Psilocybin-Assisted Physiotherapy for Refractory Motor Functional Neurological Disorder: Protocol for a Randomised Dose-Comparison Pilot Study

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Abstract

Background: Motor functional neurological disorder (FND) is a common illness associated with significant functional impairment. There are no effective pharmacotherapies, and despite the early promise of physiotherapy studies, many suffer disabling symptoms in the long term. There is a theoretical rationale for combining psychedelics with physiotherapy; however, the potential benefit of this approach and optimal treatment model remains unexplored. Here, we present the protocol for the first study investigating the tolerability, feasibility, and potential efficacy of two distinct treatment regimens of psilocybin-assisted physiotherapy for refractory motor FND: a moderate dose that incorporates movement tasks during the acute drug effects versus a standard dose alone.

Methods: Twenty-four participants with refractory motor FND will be randomised in a 1:1 ratio to either (1) psilocybin 15mg, with movement tasks conducted during the acute drug effects; or (2) psilocybin 25mg alone. All participants will receive two sessions of FND-specific physiotherapy pre-dosing, six sessions of physiotherapy post-dosing, and undergo follow-up visits one week and four weeks following their final physiotherapy session. A battery of outcome measures will be completed as scheduled, assessing tolerability, feasibility, motor FND symptom severity, psychiatric and physical symptoms, quality of life, treatment expectations, intensity of the acute drug effects, personality, motor function, force-matching performance, resting-state and task-based brain imaging, and subjective experiences of the study treatment.

Discussion: These findings will assist the design of an adequately powered randomised controlled trial in this cohort. The findings may also inform the feasibility of psychedelic treatment in related functional and neuropsychiatric disorders.

Keywords: psychiatry, neuropsychiatry, psilocybin, conversion disorder, physiotherapy

Summations

Motor functional neurological disorder (FND) poses a substantial clinical burden and has no effective pharmacotherapies. Building upon the encouraging treatment potential of psychedelics in neuropsychiatric disorders, this protocol outlines the first study investigating psilocybin-assisted physiotherapy for refractory motor FND.
The study will compare a moderate dose of psilocybin that incorporates movement tasks during the acute drug effects versus a conventional, standard-dose approach. Both treatment groups will receive a course of FND-specific physiotherapy pre- and post-dosing, accompanied by psychiatric support. A battery of measures will be assessed at baseline and up to four weeks post-treatment.
The findings will inform an adequately powered randomised controlled trial in this cohort and provide insights into the feasibility of psychedelic treatment in other functional and neuropsychiatric disorders.

Considerations

- Novel therapies for motor functional neurological disorder (FND) are required because existing treatments are insufficient. Supported by a theoretical basis, psychedelic-assisted physiotherapy in motor FND warrants further investigation.
- Given the nascency of this area, this pilot study will prioritise safety and feasibility, with any observed benefits limited by the study's open-label design and small sample size. As the field evolves, randomised controlled studies with adequate power and long-term outcomes will contribute to understanding the translational potential of this treatment.
- Testing psychedelics with physiotherapy will also provide novel insights into the potential for psychedelic-assisted therapy to target broader physiological and sensorimotor mechanisms implicated in other functional and neuropsychiatric disorders.

Introduction

Background and rationale

Functional neurological disorder (FND) presents with neurological symptoms that are considered incompatible with other neurological conditions (Hallett et al., 2022). Motor FND refers to the presence of functional motor symptoms, such as weakness, tremor, or abnormal gait. It is a common illness, with estimates of incidence of functional motor symptoms at approximately 4-5/100'000 population per year (Binzer et al., 1997; Stone et al., 2010). These are almost certainly underestimates, as many remain undiagnosed for years (Carson et al., 2000), and presentations have likely increased since the coronavirus disease 2019 pandemic (Hull et al., 2021). Many individuals continue to experience disabling symptoms in the long term, as demonstrated by a systematic review which found that 39% of individuals with functional motor symptoms remained the same or worse at follow-up (Gelauff et al., 2014).

Available treatment options in motor FND are limited. Pharmacotherapy is not indicated in its direct treatment (Aybek and Perez, 2022), and trials of psychotherapy remain inconclusive (Dallocchio et al., 2016; Hinson et al., 2006; Pompoliti et al., 2014). Preliminary evidence from pilot studies demonstrated symptom improvement with psychologically-informed, FND-specific physiotherapy (Czarnecki et al., 2012; Jordbru et al., 2014; Nielsen et al., 2017). However, a recently published phase 3 randomised controlled trial (RCT) of FND-specific physiotherapy for motor FND demonstrated mixed findings (Nielsen et al., 2024). Although a significant difference in the primary outcome measure was not observed, the physical functioning domain of the participant-reported 36-Item Short Form Survey (SF-36) indicated that 59% of the specialist physiotherapy group rated their symptoms as improved compared to 39% of the standard physiotherapy group. This suggests that while a proportion of individuals may benefit from physiotherapy alone, alternative approaches are necessary for those who are refractory to treatment.

While pathophysiological models of motor FND remain an evolving field, several proposed mechanisms have been consolidated into a Bayesian approach based upon the dynamic relationship between sensory input and neural representations of this information (Edwards et al., 2012; Friston, 2010). This model posits that in motor FND, top-down somatic self-representations, or priors, may become overly precise through factors such as abnormal

emotion processing, self-directed attention, and interoceptive dysfunction. In the context of motor control, this generates a disconnect between conscious experience and sensorimotor function, resulting in motor symptoms. Furthermore, these symptoms may become entrenched when interpreted as illness, thus reinforcing aberrant self-representations.

Based on this model, there is emerging interest in the application of classic psychedelics, such as psilocybin, for motor FND (Bryson et al., 2017). Psychedelics exert multifaceted effects upon the brain, including synaptogenesis and dendritic arborisation (Ly et al., 2018); altered connectivity across macroscopic cortical networks (Madsen et al., 2021); and both acute changes in perception and conscious state and longer-term changes in beliefs and behaviours (Studerus et al., 2011). A synthesis of these effects suggests that psychedelics can promote neuroplasticity and relax overly precise priors, while increasing the brain's sensitivity to sensory input (Carhart-Harris and Friston, 2019). Indeed, these changes are hypothesised to underlie their therapeutic effects in several neuropsychiatric disorders, including major depressive disorder (MDD), illness-related anxiety, obsessive compulsive disorder, and substance use disorder (Andersen et al., 2021).

