Research*:* The research team will utilize the CMRR Center's screening tools and adhere to the screening SOP during enrollment of all research participants in this protocol. The CMRR Center's screening tools and SOP are IRB approved under the CMRR Center Grant (HSC# 1406M51205) and information regarding screening procedures is publicly available on the CMRR website (CMRR Policies / Procedures).

6.0 Data and Specimen Banking

6.1 Storage and Access:

Data will be collected using a combination of paper and electronic measures. All paper measures will be entered and stored in an online database (REDCap), and source documents for all data collected will be scanned to PDF and stored in UMN Box. Online measures will be linked to the database for direct data upload. Staff and students will be granted access on an individual basis with individual username and password. Electronic measures will be transferred and stored to this same online database. All stored data will be de-identified. And data containing PHI will be stored in the HIPAA-compliant UMN Box location and will only be accessed by approved study personnel that have permission to access participant PHI. Additional de-identified EEG and fMRI data will be stored in OpenNeuro for possible data

sharing with the scientific community and deposition of data into repositories that are required for publishing findings in the scientific literature. Additionally, the supplier of the psilocybin compound, Usona Institute, requires access to de-identified safety data from the study. Because we are not sharing any identifiable information with Usona or OpenNeuro, neither a DUA or BAA is required. We have a signed agreement with Usona for the transfer of the compound in exchange for de-identified safety data.

Specimen blood samples will be processed for analysis and then stored by the Cytokine Reference Lab service. These samples will be stored at -80C for at least 5 years to allow for follow-up tests that may be required, such as if new tests become available, or if manuscript reviewers request additional analyses.

6.2 Data:

The following measures will be collected and stored for future analysis: Demographic information including sex, age, race, ethnicity, MINI-7, medical history, vital signs and ECG, blood test and physical exam results, neuroimaging, EEG and surround suppression task data, 5D-ASC, PANAS, RMEQ-30, NEO-FFI, EDI, CCSRS, WASI-II, cytokine assay and serum chemistry results and digital journal data, as well as all audio and video recordings.

6.3 Release/Sharing:

For data releases, request for sharing will be made to the PI, Jessica Nielson or the student investigator, Link Swanson, and/or co-investigators Michael-Paul Schallmo, Kathryn Cullen or Ranji Varghese and granted on an individual basis.

7.0 Sharing of Results with Participants

7.1 Participants that complete MRI scans will be offered a copy of their scan on disc. A written report detailing information gathered at the clinical assessment (MINI-7), including psychiatric diagnosis, will be shared with participants provider(s) of choice upon receiving signed release of records from the participant. Additional specific measures gathered will be shared with participants providers upon signed request. General findings after data analysis will be shared with all participants in the form of a mailed letter.

7.2 Sharing of genetic testing: N/A

7.2.1 Disclosure of results: N/A

7.2.2 If returning results to participants: N/A
7.2.3 Future analysis of genotypes: N/A

8.0 Study Population

8.1 Inclusion Criteria:

- Gender: Any
- Age: 25-65
- Demographic group: Any
- Have given written informed consent
- Have at least a high-school level of education or equivalent (e.g. GED), and be able to read and write in English
- General health status: Participants should be in good physical and psychiatric health.
- Experience taking psilocybin (at the PI's discretion).
- Participants must also have a person that can reliably transport them to and from the CRU for dosing session days.
- Geographic location: Minnesota counties that are approximately within 1 hour driving distance to Twin Cities, including not limited to Hennepin, Ramsey, Washington, Anoka, Wright, Carver, Scott, Dakota, Sherburn
- Agrees to adhere to current COVID-19 safety precautions implemented at MHealth/Fairview
- Agrees to refrain from using recreational drugs while enrolled in the study, including, but not limited to, hallucinogens, ketamine, and marijuana.

8.2 Exclusion Criteria:

- Current or past history of meeting DSM-5 criteria for schizophrenia spectrum or other psychotic disorders (except due to another medical condition), or Bipolar I or II Disorder, personality disorder, major depressive disorder, posttraumatic stress disorder, panic disorder, obsessive compulsive disorder, dysthymic disorder.
- Current or past history within the last 5 years of meeting DSM-5 criteria for a moderate or severe alcohol or drug use disorder (excluding caffeine, nicotine, and hallucinogens)
- Those with a first or second-degree relative with a current or past history of meeting DSM-5 criteria for schizophrenia or other psychotic disorders or bipolar I or II disorder, because they might have an underlying genetic susceptibility for psychosis.
- Presence of symptoms of the following DSM-5 disorders within the past 6 months (as assessed by the MINI-7):
    - Major depressive Episode
    - Suicidality
    - Manic and Hypomanic Episodes
    - Panic disorder
    - Agoraphobia
    - Social Anxiety Disorder
    - Obsessive-Compulsive Disorder
    - Posttraumatic Stress Disorder
    - Alcohol Use Disorder
    - Substance Use Disorder (Non-Alcoholic)
    - Psychotic Disorders and Mood Disorders with Psychotic Features

