Psilocybin and Motor Function: A Triple-Blind, Dose-Finding Study in Healthy Participants

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Background: There has been a resurgence of research into the potential therapeutic benefits of psychedelics for neuropsychiatric disorders. Classic psychedelics, such as psilocybin, exert complex effects on higher cognitive functions such as perception and awareness, but their impact on motor function remains unexplored. Moreover, there is a theoretical rationale for using psychedelics to promote motor retraining in certain neuropsychiatric conditions associated with motor dysfunction. This protocol paper outlines the first study to investigate the feasibility and safety of performing movement tasks during the acute effects of psilocybin in healthy participants. The findings from this study will further our understanding of the impact of psychedelics on motor function, and inform future studies that combine classic psychedelics with motor retraining in clinical populations.

Methods: 12 healthy participants will each receive three doses of psilocybin (between 5 and 20 mg) in a randomized order, with each dose administered at least 1 week apart. Participants, the trial physiotherapists, and statisticians will remain blinded to the psilocybin dose. A battery of measures assessing motor function will be completed during the acute drug effects. In addition, measures of safety, pre- and post-dose resting-state brain activity via functional magnetic resonance imaging, and participants' subjective experience will be assessed.

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Background and Rationale

There has been a resurgence of research into the clinical applications of classic psychedelics, such as psilocybin, and their effects upon brain function (1). Classic psychedelics are partial agonists of the serotonin 2A (5-HT2A) receptor and, following acute administration, subjects commonly report alterations in states of consciousness, sensory perception and emotion, and longer-term changes in beliefs and behaviors (2). These subjective experiences are associated with altered brain connectivity observed in functional magnetic resonance imaging (fMRI) and electroencephalography studies, including reduced integration within higher-order cortical networks such as the default mode network, and increased connectivity between lower and higher-order brain regions (3, 4). Psychedelics have also been shown to promote synaptogenesis and the growth of dendritic arbors and spines in cortical neurons (5). Although a unified explanation of these multifaceted effects is lacking, one model proposes that psychedelics can enhance the brain's sensitivity to external sensory input whilst relaxing self-representations during a window of enhanced neural plasticity (6).

HIGHLIGHTS

- Psychedelics may promote motor retraining in certain neuropsychiatric disorders.
- No clinical studies have investigated the impact of psychedelics on motor function.
- This study will assess the performance of movement tasks during the acute effects of psilocybin in healthy participants.
- This will inform the design of a follow-up study of psilocybin-assisted physiotherapy in motor functional neurological disorder.
- The findings will inform future trials exploring psychedelics to assist motor retraining in other neuropsychiatric disorders with associated motor dysfunction.

Despite their widespread effects on brain activity, no studies that we are aware of have examined the impact of psychedelics on motor function, which represents a significant gap in the literature. Motor function can be defined as goal-directed motor behavior arising from the interaction between perception, cognition, and action (7). Motor function relies upon the integration of sensory information and intact higher cognitive functions that support movement conceptualization and planning, based in part upon prior knowledge of bodily actions. Since psychedelics are thought to modulate the network integrity of lower and higher-order brain processes, including reduced segregation between the sensorimotor network and other cortical networks (8), it is likely they also modify motor function. However, this hypothesis has not previously been investigated.

From a clinical perspective, there exists a theoretical basis for the use of psychedelics combined with physiotherapy for the treatment of certain neuropsychiatric disorders associated with motor dysfunction. One such example is motor functional neurological disorder (FND), a condition characterized by motor neurological symptoms such as weakness, paralysis, or abnormal gait, without corresponding structural brain pathology (9). There is growing evidence for psychologically-informed physiotherapy in these individuals (10–12) and we have proposed that this approach may be augmented by psilocybin, modifying an individual's somatic self-representation and enhancing the brain's sensitivity to motor retraining (13, 14). Beyond FND, the impact of psychedelics on neural plasticity may hold promise for motor recovery in other neuropsychiatric illnesses (15, 16) although is yet to be assessed in this context in clinical trials.