The impact of psychedelics upon brain function suggests a promising role for psychedelic-assisted physiotherapy in motor FND. By relaxing somatic priors, sensorimotor processes may become freed from maladaptive top-down influences and more receptive to sensory input, such as proprioceptive feedback during movement retraining, thus enhancing the therapeutic potential of physiotherapy (Bryson et al., 2017). Although an encouraging exploration of psychedelics in FND was underway before the prohibition of these agents, the studies were limited by poor quality, and psychedelic treatment by itself was not universally effective (Butler et al., 2020). This may suggest a potential role for augmenting psychedelics with modern physiotherapy approaches.

Combining psychedelic treatment with physiotherapy for motor FND raises questions regarding the most appropriate treatment regimen. In previous studies of psychedelics in FND, a 'psycholytic' regimen was used in most cases, which involves low-to-moderate doses (typically 3 to 15mg of psilocybin) combined with psychotherapy during the dosing session (Passie et al., 2022). An analogous approach could be used in psychedelic-assisted physiotherapy, whereby the participant engages in movement tasks during the drug effects to take advantage of acute changes in brain dynamics and neuroplasticity following psychedelic administration (Berkovitch et al., 2025; Carhart-Harris and Friston, 2019; Weiss et al., 2025).

We recently completed a dose-finding pilot study of movement tasks undertaken during the acute effects of low-to-moderate psilocybin doses in healthy participants – the first study of its kind to assess the impact of psilocybin on motor function (Bhagavan et al., 2024) – which demonstrated the feasibility of engaging in movement tasks during the acute effects of psilocybin up to 15mg. However, whether it is also feasible to administer physiotherapy during the acute psychedelic effects in motor FND remains uncertain.

In contrast, modern studies have predominantly adopted a 'psychedelic'-assisted therapy (PAT) framework involving higher doses (typically 25mg of psilocybin) and more profound psychoactive effects (Barber and Aaronson, 2022; Passie et al., 2022). In studies of depression and anxiety, psychotherapy is also provided in the weeks following dosing to leverage a persistent 'window' of neuroplasticity, the duration of which may correlate with the intensity of the psychedelic experience (Lepow et al., 2021; Nardou et al., 2023; Watts and Luoma, 2020). Given the potential practical challenges of administering physiotherapy during acute psychedelic effects, this presents an alternative treatment model in motor FND: a standard 'psychedelic' dose alone, followed by physiotherapy in the subsequent weeks. However, whether this sustained window of neuroplasticity fosters movement retraining is also unknown. Ultimately, the optimal psilocybin dose and application of adjunctive physiotherapy for motor FND are unclear and in need of further exploration.

This protocol, therefore, details an individually randomised parallel-group pilot study assessing the tolerability, feasibility, and potential efficacy of psilocybin-assisted physiotherapy in participants with refractory motor FND. This study will compare two distinct psilocybin-assisted treatment paradigms: 1) a moderate 'psycholytic' dose (15mg) that incorporates movement tasks during the acute drug effects, and 2) a standard 'psychedelic' dose (25mg), integrated within a course of FND-specific physiotherapy for both treatment groups.

Objectives

Hypotheses

1. Both standard- and moderate-dose psilocybin will be well-tolerated in participants with refractory motor FND.

2. It is feasible for participants with refractory motor FND to perform a series of movement tasks during the acute effects of moderate-dose psilocybin.

3. Psilocybin-assisted physiotherapy can improve motor symptoms and disability in participants with refractory motor FND compared to the participants' baseline assessment.

4. There is a difference in tolerability and symptom improvement between moderate- and standard-dose psilocybin-assisted physiotherapy in participants with refractory motor FND.

Primary Aims

- To assess the tolerability of psilocybin-assisted physiotherapy in participants with refractory motor FND and compare between treatment groups, as measured by vital signs and adverse event (AE) reporting.

- To assess the feasibility of completing movement tasks during the acute effects of moderate-dose psilocybin in participants with refractory motor FND.

- To assess the effect of psilocybin-assisted physiotherapy in participants with refractory motor FND on within- and between-group changes in:

    - Clinician-rated changes in motor FND symptoms, using the Simplified Functional Movement Disorder Rating Scale (S-FMDRS).

    - Participant-reported changes in motor FND severity and improvement, using the Patient Global Impression of Severity (PGI-S) and Improvement (PGI-I).

Secondary Aims

- To assess the effect of psilocybin-assisted physiotherapy in participants with refractory motor FND on within- and between-group changes in:

    - Motor FND symptom severity and improvement, using the Clinical Global Impression of Severity (CGI-S) and Improvement (CGI-I).

    - Motor FND symptom severity, using the S-FMDRS, graded through video assessment by an independent observer.

    - Depressive symptoms, using the Patient Health Questionnaire-9 (PHQ-9).
    - Anxiety symptoms, using the Generalised Anxiety Disorder-7 (GAD-7).
    - Somatic symptoms, using the Patient Health Questionnaire-15 (PHQ-15).
    - Health-related quality of life, using the SF-36.
- To assess the impact of pre-treatment expectations on outcomes in participants with refractory motor FND and compare between groups, using the Stanford Expectations of Treatments Scale (SETS).
- To assess the impact of psilocybin on altered conscious states and ego-dissolution in participants with refractory motor FND and compare between groups, using the 5-Dimensional Altered States of Consciousness (5D-ASC) and Ego-Dissolution Inventory (EDI).
- To determine the utility of these outcome measures for an adequately powered RCT of psilocybin-assisted physiotherapy in motor FND.

Exploratory Aims

- To explore any acute benefits of performing movement tasks during the acute effects of moderate-dose psilocybin in participants with refractory motor FND.
- To explore the impact of psilocybin-assisted physiotherapy in participants with refractory motor FND on within- and between-group changes in:
    - Motor function, using the De Morton Mobility Index (DEMMI), Functional Movement Exploration (FME), Action Research Arm Test (ARAT), Box and Block Test (BBT) – original and modified versions, and video footage.
    - Sensorimotor function, using the force-matching task.
    - Resting-state and task-based measures of functional brain activity, using functional magnetic resonance imaging (fMRI).
    - Personality traits, using the Big Five Inventory-2 (BFI-2).