  - Anorexia Nervosa
  - Bulimia Nervosa
  - Binge Eating Disorder
  - Generalized Anxiety Disorder
  - Antisocial Personality Disorder
  - Mood Disorders:
  - Major Depressive Disorder (MDD)
  - MDD with Psychotic Features
  - Bipolar I
  - Bipolar II
  - Other Specified Bipolar and Related Disorder
- Presence of abuse or dependence of drugs measured by the MINI-7 in the past 12 months:
  - Lithium, Sodium Valproate (Depakote), Lamotrigine (Lamictal) – Manic/Bipolar disorders
  - **Stimulants:** amphetamines, "speed", crystal meth, “crank”, Dexedrine, Ritalin, diet pills.
  - **Cocaine:** snorting, IV, freebase, crack, "speedball".
  - **Opiates:** heroin, morphine, Dilaudid, opium, Demerol, methadone, Darvon, codeine, Percodan, Vicodin, OxyContin.
  - **Dissociative Drugs**: PCP (Phencyclidine ,"Angel Dust", "Peace Pill", “Hog”), or ketamine (“Special K”).
  - **Inhalants:** "glue", ethyl chloride, “rush”, nitrous oxide ("laughing gas"), amyl or butyl nitrate ("poppers").
  - **Cannabis:** marijuana, hashish ("hash"), THC, "pot", "grass", "weed", "reefer".
  - **Sedatives, Hypnotics or Anxiolytics:** Quaalude, Seconal ("reds"), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, barbiturates, Miltown, GHB, Roofinol, “Roofies”.
  - **Miscellaneous:** steroids, nonprescription sleep or diet pills. Cough Medicine?
- History of medication or substance induced psychosis.
- Medically significant condition considered unsuitable for the current study (e.g. diabetes, epilepsy, severe cardiovascular disease, etc)
- History of suicide attempts or mania
- Positive pregnancy test or currently breast-feeding
- Currently taking on a regular (e.g., daily) basis any prescription medications, with the exception of birth control or other hormone therapy
- A strong bias either for or against psychedelic substances, or if their responses about psychedelic use indicate that they abuse them from frequent use (more than once per month, with the exception of microdosing).
- MRI EXCLUSION: we will also exclude anyone with head trauma, claustrophobia incompatible with scanning, cardiac pacemaker, implanted cardiac defibrillator, aneurysm brain clip, inner ear implant, prior history as a metal worker and/or certain metallic objects in the body that cannot be approved for MR scanning by the CMRR safety committee, history of clinically significant vertigo, seizure disorder, middle ear

disorder, or double vision, or tattoos that were done less than 4 weeks from the first scheduled MRI.

- Significant movement disorders including tardive dyskinesia that could disrupt EEG recordings will also be excluded.
- Uncontrolled hypertension, with an average blood pressure reading across 4 measurements over 2 separate days greater than 140/90mmHg.
- ECG with a QTc greater than 450 msec, based on the FDA Guidance of Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.
- Unwilling to adhere to current COVID-19 safety precautions.

8.3 Screening:

Initial screening and consent: We will send out an initial REDCap survey via email to interested participants that contact the study team expressing interest in the study, followed by telephone or zoom interviews with potentially eligible participants using an IRB-approved script and screening form to determine eligibility. We will schedule potentially eligible participants for an in-person meeting to fully explain study procedures and risks. If they are interested in participating, we will then obtain signed consent from the participant.

Clinical assessment: Assessment interviews with participants will be conducted by the clinical research coordinator, directly after the consent process. A consensus meeting at the end of the interviews will incorporate information from interviews and all rating scales.

Assessment of General Psychopathology and Demographic Information. To describe our sample and to determine criteria for ineligibility, we will screen for the presence of DSM-5 psychiatric diagnoses (American Psychiatric Association, 2013b), including, but not limited to, schizophrenia, bipolar disorders, personality disorders, depression, post-traumatic stress disorder, obsessive compulsive disorder, substance abuse disorder, etc. We will use the COLUMBIA-SUICIDE SEVERITY RATING SCALE to assess past and current suicidal ideation (Posner et al., 2011).

9.0 Vulnerable Populations

9.1 Vulnerable Populations:

Population / Group	Identify whether any of the following populations will be targeted, included (not necessarily targeted) or excluded from participation in the study.
Children	Excluded from Participation
Pregnant women/fetuses/neonates	Excluded from Participation

Prisoners	Excluded from Participation
Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders	Excluded from Participation
Non-English speakers	Excluded from Participation
Those unable to read (illiterate)	Excluded from Participation
Employees of the researcher	Excluded from Participation
Students of the researcher	Excluded from Participation
Undervalued or disenfranchised social group	Excluded from Participation
Active members of the military (service members), DoD personnel (including civilian employees)	Excluded from Participation
Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.	Excluded from Participation
Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare.	Included/Allowed to Participate
Individual or group with a serious health condition for which there are no satisfactory standard treatments.	Excluded from Participation
Individual or group with a fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior).	Excluded from Participation
Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence	Excluded from Participation

consent to research or decision to continue in research.	

Additional Safeguards: Disadvantaged groups will be Included/Allowed to Participate as part of this research but information will not be collected as to the participants status. Therefore, this research does not add any additional risk to this group. Participant confidentiality will be protected. Participants will have the freedom to decline participation and the right to withdraw at any time without penalty. Participant confidentiality will be protected. Participants will have the freedom to decline participation and the right to withdraw at any time without penalty.

10.0 Local Number of Participants

10.1 Local Number of Participants to be Consented:

Local Number of Participants to be Consented: 46 participants are needed for data analysis and we anticipate needing to consent 75 participants to meet that goal.