This pilot study will therefore explore the feasibility and safety of undertaking movement tasks during the acute effects of low-to-moderate doses of psilocybin in healthy participants. Further exploratory measures will include pre- and post-dose changes in resting-state brain activity via fMRI, the subjective intensity of the psychedelic effect, and verbal fluency. The study will include comprehensive eligibility criteria, screening, and safety precautions, including the availability of on-site physicians, to minimize the participants' risk of harm.

This pilot study will inform the design of a proposed future study that will investigate psilocybin-assisted physiotherapy in refractory motor FND. The wide range of movement-related measures in this study may also inform the implementation of psychedelic-assisted motor retraining in other neuropsychiatric disorders.

Objectives

Hypothesis. There is a psilocybin dose between 5 and 20 mg, inclusive, at which participants are no longer able to complete a series of movement tasks during the acute drug effects.

Primary Aims.

1. To assess the feasibility of performing movement tasks during the acute effects of low-to-moderate doses of psilocybin.
2. To inform the maximum dose of psilocybin, up to 20 mg (inclusive), at which healthy participants can successfully complete a series of movement tasks during the acute drug effects.
3. To evaluate the safety of performing movement tasks during the acute effects of low-to-moderate doses of psilocybin.

Exploratory Aims.

1. To explore the effects of low-to-moderate doses of psilocybin on additional domains of motor function.
2. To explore the effects of low-to-moderate doses of psilocybin on verbal fluency.
3. To explore the subjective intensity of low-to-moderate doses of psilocybin.
4. To explore the effects of low-to-moderate doses of psilocybin on resting-state measures of brain activity.
5. To explore the qualitative effects of performing movement and cognitive tasks following acute administration of low-to-moderate doses of psilocybin.

Trial Design

Twelve healthy participants will each receive three doses of 5, 10, 15, or 20 mg psilocybin. Each dose will be provided in a randomized order and administered at least 1 week apart. Given the objectives of feasibility and safety, no comparator agent has been chosen.

Participants will be divided into two blocks:

- Six participants will take 5, 10, and 15 mg (block one).
- Six will take 10, 15, and 20 mg (block two).

Participants will perform a series of movement tasks at baseline and at three time points during the acute drug effects for each dose. Verbal fluency will be measured at baseline and during the peak drug effects for each dose, the intensity of the participants' subjective experiences will be measured at the conclusion of each dose, and resting-state fMRI scans will be performed at baseline and 1 week following one of the doses. The participants, trial physiotherapists, and statisticians will remain blinded to the order of the psilocybin dose. Mental health oversight will be provided for participants, including preparation before their first dose, supervision during each dose, and psychological integration following each dose. A further psychological integration session and qualitative interview will take place within 1 week following their final dose.

METHODS: PARTICIPANTS, INTERVENTIONS, AND OUTCOMES

Study Setting

All study visits will occur at Austin Health, a public tertiary teaching hospital in Melbourne, Australia. Resting-state fMRI scans will occur at the Melbourne Brain Centre: an academic research center at the hospital. All remaining study visits will occur within a dedicated dosing room, providing a comfortable, monitored, clinical setting with access to temperature control, blankets, headphones, and music.

Eligibility Criteria

Inclusion Criteria.

1. Adults aged 18–65 years.
2. No history of FND.
3. Volunteered for the study.
4. Capacity to provide informed consent.

Exclusion Criteria
Medical Exclusion Criteria

1. Cardiovascular conditions: poorly-controlled hypertension, angina, ischemic heart disease, a clinically significant electrocardiogram (ECG) abnormality, transient ischemic attack, stroke, or peripheral or pulmonary vascular disease.
2. A diagnosis of epilepsy or previous seizures.
3. A diagnosis of dementia.
4. Chronic kidney or liver disease.
5. Known conditions putting the participant at risk for hypercalcemia, Cushing's syndrome, hypoglycemia, syndrome of inappropriate antidiuretic hormone secretion, or carcinoid syndrome.
6. Insulin-dependent diabetes; if taking oral hypoglycemic agents, the participant is only excluded if they also have a history of hypoglycemia.
7. Females who are pregnant, nursing, or trying to conceive.
8. Use of medications contraindicated with psilocybin that are inappropriate to cease for the necessary period surrounding the dosing sessions. See section "Contraindicated Medications" for details.
9. Enrolled in another clinical trial involving an investigational product.