- Experiences of the study treatment, using a study treatment questionnaire.
- Qualitative effects through face-to-face interviews.

Trial Design

This is a two-arm, individually randomised parallel-group study in 24 participants with refractory motor FND who will be randomly assigned, in a 1:1 ratio, to one of two treatment groups:

- Psilocybin 15mg with movement tasks during the acute drug effects (moderate-dose arm), or
- Psilocybin 25mg without movement tasks during dosing (standard-dose arm).

All participants will receive specialist, FND-specific physiotherapy including two sessions pre- and six sessions post-dosing. Physiotherapy follow-up visits will occur one week and four weeks after completing their treatment. Psychiatric oversight will be provided, including a preparation session before their psilocybin dose, supervision during the dosing session, and follow-up sessions one week and four weeks after completing their physiotherapy treatment. An overview of this design is outlined in Figure 1. Statisticians and an independent assessor of symptom severity will remain blinded to treatment allocation.

Sample Size

A sample size of 12 has been chosen because, assuming an 80% chance of a participant successfully completing physiotherapy during acute dosing, this provides over a 90% chance of enrolling at least one participant who is unable to complete the intervention. We consider a completion rate of at least 80% to be tolerable, and so a sample size of 12 is likely sufficient to screen for a poorly tolerated intervention. Participants who are withdrawn before psilocybin dosing will be replaced.

Methods: Participants, Interventions, and Outcomes

Study Setting

All study visits will occur at Austin Health, a public tertiary teaching hospital in Melbourne, Australia. fMRI scans will occur at the Melbourne Brain Centre, a research centre at the

hospital. The dosing session will occur within a dedicated room providing a comfortable, monitored, clinical setting with access to temperature control, blankets, headphones, and music. Physiotherapy treatment sessions and follow-up visits will occur within the same room. Psychiatry follow-up visits and remaining scheduled outcome measures will occur within the study psychiatrist's office.

Eligibility Criteria

Study Team Eligibility

The trial physiotherapists will be registered physiotherapists trained in the Physio4FMD specialist physiotherapy intervention (Nielsen and Holt, 2024) and movement tasks administered. The psychiatrists will be registered psychiatrists with experience working with psychedelic medicines.

Recruitment

The treating psychiatrist at Austin Health's Functional Neurology Clinic will discuss the study with potentially eligible participants. The study team will also distribute a referral flyer to clinicians in Australia working with FND. Interested individuals will then be referred to the study by their treating practitioner and provided with 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 (AHHREC).

Consent and Screening

Referred participants will be invited to a screening visit with the study psychiatrist, who will undertake informed consent. Information about the study procedures, potential benefits, and risks will be provided in a clear, balanced, and neutral manner. Informed consent will be obtained for the use of de-identified data for both this study and secondary uses, including informing future related projects and safety data to be shared with the Usona Institute.

Those willing to proceed with the study will provide a dated signature on the PICF. The study psychiatrist will then conduct a medical and psychiatric history, physical examination, vital signs, and electrocardiogram to assess eligibility.

Assignment of Interventions

Allocation Sequence

Participants will be randomised in a 1:1 ratio into one of the two treatment groups until 12 participants in each group have been allocated. The randomisation list will be computer-generated by an independent statistician of the University of Melbourne, using random block sizes, and uploaded as a randomisation module into Research Electronic Data Capture (REDCap) (Harris et al., 2009). After the study psychiatrist confirms eligibility, the study coordinator, who is independent of administering interventions, will action the randomisation module, allocating the treatment group.

Blinding

The statisticians and an independent assessor of symptom severity will be blinded to treatment assignments and will not be permitted access to the randomisation module. Videos for independent assessment of symptom severity will be allocated via a random number generator. If there is an emergency requiring knowledge of a participant's allocation, the blind may be broken for that individual participant.

Interventions

Intervention Description

Following enrolment, all participants will undertake a series of baseline measures, including self-reported outcomes, clinician-rated assessments of motor function and FND symptom severity, treatment expectations, a force-matching task, and an fMRI scan.

Eligible participants will undertake a psilocybin preparation session with the study psychiatrist consistent with existing safety guidelines for psychedelic research (Johnson et al., 2008). This will involve building rapport and trust, providing education about psilocybin, intention setting, reviewing relaxation strategies, and advice for preparation, dosing, and integration.

Treatment

Participants will then be scheduled for their study treatment. This will comprise two initial physiotherapy sessions, the psilocybin dosing session, and then six physiotherapy sessions within three weeks post-dosing.

Physiotherapy

The specialist physiotherapy is based on the Physio4FMD manual used in previous studies in motor FND (Nielsen and Holt, 2024). A workbook will be completed by both the participant and the physiotherapist to help guide the intervention.

The initial two physiotherapy sessions pre-dosing will involve:

- Comprehensive assessment.
- Development of a treatment plan.
- Education on FND following a standardised biopsychosocial model.

The remaining six sessions post-dosing will comprise:

- Video analysis of movement.
- Posture and movement retraining – aiming to redirect attention away from the body and promote positive experiences of symptom-free and automatic, normal movement.
- Advice for managing common co-existing difficulties in FND, such as pain, fatigue, and memory difficulties.
- Codeveloping a self-management plan.

Psilocybin Dosing Session

The psilocybin dosing session will take place within three days of the initial physiotherapy sessions. Upon arrival, the study psychiatrist will ensure the participant's continued eligibility and safety by reviewing their medications, measuring vital signs, and conducting a urine drug screen and urine pregnancy test (if applicable). The psychiatrist will then administer the prescribed psilocybin. The participant will be encouraged to relax, with the study psychiatrist available to provide support. Vital signs will be rechecked at 0.5-, 1-, 3-, and 5-hours post-dose, and AEs monitored throughout. For participants randomised to the moderate-dose arm, the physiotherapist will attend at 1.5- and 4.5-hours post-dose to administer a series of movement tasks and any further physiotherapy as tolerated by the participant to explore any

potential treatment benefit of novel experiences of movement during the acute drug effects.