11.0 Local Recruitment Methods

11.1 Recruitment Process:

- We will post advertisements in the community via flyers and local newspapers.
- We will advertise through the internet, social media (Facebook, Twitter, Meetup, etc.) and community outlets about our study. We will engage a HIPAA compliant and IRB-approved system connected with a REDCap screening form.
- We will maintain a social media presence to promote the study and enhance visibility to the community.
- We will make regular presentations about the research to community organizations including neighborhood groups and the Psychedelic Society of Minneapolis member base.

11.2 Identification of Potential Participants:

- For physical flyers in the community, potential participants will self-identify based on limited information present. They will contact research staff via phone and/or email.
- For internet and social media advertisements, potential participants will self-identify based on limited information present. They will contact research staff via phone and/or email or REDCap form.

- Social media presence will direct traffic to IRB-approved website with contact information for the research team listed and a link to the REDCap screening survey (see Appendix A).
- At community presentations potential participants will not be identified by research staff. Potential participants will have the opportunity to self-identify and request more information about research participation.

11.3 Recruitment Materials:

- Internet advertisement (for public display, potential participant self-identify)
- REDCap survey (basic eligibility criteria to determine who to follow up with over phone/zoom)
- Phone script (study summary to potential participants during phone screen)
- Phone screen (telephone screening form for potential participant eligibility)

11.4 Payment:

Participants will be compensated directly using the Greenphire ClinCard. Each task completed will have attached a specific compensation amount. Once the task is completed research staff will load the amount attached to that task on to the participants Greenphire ClinCard. Participant compensation will provide participants $30/hour for their time on psilocybin or control dosing days (two 8-10 hour sessions, $600), and $20/hour for other assessments and study visits (Baseline testing, preparatory sessions, 7 MRIs, 4 follow up visits = 47 hours, $940). Total possible compensation per participant = $1540. All participants will complete a W-9.

12.0 Withdrawal of Participants

12.1 Withdrawal Circumstances:

Participants will be withdrawn from the research study if any of the following occur while enrolled: 1) participant meets any exclusionary criteria; 2) participant becomes suicidal with intent and plan; 3) participant engages in other harmful behavior towards themselves or others that requires urgent/emergency medical care; 4) participant experiences intolerable adverse effects from the psilocybin or niacin, including allergic reaction; 5) participant fails to adhere to protocol requirements; and/or 6) participant withdraws consent. Decision to withdraw based on these criteria will be determined at the PI's discretion.

12.2 Withdrawal Procedures:

If a participant withdraws or is withdrawn from the research study, no more data will be collected on them. Previous data collected will be stored and analyzed as planned, unless exclusionary criteria is met. If the participant is withdrawn they will be notified by phone or in-person and any scheduled appointments for the research study will be cancelled.

12.3 Termination Procedures:

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension. The study team will notify the participants of the study termination.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

The study may resume once concerns about risks, protocol compliance, and/or data quality procedures are addressed and satisfy the IRB. Data collected for the study prior to the study termination will be handled in the following manner:

- If the study is terminated due to safety reasons, the data related to adverse events will be evaluated.
- If the study is terminated for any other reason, the regulatory and/or institutional document/data retention policies will apply.

13.0 Risks to Participants

13.1 Foreseeable Risks:

Immediate risks

In controlled settings, psilocybin has a robustly established physical and psychological safety profile (Brown et al., 2017; Hasler et al., 2004; Johnson et al., 2008; Johnson and Griffiths, 2017). Psilocybin has been generally well-tolerated by subjects in experimental studies (Dos Santos et al., 2018), both in psychiatric patients (Carhart-Harris et al., 2017a, 2018; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016) and in healthy volunteers (Barrett et al., 2018; Bravermanová et al., 2018; Carhart-Harris et al., 2012, 2013; Carter et al., 2005b; Gouzoulis-Mayfrank et al., 2002; Griffiths et al., 2011; Grimm et al., 2018; Hasler et al., 1997; Kometer et al., 2015; Kraehenmann et al., 2015; Muthukumaraswamy et al., 2013; Nicholas et al., 2018; Quednow et al., 2012; Schartner et al., 2017; Turton et al., 2014; Umbricht et al., 2003; Vollenweider et al., 2007; Wittmann et al., 2007). The most common acute physiological effects include a moderate increase in pulse and blood pressure (Gouzoulis-Mayfrank et al., 1999; Griffiths et al., 2006; Johnson et al., 2008) and delayed, transient, dose-dependent headaches (Johnson et al., 2012).

Risk of adverse psychological reactions collectively known as “bad trips” involve acute states of distress characterized by fear, panic, anxiety, disturbing feelings, and troubling thoughts (Johnson et al., 2008). Acute adverse psychological reactions can be minimized and mitigated in a controlled experimental session using a variety of well-established techniques that include careful screening of subjects, training of study personnel, holding the dosing session in a secure and comfortable physical environment, careful preparation of participants, and following established pre-session, session, and post-session protocols (Johnson et al., 2008). Should such states arise, and the participant is unable to work through this reaction and resolve on its own, we will have the nurse on site to assess any major physical complications that may arise, and if needed, pre-prescribed anti-anxiety or anti-psychotics will be administered after consultation about the case with the psychiatrist/clinician on call for the testing sessions. See Appendix D for a description of our crisis communication plan, should such a situation arise.