Psychological Exclusion Criteria

1. Current or previous psychotic disorder, including schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, delusional disorder, schizotypal personality disorder, substance/medication-induced psychotic disorder, or psychotic disorder due to another medical condition.
2. Current or previous bipolar I or II disorder.
3. First-degree relative with a psychotic or bipolar disorder.
4. A history of attempted suicide or mania.
5. Current or previous substance use disorder (excluding caffeine and nicotine).
6. Previous regular use, or current use, of psychedelic agents.
7. Other psychiatric conditions deemed by research staff to be incompatible with safe exposure to psilocybin.

Study Team Eligibility. The trial physiotherapists will be registered physiotherapists trained in the movement tasks assessed in this study, aspects of which will contribute to the planned physiotherapy intervention in our proposed, future study with FND participants. The mental health professionals will be medical practitioners with experience working in psychiatric settings.

Recruitment

An advertisement will be distributed in the Austin Health staff newsletter outlining study information and contact details, and inquiries from the community via the ANZCTR trial listing will also be accepted. Information will be presented in a neutral fashion to manage potential expectancy confounds arising from public interest in psychedelic research (17).

Interested participants who contact the study team will be emailed the participant information sheet and consent form (PICF) which contains detailed study information and has been approved by the Austin Health Human Research Ethics Committee (AH HREC). Participants will then be invited to a face-to-face screening visit.

Consent

During the screening visit, a study investigator will undertake informed consent by providing written and verbal information about the study procedures, possible benefits, and risks. Participants will be informed that involvement is voluntary, and withdrawal is possible at any time.

Informed consent will be obtained to use the participants' de-identified data for both this study and secondary uses. Secondary uses include informing future related projects and de-identified safety data to be shared with the Usona Institute. Consent for the collection and use of information may be withdrawn at any time. Participants will be advised of their right to request access to information collected and request correction to information with which they disagree.

If questions, concerns, or complaints about the study arise, participants will be invited to contact the investigators, an independent complaints officer, or the AH HREC. Participants will also be invited to discuss with

their relatives, general practitioner, other healthcare professionals, or a lawyer for independent advice.

Those willing to proceed with the study and demonstrate the capacity to provide consent will provide a dated signature on the PICF. A study physician will then conduct a medical and psychiatric history, physical examination, vital signs, and ECG to assess eligibility during the screening visit. These procedures will enable the investigators to exclude participants with pre-existing medical and psychiatric conditions that place them at an elevated risk of developing adverse events (AEs).

Assignment of Interventions

Allocation Sequence. The order of each dose will be randomized for each participant in each block, with a Williams design used to generate the allocation sequence. While significant carryover effects between each dose are not anticipated, a Williams design balances any first-order carryover effects (that is, effects persisting following one dose and upon administration of the subsequent dose) (18). After the study physician confirms eligibility, the study coordinator, who is independent of administering interventions or assessments, will action the Research Electronic Data Capture (REDCap) (19) randomization module, allocating the sequence.

Blinding. The statisticians, trial physiotherapists assessing the movement tasks, and participants will be blinded to the allocation sequence. To maintain blinding, participants will be provided the same number of capsules per session, comprising psilocybin ± placebo, contingent on block assignment (see Table 1).

The study coordinator, mental health professionals, and study physicians will not be blinded as they will arrange the psilocybin prescription and its administration.

If there is an emergency requiring knowledge of a participant's allocation, the blind may be broken for an individual participant. Upon database lock, the study will be unblinded and the trial physiotherapists, participants, and statisticians will be notified of the treatment assignments.

It is possible that expectancy and familiarity may develop over sequential dosing sessions which may impact the performance and assessment of outcome measures. Randomization and blinding to the order of dosing will mitigate undue expectancy effects from both the participant and physiotherapist. Moreover, we will ask the participant and physiotherapist to guess the dose administered at the end of each psilocybin session to enable the efficacy of the blind to be assessed, and to facilitate discussion of any limitations that may arise via unmasking, expectancy, and familiarity with repeated dosing sessions.