The participant will remain under the supervision of the study psychiatrist or physiotherapist for at least 5 hours post-dose and until the acute drug effects have subsided. The participant will then complete questionnaires regarding the intensity of their experience before being taken home by a support person or taxi. The psychiatrist will telephone the participant the following day to invite any further reflections and monitor safety.

Follow-Up

After the final physiotherapy treatment session, the participant will complete the scheduled outcome measures. Follow-up physiotherapy and psychiatry visits will be scheduled for one week and four weeks post-treatment. Follow-up physiotherapy visits will review any areas of difficulty since completing the treatment, the self-management plan, and the goals. Follow-up psychiatry visits will cover psychological integration post-dosing, AEs, mental health, FND symptoms, and any corresponding changes in functioning. The psychiatrist will also conduct a semi-structured, audio-recorded qualitative interview at the one-week follow-up visit. All scheduled outcome measures will be completed at each of these study visits.

Following study exit, participants will return to the care of their usual treating practitioners, and any relevant handovers will be provided by the study psychiatrist and physiotherapist.

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

Contraindicated Medications

To be enrolled in the study, participants must not be taking:

- Opioids within 12 hours of psilocybin dosing.
- Antidepressants within five half-lives of their cessation before psilocybin dosing.
- Potent enzyme inducers or inhibitors.
- Drugs with a narrow therapeutic index within 12 hours of psilocybin dosing.
- Nicotine and caffeine within 2 hours before and 6 hours following psilocybin dosing.

Concomitant Care

Medications will be reviewed at screening and before the dosing session. If a contraindicated medication is identified at the screening visit, a discussion between the investigators, participant, and their treating practitioner will take place to determine if it is appropriate to cease the medication before the dosing session. This will include a plan for reviewing and, if required, restarting the medication post-psilocybin dosing.

For contraindicated antidepressant medications, the recommendation will be to wean gradually to mitigate discontinuation effects, cease at least five half-lives before the scheduled dosing session to avoid interactions, and restart (if required) after completing the physiotherapy treatment to avoid initial medication titration adverse effects during the treatment course.

Participants will be required to suspend external physiotherapy for their motor FND throughout study enrolment until their study exit.

Outcomes

Time points for all outcome measures are outlined in Figure 2, and their details are provided in Table 2.

Primary Outcomes

Tolerability will be assessed by checking vital signs regularly during the dosing sessions and recording AEs arising at any time 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).

The feasibility of participating in physiotherapy during the acute effects of psilocybin 15mg will be assessed by measuring the successful completion of a series of movement tasks. These will include the S-FMDRS (Nielsen et al., 2017), DEMMI (de Morton et al., 2008), FME, ARAT (Yozbatiran et al., 2008), and BBT (Mathiowetz et al., 1985) (original and modified versions) at 1.5- and 4.5-hours post-dosing.

The S-FMDRS assesses seven body regions and two functional movements (gait and speech) commonly affected by motor FND. Severity and duration are each rated from 0 to 3 for each of the nine items (higher scores indicate greater impairment), with items summed to provide a total score between 0 to 54. The scale may be completed by neurologists and physiotherapists, has high inter-rater reliability for the total score, and is sensitive to treatment-related changes. The assessment of the S-FMDRS by the study physiotherapist will comprise the primary outcome for assessing clinician-rated symptom severity. The S-FMDRS will be completed at baseline, 1.5- and 4.5-hours post-dosing for participants receiving psilocybin 15mg, completion of the physiotherapy treatment, and the one-week and four-week follow-up visits.

The PGI-S and PGI-I are self-rated, single-item scales to capture static and dynamic aspects of disease severity and change, respectively (Food and Drug Administration, 2018). The PGI-S is rated from 1 to 4 (higher scores indicate greater impairment), and the PGI-I is rated from 1 to 7 (lower scores indicate greater improvement and higher scores indicate worsening). These measures have shown satisfactory feasibility, validity, and sensitivity to treatment-related changes in studies on neuropsychiatric symptoms (Mohebbi et al., 2018; Remigio-Baker et al., 2024; Snyder et al., 2021). The PGI-S will be completed at baseline, and both scales completed on the morning of each day of the physiotherapy treatment and dosing session, following completion of the physiotherapy treatment, and at the one-week and four-week follow-up visits.

Secondary Outcomes

An independent assessment of each S-FMDRS measure, as captured using video footage, will be completed by the study neurologist who will be blinded to treatment allocation. This will comprise a secondary outcome to help assess the interrater reliability and utility of this measure for this and subsequent studies. To complement the participant-reported PGI-I and PGI-S scales, the clinician-rated CGI-I and CGI-S (Busner and Targum, 2007) will be

administered to objectively assess disease severity and change, respectively, post-treatment.

Depressive symptoms will be measured by the PHQ-9 (Kroenke et al., 2001), anxiety symptoms by the GAD-7 (Spitzer et al., 2006), somatic symptoms by the PHQ-15 (Kroenke et al., 2002), and health-related quality of life by the SF-36 (Ware et al., 1993). Treatment expectations will be assessed pre-dosing by the SETS (Younger et al., 2012), and intensity of the acute drug effects assessed post-dosing by the 5D-ASC (de Deus Pontual et al., 2023) and EDI (Nour et al., 2016).

Exploratory Outcomes

Video footage and individual scores for each of the DEMMI, FME, ARAT, and BBT (original and modified versions) will be assessed to explore the impact of psilocybin-assisted physiotherapy on several domains of motor function. Resting-state fMRI will be used to investigate alterations in large-scale brain networks and potential treatment mechanisms (Berkovitch et al., 2025; Daws et al., 2022). This will be complemented by a Bayesian belief updating fMRI task, which will assess changes in optimism bias and any underlying neuroimaging correlates (Korn et al., 2014; Marks and Baines, 2017; Sharot et al., 2011). This task has revealed differences between healthy subjects and patients with MDD and is of relevance given the hypothesised role of aberrant predictive processing in motor FND. Given previous findings of reduced sensory attenuation in motor FND, which may arise through related mechanisms, treatment-induced normalisation of sensorimotor performance using a force-matching task will also be assessed (Pareés et al., 2014). In line with previous studies demonstrating changes in personality following psychedelics, such as increased 'openness', and the relevance of these changes to therapeutic effects, personality traits will be measured via the BFI-2 (Soto and John, 2017). Subjective experiences will also be assessed by surveying participant perspectives on the intervention and conducting a qualitative interview following the treatment.