Long-range risks

Long-range risks, while very unlikely, include the possibility of triggering substance abuse, prolonged psychotic episodes, and lasting perceptual abnormalities (Johnson et al., 2008). Psilocybin has an extremely low abuse potential (Johnson et al., 2018a), does not induce cravings or withdrawal (Johnson et al., 2018a), and does not activate dopaminergic reward circuits critical to substance use disorders (Nichols, 2004). Psilocybin is thus generally regarded as safe to introduce to drug-naive subjects without risk of initiating abuse or habitual use (Johnson et al., 2008, 2018a). Lasting perceptual abnormalities can occur, especially in naive users, although their occurrence is rare and in most cases are very brief, not regarded as detrimental, and sometimes even regarded as pleasurable (Johnson et al., 2008). Hallucinogen persisting perception disorder (HPPD), a condition in which the acute perceptual effects of the drug persist for prolonged periods after the peak effects have subsided, is extremely rare, mostly associated with LSD use in combination with cannabis, and has not been reported as having occurred in participants in any modern studies with psychedelic drugs (Martinotti et al., 2018). Nonetheless, careful follow-up on perceptual abnormalities is recommended (Johnson et al., 2008). Prolonged psychotic reactions to psilocybin in clinical settings is extremely rare and has not occurred in participants in studies.

The relative safety of psilocybin extends beyond controlled clinical settings, as epidemiological data on illicit and ritual use shows that adverse reactions leading to hospitalization are relatively rare (Johnson et al., 2018b; Leonard et al., 2018). Since there is little to no risk of physical overdose (Brown et al., 2017; Johnson et al., 2008), most hospitalizations resulting from illicit use in the general population are due to emotional distress and unstable mental states (Leonard et al., 2018) and subside within 48 hours (Johnson et al., 2018b; Tylš et al., 2014).

In summary, psilocybin has a proven track record of safety when administered in controlled experimental settings that follow established protocols (Brown et al., 2017; Dos Santos et al., 2018; Hasler et al., 2004; Johnson et al., 2008; Johnson and Griffiths, 2017).

Although not completely without risks, psilocybin does not impose unusual danger compared with other standard experimental treatments and interventions.

Niacin can elevate heart rate and cause the skin to become flushed, and some digestive complications at high doses, however we will not be giving participants a high enough dose to induce serious forms of these complications, but participants may experience them to some degree.

Risks of a Blood Draw: Events associated with venipunctures include discomfort, slight bruising, bruising, bleeding, lightheadedness, fainting, infection at the venipuncture site, nausea, anxiety and swelling at the venipuncture site. Blood draws will occur in a lab or clinical research unit and done by qualified medical professionals trained in phlebotomy.

EEG: Use of the electrodes during the electrophysiology session requires that subjects wear an electrode cap, which some people find uncomfortable. We will measure the subject's brain waves while they are at rest and when the subject is performing a number of tasks. Some minor skin irritation is possible in reaction to the electrode cap application; however, reddening of the skin from the pressure of the electrodes typically resolves within 24 hours. Subjects will be notified that scalp discomfort from the use of EEG equipment typically resolves within 24 hours. Study staff will provide support for the participants should they appear to become fatigued or frustrated during EEG. Subjects have the liberty of discontinuing this procedure at any point.

MRI Scanning: The MRI scanning device will be a 3.0 Tesla MRI scanner. This device has been evaluated by the FDA as having non-significant risk for persons more than one month of age and data already reviewed by the UMN IRB indicate that the 3.0 Tesla magnetic field does not pose a significant risk to human volunteers. All participants will be screened according to CMRR policies to minimize risks to participants. These are the specific risks related to MRI scanning:

1) Exposure to high magnetic field: The primary known hazard associated with exposure to a static high magnetic field is that the magnet exerts a strong force on ferromagnetic objects. Metallic objects that are entered the magnetic field can accelerate into the magnet potentially causing damage to the magnet or persons in the magnet room. In addition, implanted metallic objects can be displaced. MRI may not be appropriate in the presence of the following conditions: cardiac pacemaker; metal fragments in eye, skin, body; mechanical heart valve replacement; brain clips; venous umbrella; being a sheet-metal worker or welder; aneurysm surgery; intracranial bypass; renal, aortic clips; middle ear, eye, joint, or penile implants; joint replacements; hearing aid; neurostimulator; insulin pump; intra-uterine device (IUD); shunts/stents anywhere in the body; metal mesh/coil implants; metal plate/pin/screws/wires anywhere in the body, any other metal implants; permanent eyeliner or permanent artificial eyebrows. All participants will be thoroughly screened first over the phone before enrollment, then using the CMRR Safety Screening Form at the day of MR scanning. Participants that do not pass screening will not enter the CMRR where magnetic fields exist.

2) Radiofrequency (RF): Radiofrequency pulses impart small amounts of energy into the participant. No ionizing radiation is used with MRI. Because the pulse sequences to be used fall within FDA guidelines and will not be operated outside of safe limits, we do not expect any hazard associated with power deposition. To prevent inadvertent application of significant energies which may result in heating, the scanning systems include monitoring with both a hardware and a software monitor. Participants will be instructed to report any heating sensation immediately, and that the scan could be stopped at any time if this occurs.

3) Peripheral nerve stimulation: Peripheral nerve stimulation from rapidly switching magnetic fields (dB/dt) during the scanning procedure may occur. As a result, the participant may experience muscle twitching or tingling sensations lasting seconds to minutes. This is considered to occur seldomly. Participants are instructed that if twitches do occur, they should immediately inform the operator. This would be a short-lived side effect and reversible.