Interventions

Intervention Description

Eligible participants will meet their assigned mental health professional for a preparation visit in the same setting as where the intervention will take place. This will be with a view to build rapport and discuss information for safe preparation, dosing, and psychological integration, consistent with existing guidelines for safety in psychedelic research (20). Assessment of baseline movement tasks will then be administered by the trial physiotherapist during this visit.

Participants will then be scheduled for three psilocybin dosing sessions. Each dose will be allocated in a randomized order and dosing sessions will be separated by at least 1 week. The first six participants will take 5, 10, and 15 mg (block one) and the last six will take 10, 15, and 20 mg (block two). Baseline and follow-up fMRI scans will be scheduled before their first dose, and 1 week following a subsequent dose.

Upon arrival at each dosing session, the mental health professional will review the participant's medications, record baseline vital signs, and complete a urine drug screen and urine pregnancy test (if applicable) to ensure continued eligibility and safety to proceed with psilocybin administration. Baseline verbal fluency will then be assessed. The prescribing physician will then obtain the participant's psilocybin ± placebo capsules (contingent on their randomly allocated dose—see Table 1) from the Austin Health clinical trials pharmacy and the mental health professional will administer these to the participant. The participant will be encouraged to relax, and the mental health professional will provide support and be available to discuss any experiences arising during the dosing session. Vital signs will be rechecked at 0.5, 1, 3, and 5 h post-dosing, and AEs monitored throughout. Verbal fluency will be reassessed at 2 h post-dosing. Movement tasks will be administered and video-recorded by the trial

TABLE 1. Dispensing schedule.

Block 1 (n = 6); max psilocybin dose = 15 mg	
5 mg dose	1 × 5 mg psilocybin capsule + 2 × placebo capsules
10 mg dose	2 × 5 mg psilocybin capsule + 1 × placebo capsules
15 mg dose	3 × 5 mg psilocybin capsule
Block 2 (n = 6); max psilocybin dose = 20 mg	
10 mg dose	2 × 5 mg psilocybin capsule + 2 × placebo capsules
15 mg dose	3 × 5 mg psilocybin capsule + 1 × placebo capsules
20 mg dose	4 × 5 mg psilocybin capsule

physiotherapist at 1.5, 3, and 4.5 h post-dosing. The participant will remain under supervision for at least 5 hours post-dosing and until the acute drug effects have subsided. The participant will then be invited to debrief about their experiences and share any reflections from the dosing session with the mental health professional. They will then complete self-administered questionnaires regarding the subjective intensity of their experience. The participant and physiotherapist will independently guess the dose administered that day. The participant will then be taken home by a support person or taxi.

The mental health professional will telephone the participant one day following each dose for psychological integration and monitoring for AEs. This will provide the opportunity for participants to reflect on and discuss thoughts and feelings arising from the dosing session and to monitor psychological and physical safety (20). One week following the final dose, participants will engage in a further psychological integration session and a qualitative feedback interview which will be audio-recorded and transcribed. Participants will then exit the study. The expected duration for enrollment is 30 days.

Discontinuing or Modifying Allocated Interventions

Participants may withdraw from the study at any point. Investigators can withdraw participants if it is deemed in their best interest, they engage in protocol deviations placing them at risk, exclusion criteria develop, or an AE occurs that affects their safety.

The Principal Investigator has the right to terminate the study at any time and will make the final decision to terminate the study upon completion. If terminated prematurely, investigators will inform participants promptly and all requirements regarding the storage and secure destruction of study documents and investigational products will be observed.

Concomitant Care

Medications will be reviewed at screening and before each dosing session. If a participant is taking a contraindicated medication, a discussion between the investigators, participant, and their prescribing clinician will take place to determine if it is medically reasonable to cease the treatment during the study, and whether the participant wishes to do so.

Contraindicated medications

- Opioids within 12 h of psilocybin dosing.
- Antidepressants.
- Potent enzyme inducers or inhibitors.
- Drugs with a narrow therapeutic index within 12 h of psilocybin dosing.
- Nicotine and caffeine within 2 h before and 6 h following psilocybin dosing.