Data Collection, Management, and Analysis

Data Collection and Assessment

The study physiotherapist will provide the physiotherapy treatment and physiotherapy follow-up visits, administer movement tasks, and assess symptom severity. The study neurologist will conduct independent assessments of the S-FMDRS, as captured using video

footage. Qualified radiographers will conduct fMRI scans. The study psychiatrists will conduct the screening visit, preparation session, dosing session, post-dosing phone call, psychiatry follow-up visits, qualitative interview, and remaining scheduled measures at 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 (Harris et al., 2009) – a secure, browser-based application for managing online surveys and databases – hosted at the University of Melbourne. Scanned paper-based Case Report Forms (CRFs), 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. Results from urine tests will be recorded, and urine samples will be disposed of in biological hazard waste bins.

Confidentiality will be maintained by assigning participants a unique code to record any data collected, and paper-based CRFs will be stored in locked filing cabinets. 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 (International Council for Harmonisation, 2015). Data will be handled only by the research team and held at the Department of Psychiatry, University of Melbourne, Austin Health.

Adherence and Retention

Before their study treatment, participants will receive a detailed appointment handout, which also reiterates pre- and post-dosing requirements and recommendations. Travel costs incurred for attending each study visit will be reimbursed, up to $50 per visit, and food and drink will

be provided at the dosing session. No additional financial inducements will be provided. The psychiatry follow-up visits and qualitative interview will be offered either in-person or via video call, as per participant preference, to promote retention by reducing the required number of in-person visits. The study team will monitor data in real time to ensure completeness and will document attempts to obtain follow-up data and any protocol deviations.

To assess the fidelity of the physiotherapy treatment (the extent to which the treatment followed the intervention protocol):

1. The study physiotherapist will complete a checklist for each participant based on the template for intervention description and replication (TIDieR) checklist description (Hoffmann et al., 2014).

2. The content, length, and number of physiotherapy sessions by participant report will be monitored with a structured telephone survey following completion of the physiotherapy treatment.

3. A random sample of completed physiotherapy workbooks will be assessed by an independent physiotherapist against predetermined criteria.

Statistical Methods

Prior to the study database being locked, a comprehensive statistical analysis plan will be finalised. The analysis will encompass all participants who were randomised, regardless of whether they completed their full study enrolment. All available data from these participants will be included. The reasons for any participant's early withdrawal from the study will be documented.

An interim analysis using unblinded data will be performed after 50% (n = 12) of the target sample size has completed their study enrolment. This analysis will consist of summary statistics of tolerability and efficacy outcomes by treatment groups. These interim results will support planning for a follow-up RCT in motor FND participants. As such, the goal of the interim analysis is not related to this pilot study, and no sample size adjustment will be made as a result. Blinding will be maintained as described earlier.

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 limited known risks, short study duration, and Phase 1 objectives centred on feasibility and safety.

Adverse Event Reporting and Harms

Common acute AEs reported following psilocybin administration included headache, nausea, anxiety, dizziness, and blood pressure elevations, and were mostly mild-to-moderate in severity and transient (Breeksema et al., 2022; Johnson et al., 2012; Yerubandi et al., 2024). When incorporating long-term outcomes, contemporary clinical studies revealed no reports of death by suicide, persisting psychotic disorder, or hallucinogen persistent perceptual disorder (Hinkle et al., 2024). However, concerns for incomplete reporting and identification have been raised, and further research is required into the preferred management of AEs and long-term safety (Hinkle et al., 2024; Simonsson et al., 2024). Therefore, safeguards will be implemented throughout this study to comprehensively monitor, report, and respond to safety concerns.

During psilocybin dosing, the study psychiatrist will be available to respond to any psychological distress. If severe, benzodiazepines and antipsychotics will be available for administration. A Medical Emergency Team notification will be initiated if these measures are ineffective, heart rate exceeds 130 beats per minute, systolic blood pressure exceeds 180mmHg, 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 enrolment.

All AEs will be monitored by the study physicians until resolution or, if unresolved or chronic, further follow-up is arranged as warranted. All SAEs and SSIs will be reported as per Austin Health's safety reporting policy.

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 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.

Discussion

Conceptual frameworks for FND have evolved from exclusively psychological to biopsychosocial models, supported by evidence implicating physiological and sensorimotor processes (Drane et al., 2021; Pareés et al., 2014; Perez et al., 2021; Raynor and Baslet, 2021; Ricciardi et al., 2016; Sojka et al., 2021). This shift in understanding is reflected in expert consensus recommendations of physiotherapy as part of multidisciplinary treatment of motor FND (Nielsen et al., 2015). However, the limited efficacy of existing interventions and the impact of the disorder emphasise the need for new treatments that target other aspects of FND pathophysiology. Research into psychedelics has demonstrated encouraging potential in several neuropsychiatric disorders, and this pilot study was conceptualised based on these advances in the pathophysiological understanding of motor FND and hypothesised treatment mechanisms of psychedelics.

Given the uncertainties regarding the therapeutic mechanisms of psychedelics and the most appropriate treatment model, this study will therefore compare additional active physiotherapy during the acute effects of moderate-dose psilocybin versus a more conventional, standard-dose PAT approach.

This study will enrol participants with treatment-refractory motor FND. This provides an opportunity to evaluate the potential added benefit of psychedelic treatment in those who have already received the current gold standard physiotherapy approach. The comprehensive screening and eligibility criteria in this trial will help exclude participants at greater risk of harm following psychedelic treatment (MacCallum et al., 2022). The regular safety reporting, psychiatric support, and availability of study physicians throughout the study will enable prompt action to address any concerns arising and provide a greater understanding of the tolerability of this intervention.

The wide range of validated outcome measures spanning motor function, psychiatric and physical symptoms, and quality of life domains will enable assessment of benefits beyond core symptom relief and the potential for this treatment to address shared biopsychosocial factors across these areas (Butler et al., 2021). Exploratory outcomes examining underlying mechanisms, such as fMRI and the force-matching task, may deepen these insights and identify potential biomarkers and mediators of treatment response. The inclusion of both clinician-rated and self-rated outcomes, including qualitative interviews, will facilitate balanced inquiries into objective and subjective changes. The utility of these measures will also be assessed for their consideration in future, adequately powered studies.