4) Acoustic noise: MR imaging creates acoustic noise because of pulsing currents through the gradient coils within the magnetic field. A repetitive tapping sound occurs as a result. Ear plugs are provided to the participant to prevent hearing damage and provide comfort

5) Claustrophobia: Some people undergoing this procedure become anxious and afraid when in closed spaces. Participants will be instructed that they can stop procedure at any time. The MRI technologist will be in communication with the participant during the scan and ask them how they are doing. In addition, participants will be given a squeeze ball to communicate an urgent need or concern. Participants are screened for claustrophobia before enrollment.

6) Anatomical abnormalities revealed: There is a possibility that the MRI scan would reveal unknown and unlooked for abnormalities such as a cyst, vascular abnormality or a tumor. The scan results will be routinely sent to a radiologist for review. If an abnormality is uncovered, the participants are informed of the results of the radiology review and are encouraged to follow up with their physician. We would provide participants physicians with a copy of the imaging data that we collect upon request.

7) Dizziness and nausea: Dizziness and nausea are rare though may occur if the participants head moves around while they are inside the magnet. If this occurs, this would be acute and reversible, and should resolve within a few minutes without intervention.

Clinical Assessment: Some of the question's participants will be asked may make them feel uncomfortable or upset. These pertain to psychiatric and medical history, behavioral and psychiatric symptomatology, and personal illegal drug use. Participants are informed that they do not have to answer any question that makes them feel uncomfortable. Coordinators interviewing the participants will remind them of this, as well as use empathy to gauge their discomfort. Staff will be sufficiently trained to handle these situations.

Privacy/Confidentiality Risks: Participation in research may involve a loss of privacy due to the nature of the questions that are asked during assessment visits and/or data collected. However, records will be handled as confidentially as possible. All participants will be assigned a unique study identifier that will be used to label all of their records only be accessible to specific study staff listed in the Delegation of Authority log. This link will connect the participant's

identifying information, such as name, etc., to their assigned ID number. No identifying information will be used in any report or publications that may result from this study. All study records will be kept in a secure database. Paper records will be kept in locked cabinets in locked rooms.

Severity and relationship of adverse events: The Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

The following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

The degree of certainty about causality will be graded using the categories below.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

13.2 Reproduction Risks:

There are no known risks of MRI imaging to someone who is pregnant or an unborn fetus, however we will not scan someone who is pregnant. Participants will be screened for pregnancy over the phone before enrollment and a pregnancy test will be administered at the CMRR before scanning to ensure the participant is not pregnant.

There are no known risks of psilocybin to someone who is pregnant, however niacin is not recommended, so we will be screening participants who are pregnant and performing pregnancy tests before administering any intervention.

13.3 Risks to Others: There are no risks to individuals who do not participate.

14.0 Potential Benefits to Participants

14.1 Potential Benefits:

Benefits have been reported anecdotally and therapeutically in many published scientific research studies using psilocybin. Participants from previous research in healthy controls report having mystical experiences induced by taking psilocybin which were some of the most significantly meaningful experiences of their lives. This resulted in a sense of well-being that lasted long after the experience (Griffiths et al., 2006, 2011, 2018; MacLean et al., 2011). However, this benefit is not guaranteed.

15.0 Statistical Considerations

15.1 Data Analysis Plan:

For this pilot study, EEG and fMRI data will be analyzed using standard software and toolboxes. EEG data will be processed to eliminate artifacts (e.g., eye movements). EEG signal amplitudes will be analyzed statistically to compare across subject groups and experimental conditions, as with the behavioral data. fMRI data will be analyzed using standard software (e.g. FMRIB Software Library, others) according to standard protocols used previously in psychedelic neuroimaging research (Atasoy et al., 2017; Carhart-Harris et al., 2017b; Deco et al., 2018; Roseman et al., 2018) and human connectome project pipelines used at CMRR. Data will either be analyzed on CMRR secure servers, or on the Minnesota Supercomputing Institute (MSI) servers. Other measures of RMEQ-30, WASI-II, 5D-ASC, EDI, EBI, PANAS, NEO-FFI, HVLT-R, BVMT-R, CSSRS, cytokines, vital signs and diagnostic tests will be analyzed in statistical software programs (e.g. R, SPSS, etc) for significant differences between groups, and assessed for statistically significant relationships with EEG, fMRI and the psychophysics tasks. The team investigators and coordinator will be blinded to condition, however an independent study statistician that will not have any interaction with study participants will perform all blinded data analysis, with unblinded secondary analyses performed by Dr. Nielson, Dr. Swanson and the study coordinator.

15.2 Power Analysis:

Previous work with surround suppression tasks by Co-Investigator (Schallmo et al., 2019) determined the appropriate number of participants with the smallest effect sizes and corresponding standard deviations found that 16 subjects would provide an a priori power of 92% for detecting a significant difference in surround suppression between experimental conditions. Assuming that some drop out may occur, we decided to have 20 participants per drug group (age, sex and baseline clinical variables balanced).

15.3 Statistical Analysis:

We will test hypotheses about differences between baseline EEG signal and psychophysics tasks performed under both psilocybin and the active placebo control during the surround suppression task. We will test changes in primary and secondary endpoints between baseline and each of the drug conditions using univariate repeated measures ANOVA, as well as a mixed-effects regression model (random intercept by participant) controlling for additional co-variates such as treatment order, age, sex, and other relevant predictors at baseline that are significantly different between groups. If diagnostic tests reveal poor adherence to model assumptions, equivalent non-parametric tests will be used instead. We will also test changes in resting state fMRI networks from baseline, and 1-day, 3-days and 7-days after exposure to the experimental compound and placebo control. Will use independent component analysis (ICA) to identify functionally meaningful resting state networks using the FMRIB Software Library (FSL). Significance will be tested at $p<.05$.