Follow-Up, Adherence, and Retention

Participants will not be required to pay to take part in the study. Travel costs incurred for attending each study visit will be reimbursed, and food and drink will be provided at each dosing session. To minimize the number of required study visits, outcome measures will be collected during the same visit, where appropriate. For example, resting-state fMRI scans will be performed on dosing days. The participant's psychological integration session and qualitative interview will be offered either in-person or via video call, as per participant preference. This option allows an in-person session to be arranged if participants require or feel they will benefit from this. Alternatively, participants may choose a video call if they prefer, which may promote participant retention by reducing the required number of in-person study visits.

Before face-to-face study visits, participants will receive an email reminder from study staff. This email will include the participant appointment handout before their first dosing session outlining pre- and post-dosing requirements and recommendations. Participants will be encouraged to contact the study team throughout enrollment should questions or concerns arise to ensure timely resolution of any issues. The study team will monitor data in real-time to ensure complete data collection and will document attempts to obtain follow-up data and any protocol deviations.

Outcomes. Details regarding the primary and exploratory outcomes are provided in Table 2 and their time points are outlined in Figure 1.

Primary Outcomes

The primary outcome is to determine the participant's ability to successfully complete each component of (1) the De Morton Mobility Index (DEMMI) (21), and (2) the Functional Movement Exploration measures of motor function, whilst under physiotherapist supervision during the acute effects of psilocybin. The DEMMI and Functional Movement Exploration measures have been selected as primary outcome measures because they incorporate movements that will comprise the physiotherapy intervention used in our proposed study exploring psilocybin-assisted physiotherapy in participants with a diagnosis of FND (21, 22). A combined score from both measures will also be calculated.

Safety will be assessed by checking vital signs regularly during dosing sessions and recording AEs at each visit following screening and at any other times arising during the study. AEs will be classified based on the type, number, severity, relatedness to the study drug, and whether the event constitutes a serious adverse event (SAE) or significant safety issue (SSI).

An AE is defined as any untoward or unfavorable medical occurrence in a participant temporally associated with their study involvement, whether or not directly

TABLE 2. Primary and exploratory outcomes.

	Domain	Measures	Application and clinical relevance
Primary outcomes	Movement tasks	De Morton Mobility Index (DEMMI) (15)	15-Item unidimensional instrument that assesses mobility from bed-bound to independent mobility including balance, gait, seating, and strength. Eleven items are dichotomous (scored 0 or 1), and four items have three response options (scored 0, 1, or 2) based on ability and time to completion. It has high reliability (Pearson's $r = 0.94$), and high convergent and discriminant validity
		Functional Movement Exploration	FND extension module developed by our team, based on the Physio4FMD randomized controlled trial in FND participants (16), to assess additional movements including standing up from a chair, weight shifting, balance, and coordination. Items are dichotomous (scored 0 or 1) based on ability, with additional scores for duration where relevant
	Safety	Vital signs and adverse events form	Safety will be assessed throughout the study via monitoring vital signs and recording treatment-emergent adverse events in the adverse events form. These will be classified based on the type, number, severity, relatedness to the study drug, and whether the event constitutes a serious adverse event or significant safety issue
Exploratory outcomes	Movement tasks	Action Research Arm Test (ARAT) (18)	19-Item instrument assessing upper limb coordination, dexterity, and functioning. It has shown excellent inter-rater and intra-rater reliability and validity in this setting
		Box and Block Test (BBT) (19) —original and modified	Original—movement of blocks from one box to another over 60 s, assessing unilateral gross manual dexterity. It has shown high test-retest validity from normative data in adults without disability
			Modified—places a shield between the participant's vision and their hands, with access to a mirror to view their movements via reflection. This modulates attentional mechanisms of movement—an important feature of motor FND management
		Digit Symbol Substitution Test (DSST) (20)	Symbols are written according to numbers presented via a key within 90 s. This recruits a range of cognitive operations including motor speed, attention, and visuoperceptual functions, and has shown good reliability
		Reaction Time Ruler Drop Test (RTRDT) (21)	Participants catch a ruler dropped by the examiner from a vertical height. It has shown excellent test-retest and interrater reliabilities and has shown to be useful in assessing reaction time
		Video footage	Review of video footage of movement tasks to assess psilocybin's effects on movement quality
	Verbal fluency	Phonemic and semantic fluency	Participants name as many words as possible beginning with the same letter (phonemic) or of the same category (semantic) in the space of 1 min. These tests recruit a range of cognitive functions across attention, executive function, memory, and language (22)
	Brain activity	Resting-state fMRI	Changes in resting-state measures of brain activity 1 week following low-dose psilocybin
	Subjective intensity	5-Dimensional Altered States of Consciousness (5D-ASC)	94-Item scale across five dimensions: oceanic boundlessness, dread of ego dissolution, visionary restructualization, auditory alterations, and vigilance reduction (23). Responses are rated on a visual analog scale, from "No, not more than usually" to "Yes, much more than usually"
		Ego-Dissolution Inventory (EDI)	8-Item focused assessment of the experience of ego-dissolution (24). Each item is rated on a visual analog scale from "No, not more than usually," to "Yes, entirely or completely." It has shown discriminant and convergent validity and excellent internal consistency
	Qualitative experiences	Qualitative interview	Qualitative interview exploring subjective experiences of psilocybin and completing movement tasks and other assessments during the acute drug effects