These findings may inform psychedelic-assisted therapy studies in other FND subtypes, such as functional seizures, and related neuropsychiatric disorders with shared pathophysiological mechanisms, such as chronic pain, fibromyalgia, and chronic fatigue syndrome (Butler et al., 2024; Castellanos et al., 2020; Glynos et al., 2023; Wilde, 2023). Beyond the rationale for combining psychedelics with physiotherapy for motor FND, there exists a theoretical basis for the use of psychoplastogens in treating other neuropsychiatric disorders associated with motor dysfunction, such as stroke and acquired brain injury (Allen et al., 2024; Nardou et al., 2023; Yang et al., 2025). This is of considerable interest given the known impact of psychedelics upon perceptual function closely related to motor control, and this will be the first study combining psychedelics with movement retraining in a clinical population, providing valuable insights into the feasibility of this approach in these related conditions.

While not investigated in this pilot study, a future consideration is the role of psychedelic microdosing. This involves consumption of 'sub-perceptual' psychedelic doses with purported cognitive and therapeutic benefits (Andersson and Kjellgren, 2019; Fadiman and Korb, 2019; Lea et al., 2020). However, evidence for micro-dosing is constrained by a lack of controlled studies (Murphy et al., 2024; Polito and Liknaitzky, 2022) and the reduced psychoplastogenic effects at these low doses (Barksdale et al., 2024; Jefsen et al., 2021). Nevertheless, it is possible that this treatment paradigm may be worth exploring in the future as the field evolves.

Given this study's primary objectives focus on tolerability and feasibility, the therapeutic outcomes will be limited by the open-label design, small sample size, and relatively short follow-up. We also acknowledge challenges arising via the temporary cessation of psychotropic medications, including ongoing uncertainty and study into how best to

incorporate these pre-existing medications with psychedelic treatment (Goodwin et al., 2023; Tap et al., 2025).

This protocol outlines the first study of psychedelic treatment for motor FND in over 50 years. The study design builds upon recent findings of the safety and feasibility of performing physiotherapy following psilocybin administration in healthy participants. The results from this study will inform the design of a planned, adequately powered RCT of psilocybin-assisted physiotherapy in motor FND.

Administrative information

Trial Registration

Trial registered on Australian New Zealand Clinical Trials Registry (ANZCTR).

Registration Number: ACTRN12621000578808

Date Registered: 17 May 2021

URL: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=381745

Protocol Version

1 April 2025

Version 6.0

Identifier: 2025_APR_01_PROTOCOL_PsyFND_V6

Ethics

Ethics approval for this protocol has been awarded by the AHHREC (HREC/57390/Austin-2020). Significant protocol amendments will be reviewed by the TMG and submitted to the AHHREC. Active participants affected by amendments will be notified and provided with an updated PICF to review and reconsent if required.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Disclosures and Acknowledgements

Authors' Contributions

R.K. is the Principal Investigator and the senior researcher. C.B. and A.B. drafted this manuscript. All authors contributed to the development of the protocol and approval of the final manuscript.

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The Usona Institute provided the study drug. They have not offered or provided payments to the investigators.

Trial Sponsor

Austin Health, Austin Hospital, 145 Studley Rd, Heidelberg VIC 3084.

Role of Sponsors and Funders

The study sponsors and funders are not involved in study design; collection, management, and analysis of data; writing of the report; and the decision to submit the report for publication.

Competing Interests

R.K. is on the advisory board of Psychae Institute, a non-profit psychedelic research institute. R.K. has received grant funding from the Wellcome Trust, the Medical Research Council (U.K.), the National Health and Medical Research Council (Australia), and the Weary Dunlop Foundation for research on FND. R.K. receives royalties from Guildford Press for a book chapter on FND.

J.R. has undertaken paid advisory boards for Clerkenwell Health (Past), Beckley PsyTech (Past), Delica Therapeutics (Past), and paid articles for Janssen. J.R. has received assistance for attendance at conferences from Compass Pathways (past) and Janssen. J.R. 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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C.B. has received funding from the Graham Burrows Travelling Scholarship, University of Melbourne.

G.N. is a founding member and on the board of directors of the Functional Neurological Disorder Society. He is on the medical advisory boards of the charities FND Hope U.K. and FND Action. He receives research funding from the National Institute for Health and Care Research (U.K.).

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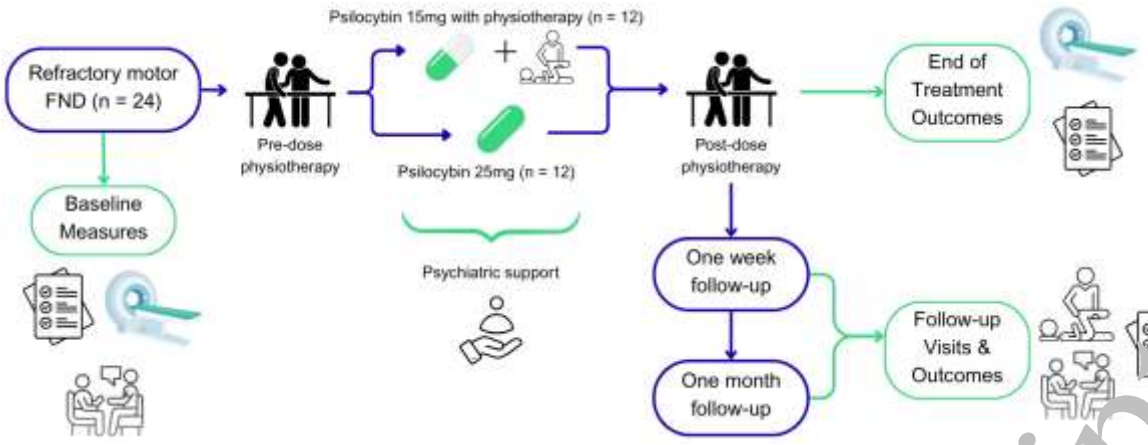