15.4 Data Integrity:

Data collection is the responsibility of the clinical trial staff under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All information and data collected from and about participants during the research study will be de-identified and kept in the participants folder in a locked cabinet in a locked room accessible only by research staff. Identifiable forms such as screening forms containing DOB and consent forms will be kept separate from participant data. All research staff and volunteers are required to complete data safety and security and HIPAA training according to University of Minnesota policy. All data electronically stored and transferred will be de-identified and any identifiable pieces of information stored electronically will be kept secure accessible by only research staff and will be encrypted if transferred or using secure portal such as Box.

16.0 Health Information and Privacy Compliance

16.1 Select which of the following is applicable to your research:

☐ My research does not require access to individual health information.

☒ I am requesting that all research participants sign a HIPCO approved HIPAA Disclosure Authorization to participate in the research (either the standalone form or the combined consent and HIPAA Authorization).

☐ I am requesting the IRB to approve a Waiver or an alteration of research participant authorization to participate in the research.

Appropriate Use for Research:

We will only be accessing and retaining records from research participants who have consented to be in the study. We will carefully match the participants information with their appropriate records, and only IRB-approved study staff will have access to these records. If at any time the participant decides to withdraw their consent from the study, all copies of their records will be destroyed in a HIPAA-compliant shredder.

16.2 Identify the source of Private Health Information you will be using for your research (Check all that apply)

☐ I will use the Informatics Consulting Services (ICS) available through CTSI (also referred to as the University's Information Exchange (IE) or data shelter) to pull records for me

☒ I will collect information directly from research participants.

☐ I will use University services to access and retrieve records from the Bone Marrow Transplant (BMPT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) database.

☐ I will pull records directly from EPIC.

☐ Other. Describe:

16.3 Explain how you will ensure that only records of patients who have agreed to have their information used for research will be reviewed. N/A

☐ I will retrieve record directly from axiUm / MiPACS

☐ I will receive data from the Center for Medicare/Medicaid Services

☐ I will receive a limited data set from another institution

16.4 Approximate number of records required for review: N/A

16.5 Please describe how you will communicate with research participants during the course of this research. Check all applicable boxes

☐ This research involves record review only. There will be no communication with research participants.

☐ Communication with research participants will take place in the course of treatment, through MyChart, or other similar forms of communication used with patients receiving treatment.

☒ Communication with research participants will take place outside of treatment settings. If this box is selected, please describe the type of communication and how it will be received by participants.

- We will communicate with participants via telephone (using a study-specific phone number) for pre-screening, appointment scheduling, appointment reminders, etc. We will also communicate through text message or unsecure email if the participant agrees in writing by signing the GUIDELINES AND CONSENT FOR TEXT MESSAGE CORRESPONDENCE FOR RESEARCH PARTICIPANTS and/or GUIDELINES AND CONSENT FOR UNSECURED EMAIL CORRESPONDENCE FOR RESEARCH PARTICIPANTS.

16.6 Access to participants

The research team will be permitted to access sources of private information because all participants will be required to sign a HIPAA waiver at the time of informed consent.

16.7 Location(s) of storage, sharing and analysis of research data, including any links to research data (check all that apply).

☐ In the data shelter of the Information Exchange (IE)

☐ Store ☐ Analyze ☐ Share

☐ In the Bone Marrow Transplant (BMT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) Database

☐ Store ☐ Analyze ☐ Share

☒ In REDCap (recap.ahc.umn.edu)

☒ Store ☐ Analyze ☐ Share

☐ In Qualtrics (qualtrics.umn.edu)

☐ Store ☐ Analyze ☐ Share

☒ In OnCore (oncore.umn.edu)

☒ Store ☐ Analyze ☐ Share

☒ In the University's Box Secure Storage (box.umn.edu)

☒ Store ☐ Analyze ☐ Share

☐ In an AHC-IS supported server. Provide folder path, location of server and IT Support Contact:

The path should be in the form of "\\vp.ahc.umn.edu\vp\Research\Study0004" HIPCO requires this information to verify the data are in a properly encrypted server.

☐ Store ☐ Analyze ☐ Share

☒ In an AHC-IS supported desktop or laptop. Provide UMN device numbers of all devices where such information will be stored, location(s) of device(s) and IT Support Contact:

AHC-IS supported laptop, device # 20170890, # 20192519, and # 20191654; and AHC-IS supported desktops, device # 20201941 and # 20201942.