Abbreviations: 5D-ASC, 5-Dimensional Altered States of Consciousness; ARAT, Action Research Arm Test; BBT, Box and Block Test; DEMMI, De Morton Mobility Index; DSST, Digit Symbol Substitution Test; ECG, electrocardiogram; EDI, Ego-Dissolution Inventory; fMRI, functional magnetic resonance imaging; RTRDT, Reaction Time Ruler Drop Test.

FIGURE 1. Study schedule. [a]Movement tasks: DEMMI; Functional Movement Exploration; ARAT; BBT—Original and Modified; DSST; RTRDT; Video footage. *Serial fMRI scans will either occur during visits 3 and 5, or visits 3 and 7. 5D-ASC, 5-Dimensional Altered States of Consciousness; ARAT, Action Research Arm Test; BBT, Box and Block Test; DEMMI, De Morton Mobility Index; DSST, Digit Symbol Substitution Test; ECG, Electrocardiogram; EDI, Ego-Dissolution Inventory; fMRI, Functional magnetic resonance imaging; H, hour; RTRDT, Reaction Time Ruler Drop Test.

	STUDY PERIOD																							
	Screening & Enrolment	Preparation Visit	Post-allocation																					Close-out
TIMEPOINT	Visit 1	Visit 2	Visit 3 / Dose 1						Visit 4	Visit 5 / Dose 2						Visit 6	Visit 7 / Dose 3						Visit 8	Visit 9
			Pre-dose	Dose	0.5 H 1 H 3 H	1.5 H 3 H 4.5 H	2 H	5 H		Pre-dose	Dose	0.5 H 1 H 3 H	1.5 H 3 H 4.5 H	2 H	5 H		Pre-dose	Dose	0.5 H 1 H 3 H	1.5 H 3 H 4.5 H	2 H	5 H		
ENROLMENT																								
Informed consent	X																							
Assign trial code	X																							
Eligibility criteria	X																							
INTERVENTIONS																								
Preparation session		X																						
Randomization		X																						
Dosing				X							X							X						
Post-dose phone-call									X							X							X	
ASSESSMENTS																								
Demographics	X																							
Medical & psychiatric history	X																							
Physical exam	X																							
Urine pregnancy			X							X							X							
Urine drug screen			X							X							X							
Concomitant medications	X		X							X							X							
12-lead ECG	X																							
Vital signs	X		X		X			X		X		X			X		X		X			X		
Adverse events			X		X			X	X	X		X			X	X	X		X			X		
Movement tasks[a]		X				X							X							X				
Verbal fluency			X				X			X				X			X				X			
5D-ASC								X							X							X		
EDI								X							X							X		
Blinding assessment								X							X							X		
Resting-state fMRI			X							X*							X*							
Integration & qualitative interview																								X

caused by their participation in the study (23). An unexpected AE is one that is not listed in the Investigator's Brochure supplied by the Usona Institute, the supplier of the investigational product, or is more specific or more severe than a listed event. An SAE is defined as any untoward medical occurrence that results in death, is life-threatening, requires prolonged hospitalization, results in significant disability, or requires intervention to prevent permanent impairment or damage. An SSI refers to safety issues that could adversely affect participant safety or materially impact the continued ethical acceptability or conduct of the trial.