Figure 1

Figure 2 – Study Schedule

	STUDY PERIOD														
	Screening & Enrolment	**Preparation Visit**	**Post-Allocation**												**Close-Out**
TIMEPOINT	**Visit 1**	**Visit 2**	**Visit 3**		**Visit 4 / Dose**					**Visit 5**	**Visit 6**	**Visit 7**		**Visit 9**	**Visit 10**
			Pre-PT	PT 1-2	Pre-dose	Dose	0.5 1 H 3 H	1.5 H* 4.5 H*	5 H	PT 3-8			Post PT	1-week review	1-month review
ENROLMENT															
Informed consent	X														
Assign trial code	X														
Eligibility criteria	X														
INTERVENTIONS															
Preparation session		X													
Randomisation		X													
Physiotherapy treatment session				X						◆	—	◆		X	X
Dosing						X									
Post-dose phone-call										X					
Psychiatry review														X	X
ASSESSMENTS															
Demographics	X														
Medical & psychiatric history	X														
Physical exam	X														
Urine pregnancy					X										
Urine drug screen					X										
Concomitant medications	X														
12-lead ECG	X														
Vital signs	X						X		X						
Adverse events				X	X		X		X	X	X	X	X	X	X
SETS	X														
Movement tasks[a]	X							X					X	X	X
S-FMDRS[b]	X							X					X	X	X
PGI-S	X			X					X	X	X	X	X	X	X
PGI-I				X					X	X	X	X	X	X	X
CGI-S	X												X	X	X
CGI-I													X	X	X
SF-36	X												X	X	X
PHQ-15	X												X	X	X
PHQ-9	X												X	X	X
GAD-7	X												X	X	X
5D-ASC									X						
EDI									X						

BFI-2	X												X		X
Force-matching task	X												X		
Resting-state fMRI			X										X		
Task-based fMRI			X										X		
Qualitative interview														X	
Perspectives on study treatment														X	
Fidelity (physiotherapist)													X		
Fidelity (participant)														X	

[a] Movement tasks:

- De Morton Mobility Index
- Functional Movement Exploration
- Action Research Arm Test
- Box and Block Test – Original & Modified
- Video footage

[b] SFMDRS assessed by:

- Treating physiotherapist
- Independent rater

* Only completed by participants randomised to the moderate-dose arm

Abbreviations

- 5D-ASC 5-Dimensional Altered States of Consciousness
- BFI-2 Big Five Inventory-2
- CGI-I Clinical Global Impressions of Improvement
- CGI-S Clinical Global Impressions of Severity
- ECG Electrocardiogram
- EDI Ego-Dissolution Inventory
- fMRI Functional magnetic resonance imaging
- GAD-7 General Anxiety Disorder-7
- PGI-I Patient's Global Impressions of Improvement
- PGI-S Patient's Global Impressions of Severity
- PHQ-9 Patient Health Questionnaire-9
- PHQ-15 Patient Health Questionnaire-15
- PT Physiotherapy
- S-FMDRS Simplified Functional Movement Disorder Rating Scal
- SETS Stanford Expectations of Treatments Scale
- SF-36 36-Item Short-Form Health Survey

Table 1 – Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
1. Adults aged 18 to 65 years. 2. A diagnosis of refractory motor FND, supported by relevant neurological investigations and independent assessment by a psychiatrist and neurologist. • Motor FND is defined as upper or lower limb motor weakness, gait disorder, or movement disorder (e.g., tremor or dystonia) of at least six months duration. • Symptoms are deemed refractory if these are of at least six months duration, persist following physiotherapy and psychiatry management, and are considered by the participant to be impacting their functioning or quality of life. 3. Understanding of their diagnosis of FND. 4. Capacity to provide informed consent for the study.	Medical Exclusion Criteria 1. Cardiovascular conditions: poorly-controlled hypertension, angina, ischaemic heart disease, a clinically significant ECG abnormality, transient ischaemic attack, stroke, or peripheral or pulmonary vascular disease. 2. A diagnosis of epilepsy or previous epileptic seizures. 3. A diagnosis of dementia. 4. Chronic kidney or liver disease. 5. Known conditions putting the participant at risk for hypercalcaemia, Cushing's syndrome, hypoglycaemia, syndrome of inappropriate antidiuretic hormone secretion, or carcinoid syndrome. 6. Insulin-dependent diabetes if taking oral hypoglycaemic agents, the participant is only excluded if they also have a history of hypoglycaemia. 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.