☒ Store ☒ Analyze ☐ Share

☒ Other. Blood samples that are collected from participants at the CRU will be labeled with a de-identified subject code and date, and aliquoted by the study staff and stored by the Cytokine Reference Lab (CRL). Samples will be logged using a de-identified label/code for study participants to keep track of their location within the storage boxes housed in the CRL freezer. De-identified samples will be analyzed by the cytokine laboratory. Only approved study staff will have access to identifying information for these samples. Additional data processing and analysis for MRI and EEG data will be done on either the CMRR server, or on the MSI server due to the size and complexity of the data. Additionally, de-identified processed EEG and fMRI data will also be shared in OpenNEURO (openneuro.org). Audio and video recording from Zoom sessions will be stored on the AHC-IS supported laptop temporarily after each study visit, and then transferred to the UMN Box secure storage for the study. Audio and video recordings from video camera collected during in-person dosing sessions will be transferred to the AHC-IS supported laptop temporarily after each session and then transferred to the UMN Box secure storage for the study. A secure, encrypted, AHC-IS supported external hard drive will be used for temporary storage and analysis of video data, due to large file sizes of the videos. Only approved study personnel will have access to the UMN Box folder for this study, and audio/video data will be used to monitor adherence to lab protocols and for education and training purposes for study personnel.

16.8 Consultants. Vendors. Third Parties. None

16.9 Links to identifiable data: Identifying information about research participants will be contained in a password-protected spreadsheet that is stored on AHC-IS approved devices by the approved study team members, as well as backed up in UMN Box. Only approved study staff will have access to identifying information and will only be permitted to access this on approved devices and on UMN Box.

16.10 Sharing of Data with Research Team Members. Data will only be shared with research team members through UMN Box. De-identified EEG and fMRI data will also be deposited into OpenNEURO (openneuro.org).

16.11 Storage and Disposal of Paper Documents: Any paper documents will be scanned to PDF and stored in the HIPAA compliant UMN Box. Paper records containing any PHI will be shredded in a HIPAA approved paper shredder/disposal container.

17.0 Confidentiality

17.1 Data Security:

All information and data collected from and about participants during the research study will be de-identified and kept in the participants folder in a locked cabinet in a locked room accessible only by approved research staff. Identifiable forms such as screening forms containing DOB and consent forms will be kept separate from participant data. All research staff and volunteers are required to complete data safety and security and HIPAA training according to University of Minnesota policy. All data electronically stored and transferred will be de-identified and any identifiable pieces of information stored electronically will be kept secure accessible by only research staff and will be encrypted if transferred or using secure portal such as Box or REDCap. We will be applying for a Certificate of Confidentiality (CoC) through the FDA once we have IRB approval.

18.0 Provisions to Monitor the Data to Ensure the Safety of Participants

18.1 Data Integrity Monitoring.

Data integrity monitoring will be conducted at outset, every 6 months, and upon study closing by the Clinical and Translational Science Institute monitor assigned to the Department of Psychiatry and Behavioral Sciences. The monitor will review an on-site regulatory binder as well as participant folders to ensure compliance to the protocol, SOP and other regulatory requirements. The monitor will review consent forms, completion of source documents and case report forms, and appropriate documentation for protocol deviations, personnel changes, staff training, and adverse events, etc. The monitor will have access to and review all necessary documents at a set appointment time. Monitoring reports will indicate enrollment numbers, select changes since the last monitoring visit and any unresolved queries. The research staff will be expected to resolve all queries, and notify monitor of these resolved queries, within 10 days of receiving the monitoring report.

18.2 Data Safety Monitoring.

A Data Safety Monitoring Board will be appointed for this research study. The DSMB will initially meet prior to enrolling the first participant, and then again after we have completed the

first three participants during the pilot phase to assess any SAE/AE or other issues. We will determine together whether we can move forward with the full study design or if modifications need to be made. For the full study design, the team will meet regularly after each additional 10 participants are enrolled and complete the study protocol throughout the duration of the study. Research staff will prepare a report for the DSMB at least 1 week prior to each scheduled meeting. This report will include a protocol synopsis, study personnel, brief statement of purpose, projected timetable and schedule, study summary including a summary of protocol changes, enrollment/participant status, protocol deviations, and adverse event tables (incidence, severity, listing of serious adverse events, adverse events, and deaths) and anything else pertinent to the study, participant safety or DSMB oversight. Safety information will be collected on Case Report Forms, adverse event and protocol deviation logs, and on memos (memo-to-file) requiring additional explanation and PI signature.

The DSMB, along with FDA and UMN IRB, would determine the need to immediately suspend research based on any individual SAE/AE as well as collective AE/SAE parameters. The DSMB, in addition to the FDA and UMN IRB, will be notified of any SAE immediately. The DSMB will be notified in each annual report of the following: AE log (frequency, severity, corrective treatment, duration, relation to study drug, and serious or not serious of each event by participant ID), AE incidence and severity by body system, and listing SAE/deaths.

See Appendix (G) for the DSMB members and charter.

19.0 Provisions to Protect the Privacy Interests of Participants

19.1 Protecting Privacy:

At initial screening, potential participants will be screened for a privacy interest request to gauge ability to accommodate such request and still compete the study. If the potential participant passes initial screening and indicates interest, they will be informed that if they have specific privacy request throughout the course of the study, to let study staff know and we will accommodate such request within the limits of the protocol and if unable to meet request staff will inform participant. If the participant indicates a specific “privacy interest” request research staff will discuss the feasibility of such request with participant and jointly decide feasibility of participation. If the request appears feasible within the activities of the study, such request will be met by research staff. In addition, upon review of the activities of the research study at the consent process, the participant will be asked if they would care to place limits on whom they interact with or whom they provide personal information within the confines of the research study. If the participant indicates they do not wish to place limits on their “privacy interest”, no further action will be taken. At the start of each subsequent research study visit, while engaging with the participant on their continued willingness to participate, the participant will be asked again about any changes they would like to make to their “privacy interest” request.