Exploratory Outcomes

This study provides a unique opportunity to assess the broader impact of psilocybin on motor function. Therefore, participants' performance in the following motor tasks will also be assessed: the Action Research Arm Test (ARAT) (24), Box and Block Test (BBT, original and modified versions) (25), Digit Symbol Substitution Test (DSST) (26), Reaction Time Ruler Drop Test (RTRDT) (27), and video footage to assess movement quality. Additional exploratory analyses will include verbal fluency (28), resting-state derived measures of brain activity, subjective intensity via the 5-Dimensional Altered States of Consciousness (5D-ASC) (29) and Ego-Dissolution Inventory (EDI) (30), and qualitative experiences of taking low-to-moderate doses of psilocybin and performing movement and cognitive tasks during the acute drug effects.

Sample Size. The sample size is not based on statistical power and a sample size of 12 is considered likely to be sufficient to determine movement task performance after each of the three low-dose psilocybin sessions. Further, this sample size enables an equal number of participants for each possible dosing sequence of a 3-dose 3-period cross-over Williams design (18) within each block of six.

Participants who are withdrawn before psilocybin dosing will be replaced. If withdrawn before completing sequential dosing sessions, a replacement will be considered at the discretion of the investigators.

DATA COLLECTION, MANAGEMENT, AND ANALYSIS

Data Collection Methods

Study physicians will conduct the full screening assessments, the resting-state fMRI scans will be conducted by qualified radiographers, and the trial physiotherapists will

administer the movement tasks. Self-administered questionnaires on subjective intensity will be completed by participants and the mental health professionals will confirm their completion. The mental health professionals will conduct the preparation session, dosing sessions, post-dose phone calls, psychological integration session and qualitative interview, and remaining scheduled measures during these visits. At all times, the study team member administering the assessment has full responsibility for the accuracy, completeness, and timeliness of all data captured.

Data Management

The majority of study data will be collected and managed using REDCap—a secure, browser-based application for managing online surveys and databases—hosted at the University of Melbourne (19). Each participant will have a study file that contains any paper-based Case Report Forms (CRFs) which will also be scanned. Scanned paper-based CRFs, physiotherapy task video footage, recordings and transcripts of qualitative interviews, and fMRI images will be uploaded and stored in secure, password-protected servers hosted by the University of Melbourne and available only to permitted trial staff. The remaining relevant data will be entered directly into REDCap. Results from urine pregnancy and drug screening will be recorded, and urine samples disposed of in biological hazard waste bins. No other biological specimens will be collected for this study.

Confidentiality will be maintained by assigning participants a unique code to record any data collected. Identifiable data from paper-based files will be de-identified before being entered into REDCap according to their participant code, and paper-based CRFs will be stored in locked filing cabinets throughout the study. Videos of physiotherapy task performance will be de-identified using facial blurring and qualitative interview audio recordings will be transcribed in a de-identified manner.

On study completion, scanned and electronic source documents will be archived on password-protected servers, and paper-based CRFs kept in locked cabinets. All CRFs will be retained for 15 years and then destroyed by secure shredding and deletion from protected servers according to the University of Melbourne records management policy.

Data management will be carried out to a standard of security and confidentiality consistent with Good Clinical Practice (31). Data will be handled only by the research team and held at the Department of Psychiatry, University of Melbourne, Austin Health.

Statistical Methods

A detailed statistical analysis plan will be finalized before locking of the study database. The analysis will include all randomized participants, irrespective of completing their sequence, and all their available non-missing data. Reasons for early stopping of study participation will be recorded.