Abbreviations
- ECG Electrocardiogram
- FND Functional neurological disorder

Table 2 – Primary, Secondary, and Exploratory Outcomes

	Domain	Measures	Administration	Application and Clinical Relevance
Primary Outcomes	Tolerability	Vital signs	Clinician-administered	Heart rate, blood pressure, and oxygen saturation on room air will be monitored.
		Adverse events form	Clinician-administered	Treatment-emergent adverse events will be recorded 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.
	Feasibility	Completion of movement tasks	Clinician-administered	The S-FMDRS (Nielsen et al., 2017), DEMMI (de Morton et al., 2008), FME, FAT (Yozbatiran et al., 2008), and BBT (Mathiowetz et al., 1985) (original and modified versions) measure several domains of motor function to assess the feasibility of competing movement tasks during the acute drug effects.
	Symptom severity	S-FMDRS	Clinician-administered	9-item instrument assessing seven body regions and two functional movements commonly affected in motor FND (Nielsen et al., 2017). Severity and duration are each rated from 0 to 3 for each of the nine items, with scores summed to provide a total score between 0 to 54 (higher scores indicate greater impairment).
		PGI-S & -I	Self-administered	• PGI-S: 1-item instrument, scored from 1 to 4 (higher scores indicate greater severity), assessing disease severity (Food and Drug Administration, 2018). • PGI-I: 1-item instrument rated from 1 to 7 (lower scores indicate greater improvement and higher scores indicate worsening) assessing change following an intervention (Mohebbi et al., 2018; Remigio-Baker et al., 2024).
Secondary Outcomes	Symptom severity	S-FMDRS – video assessment	Clinician-administered	Clinician-rated severity of functional motor symptoms, graded through video assessment by a blinded, independent assessor.
		CGI-S & -I	Clinician-administered	• CGI-S: 1-item instrument, scored from 1 to 7, assessing disease severity (higher scores indicate greater severity) (Busner and Targum, 2007). • CGI-I: 1-item instrument rated from 1 to 7 assessing change following an intervention (lower scores indicate greater improvement and higher scores indicate worsening) (Busner and Targum, 2007).
	Co-occurring symptoms	PHQ-9	Self-administered	9-item scale, scored from 0 to 3, assessing the severity of depressive symptoms over the past two weeks (higher scores indicating greater frequency of symptoms) (Kroenke et al., 2001). Items are summed to provide a total score between 0 to 27. An additional 10th item is provided to ascertain the impact on functioning, scored 1 to 4 (higher scores indicating greater impairment).
		GAD-7	Self-administered	7-item scale, scored from 0 to 3, assessing the severity of anxiety symptoms over the past two weeks (higher scores indicating greater frequency of symptoms) (Spitzer et al., 2006). Items are summed to provide a total score between 0 to 21. An additional 8th item is provided to ascertain the impact on functioning, scored 1 to 4 (higher scores indicating greater impairment).
		PHQ-15	Self-administered	15-item scale, scored from 0 to 2, assessing the impact of various somatic symptoms over the past week (higher scores indicate greater impact) (Kroenke et al., 2002). Items are summed to provide a total score between 0 to 30.
	Quality of life	SF-36	Self-administered	36-item scale, grouped into 8 subscales representing core health-related quality of life dimensions (physical functioning, role limitations due to physical health, pain, general health, emotional wellbeing, social functioning, role limitations due to emotional problems, energy/fatigue, and mental health) (Ware et al., 1993). Item responses range from the lowest option at 1 to the highest option from 2 to 6 (depending on the item), with reverse scoring for some items. Each item is then converted to a 0 to 100 range, with higher scores indicating a more favourable health state.
	Treatment expectations	SETS	Self-administered	6-item scale, 3 each for positive and negative expectations, and each item scored on a 7-point Likert scale (lower scores indicate greater disagreement and higher scores indicate greater agreement) (Younger et al., 2012).
	Drug intensity	5D-ASC	Self-administered	94-item scale across 11 subscales (de Deus Pontual et al., 2023). Responses are rated on a visual analog scale, from 'No, not more than usually' to 'Yes, much more than usually'. Items are summed for each subscale to provide a total score. Higher scores indicate greater alterations in states of consciousness.
		EDI	Self-administered	8-item focused assessment of the experience of ego-dissolution (Nour et al., 2016). Each item is rated on a visual analog scale from 'No, not more than usually', to 'Yes, entirely or completely'. Scores are provided for each item and summed to provide a total score. Higher scores indicate greater ego-dissolution.
Exploratory Outcomes	Movement tasks	DEMMI	Clinician-administered	15-item unidimensional instrument that assesses mobility from bed-bound to independent mobility, including balance, gait, seating, and strength (de Morton et al., 2008). 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 (lower scores indicate greater impairment). Raw scores (from 0 to 19) are converted to a total DEMMI score (0 to 100) as defined by the scoring key. Additional comments for duration are provided where relevant.

		FME	Clinician-administered	FND extension module developed by our team, assessing movements incorporated in the physiotherapy intervention used in this study (Nielsen and Holt, 2024), to assess additional movements, including standing up from a chair, weight shifting, and balance. Items are dichotomous (scored 0 or 1) based on ability (lower scores indicate greater impairment). Items are summed to provide a total score between 0 to 4. Additional comments for duration are provided where relevant.
		ARAT	Clinician-administered	19-item instrument assessing upper limb coordination, dexterity, and functioning (lower scores indicate greater impairment) (Yozbatiran et al., 2008). Items are scored from 0 to 3 (lower scores indicate greater impairment). Scores are provided for four subscales, defined as grasp (sum of six items, range 0 to 18), grip (sum of four items, range 0 to 12), pinch (sum of six items, range 0 to 18), and gross movement (sum of three items, range 0 to 9). Items are summed to provide a total score from 0 to 57.
		BBT – original and modified	Clinician-administered	▪ Original – movement of blocks from one box to another over 60 seconds, assessing unilateral gross manual dexterity. It has shown high test-retest validity from normative data in adults without disability (Mathiowetz et al., 1985). ▪ Modified – as above, but with a shield placed between the participant's vision and their hands and access to a mirror to view their movements via reflection. This modulates attentional mechanisms of movement – an important feature of motor FND management. Lower scores for each scale are indicative of greater impairment.
		Video footage	Clinician-administered	Review of video footage of movement tasks to assess movement quality.
	Sensorimotor function	Force-matching task	Clinician-administered	Force-matching performance and sensory attenuation caused by self-generated movement (Pareés et al., 2014).
	Brain activity	Resting-state fMRI	Clinician-administered	Resting-state measures of brain activity (McCulloch et al., 2022).
		Task-based fMRI	Clinician-administered	Measures of brain activity during a Bayesian belief updating task (Korn et al., 2014; Marks and Baines, 2017; Sharot et al., 2011).
	Personality	BFI-2	Self-administered	60-item scale based on the five-factor model of personality (Soto and John, 2017). Items are scored on a 5-point Likert scale (lower scores indicate greater disagreement and higher scores indicate greater agreement, with reverse option wording across some items). Items are summed for 5 domains and 15 facet subscales.
	Subjective experiences	Perspectives on study treatment	Self-administered	9-item questionnaire including responses on ordinal scales, a visual analog scale, and free-text, exploring perspectives on aspects of the study treatment, including physiotherapy and psilocybin.
		Qualitative interview	Self-administered	Qualitative interview exploring subjective experiences of psilocybin, completing movement tasks during the acute drug effects, and the study treatment.

Abbreviations

- 5D-ASC 5-Dimensional Altered States of Consciousness
- ARAT Action Research Arm Test
- BBT Box and Block Test
- BFI-2 Big Five Inventory-2
- CGI-I Clinical Global Impressions of Improvement
- CGI-S Clinical Global Impressions of Severity
- DEMMI De Morton Mobility Index
- EDI Ego-Dissolution Inventory
- FME Functional Movement Exploration
- fMRI Functional magnetic resonance imaging
- GAD-7 General Anxiety Disorder-7
- PGI-I Patient's Global Impressions of Improvement
- PGI-S Patient's Global Impressions of Severity
- PHQ-9 Patient Health Questionnaire-9
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