19.2 Access to Participants*:*

The research team will not access any medical records or other sources of private information outside of information without the participants written consent.

20.0 Compensation for Research-Related Injury

20.1 Compensation for Research-Related Injury:

In the event that research-related activities result in an injury, treatment will be provided to the participant (e.g., first aid, emergency treatment, and follow-up care as needed). Care for such injuries will be billed in the ordinary manner to the participant or the participant's insurance company.

20.2 Contract Language: N/A

21.0 Consent Process

21.1 Consent Process (when consent will be obtained):

Potential participants will participate in the consent process at the very first scheduled visit, the Enrollment/Baseline Study Visit 1, before any study procedures are conducted or remotely via Zoom using REDCap e-consent. They will receive copies of the combined consent and HIPAA form via email or USPS mail at least 24 hours before this appointment. The initial consent process will take place with research staff in a previously reserved room within the Ambulatory Research Center (ARC) at the University of Minnesota Department of Psychiatry (F212) Fairview Riverside West Building. During the initial consent visit staff will review the consent forms highlighting the most salient points such as study title, purpose, procedures, risks, benefits, alternatives, confidentiality, research related injury, voluntariness, and any additional signing/initial blocks such as permission to re-contact in the future and share data outside of this research study. Talk back method will be used during the consent visit to ensure potential participants are understanding these points. In addition, an approved version of the The MacArthur Competence Assessment Tool for Clinical Research

(MacCAT-CR) specific to this study will be used with all participants during the consent process. Potential participants that are not able to complete the MacCAT-CR or score less than 2 points on each question will not be consented and enrolled into the study. If a potential participant scores 0 or 1 on any question the information pertinent to that question will be reviewed and discussed with the participant. If the potential participant is then able to answer the question in full and research staff determines the potential participant fully understands the material, they will be scored the 2 points and then consented and enrolled (assuring all answers are scored 2 points). In addition to University and department mandatory consent training for appropriate research staff, all new staff will be trained in consent for this research study including observing the consent process, mock consent and observed for consent process. Throughout the course of the research study, participants will be gauged of their comprehension of scheduled procedures as well as comfort and willingness to complete these procedures by staff at each

visit/procedure. Consent will be documented in writing by signature on the Consent Form and completed MacCAT-CR form. Research staff obtaining consent will also sign each of these applicable forms.

Additionally during the consent process, participants will be instructed on criteria that would disqualify them during the course of the study, including 1) participant meeting any exclusionary criteria during the course of the study; 2) participant becomes suicidal with intent and plan; 3) participant engages in other harmful behavior towards themselves or others that requires urgent/emergency medical care; 4) participant experiences intolerable adverse effects from the psilocybin or niacin, including allergic reaction; 5) participant fails to adhere to protocol requirements; and/or 6) participant withdraws consent. Decision to withdraw based on these criteria will be determined at the PI's discretion.

21.2 Waiver or Alteration of Consent Process (when consent will not be obtained): N/A

21.3 Waiver of Written/Signed Documentation of Consent (when written/signed consent will not be obtained): A waiver of written/signed consent will be needed for the REDCap survey and phone screen.

21.4 Non-English Speaking Participants:

This study will not be enrolling non-English speaking participants.

21.5 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent: N/A

21.6 Adults Unable to Consent:

- Permission: N/A
- Assent: N/A
- Dissent: N/A

22.0 Setting

22.1 Research Sites:

Sites for Recruitment:

- Community bulletin boards: IRB-approved Flyers will be posted on community boards such as in coffee shops, cafes and community centers, and around the Twin Cities campus, where permission is granted.
- Internet advertisement: Similar advertisements will be posted through internet forums where IRB approved.
- Community groups: We will engage community groups, including the Psychedelic Society of Minneapolis, which has over 780 members on Meetup, and over 2500

followers across social media platforms who have experience taking psychedelics in their past (and growing).

Sites for Research Procedures

- Ambulatory Research Center, UMN Department of Psychiatry: Consent process, clinical and baseline assessments will take place in rooms within the ARC, and blood draws at Fairview laboratory in the same building.
- Clinical Research Unit, Phillips-Wangensteen Building: Dosing sessions and EEG recordings
- Center for Magnetic Resonance Research (CMRR): The CMRR will be used for 3T MR scanning at baseline, and at repeated time points after dosing sessions.
- The study coordinator will greet and escort the participants between sites when necessary.

22.2 International Research: N/A

23.0 Multi-Site Research: N/A

24.0 Coordinating Center Research: N/A

25.0 Resources Available

25.1 Resources Available:

- Recruitment feasibility: Research coordinator and study staff will work on recruitment.
- Student investigator will be monitored and accompanied by the study PI/mentor during all study procedures.
- Workload feasibility: Research coordinator will work on this study at 100% time. In addition, the student investigator and study staff will be assisting the work. CMRR data acquisition and infusions/blood draws will enlist paid staff of Fairview/M Health to perform these procedures.
- Facility resources: The facilities listed above are adequate for these procedures.
- Medical resources available to participants
- Training oversight
    - Delegation of Authority log will show which personnel are delegated to which study procedures.
    - Protocol training log will show all personnel up-to-date on current protocol versions.

  - Psychological assessment training will be conducted by Department training programs for the MINI-7, and Kathyrn Cullen or Ranji Varghese will consult on results.

- Phlebotomy will be conducted by trained Fairview/M Health staff.

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