No specified interim analysis is planned. The study initially proposed 12 participants to be recruited in two blocks of six, each receiving 5, 10, and 15 mg in a randomized order. However, after three participants, they each successfully completed the movement tasks at 15 mg. Therefore, the dose range has been expanded to increase the likelihood that a suitable maximum dose at which participants can safely complete the movement tasks will be investigated. The protocol was amended, maintaining the same dose range for the first six participants (block one), and changing the dose range to 10, 15, and 20 mg for the last six participants (block two). In doing so, this retains each possible dose sequence of the Williams design for the six participants in each block.

MONITORING

The trial management group (TMG) will comprise all authors listed and provide overall supervision of the trial including protocol development, oversight of trial progress, and publication and dissemination of trial results.

A data monitoring committee is not needed for this study because of the healthy sample population, limited known risks, short study duration, and Phase 1 objectives centered on feasibility and safety. Regulatory authorities, independent of the investigators and sponsor, may audit the study site during or after the study.

ADVERSE EVENT REPORTING AND HARMS

Comprehensive study procedures, screening, and eligibility criteria have been developed based on Phase 1 and 2 clinical trials on psychedelics to exclude participants with pre-existing conditions and concomitant medications that may exacerbate their risk of harm (32).

During psilocybin dosing, the participant will be encouraged to report any psychological distress and will be counseled by the mental health professional as needed. If severe distress occurs, benzodiazepines and antipsychotics will be available for administration from the pharmacy. A Medical Emergency Team notification will be initiated if these measures are ineffective, heart rate exceeds 130 beats per minute, systolic blood pressure exceeds 180 mmHg, oxygen saturation falls below 90%, there is a reduced level of consciousness, or symptoms arise that warrant urgent medical assessment. The site physicians will be available via mobile phone throughout enrollment, including for any problems when participants are not on-site.

AEs will be assessed at each data point following screening and throughout enrollment. All AEs will be monitored by the study physicians until resolution or, if unresolved or chronic, a cause is identified, and further follow-up is arranged as warranted. All SAEs and SSIs will be reported as per Austin Health's safety reporting policy. SAEs will also be reported to the Usona Institute

within 5 days of the investigator's awareness of their occurrence.

ETHICS

Ethics approval for this protocol has been awarded by the Austin Health Human Research Ethics Committee (AH HREC; EC00204). Significant protocol amendments will be reviewed by the TMG and submitted to the AH HREC. Active participants affected by amendments will be notified and provided with an updated PICF to review and reconsent if required.

DISSEMINATION PLANS

Results will be submitted to peer-reviewed journals for publication and presented at psychiatry, neurology, physiotherapy, or other relevant conferences.

De-identified safety data will be shared with the Usona Institute. Access to the full final trial dataset will only be available to investigators and any other relevant regulatory bodies. Study intellectual property arising from this study will be owned by the University of Melbourne.

CLINICAL IMPLICATIONS

Classic psychedelics hold significant promise as a component of the management of neuropsychiatric disorders such as depression, anxiety, and substance use disorder (33). More recently, there has been growing interest in the therapeutic potential of psychedelics for conditions associated with motor dysfunction such as FND (13, 14, 34, 35), stroke (36), and acquired brain injury (15) due to their effects upon neuroplasticity and hierarchical brain dynamics. This study will inform the conduct of future trials involving clinical populations with motor dysfunction by providing crucial information regarding the feasibility of movement tasks during the acute effects of psilocybin. Furthermore, the findings from this study will guide the doses used in a follow-up trial exploring the feasibility and signals of efficacy of psilocybin-assisted physiotherapy in FND.

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RK is on the advisory board of Psychae Institute, a non-profit psychedelic research institute.

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JR has undertaken paid advisory boards for Clerkenwell Health (Past), Beckley PsyTech (Past), Delica Therapeutics (Past), and paid articles for Janssen. JR has received assistance for attendance at conferences from Compass Pathways (past) and Janssen. JR has been awarded grant funding (received and managed by King's College London) from Compass Pathways, Beckley PsyTech, Multidisciplinary Association for Psychedelic Studies, National Institute for Health Research, Wellcome Trust, Biomedical Research Centre at the South London and Maudsley NHS Foundation Trust.

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