STUDY PROTOCOL

REVISED Probing the functional magnetic resonance imaging response to psilocybin in functional neurological disorder (PsiFUND): study protocol

[version 2; peer review: 3 approved, 1 approved with reservations]

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Abstract

Background

Functional neurological disorder (FND) is a common cause of neurological symptoms including seizures and movement disorders. It can be debilitating, is associated with high health and social care costs, and can have a poor prognosis. Functional magnetic resonance imaging (fMRI) has suggested FND is a multi-network disorder. Converging evidence suggests that other mechanisms including dissociation, interoception, and motor agency may be abnormal in people with FND. Psychedelics are currently under investigation for numerous neuropsychiatric disorders and have been shown to disrupt functional brain networks. Administering psychedelics to people with FND will help us to probe mechanistic theories of the disorder.

Protocol

Open Peer Review

Approval Status ✓ ✓ ? ✓

	1	2	3	4
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version 1 24 Jul 2024	? view	? view	? view	✓ view

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In this open-label neuroimaging study, we will administer 25mg oral psilocybin with psychological support to people with chronic FND (target n = 24). Participants will undergo resting-state and task-based (Libet's clock, a measure of motor agency) fMRI sequences which will be compared in a pre-post manner. Additional mechanistic outcomes including measures of interoception (heartbeat tracking task), somatisation, illness perceptions, suggestibility, and dissociation will be collected. Data on expectancy, preparedness, and subjective experience of the psychedelic experience will also be gathered. Participants will be followed up for three months following psilocybin administration. fMRI changes in networks will be analysed using seed-based approaches, and additional exploratory analysis of resting-state imaging will take place.

Discussion

The study will help us to probe the mechanisms thought to potentially underpin FND. As the first modern study of psychedelics in FND, it will also help us to understand whether psychedelic administration alongside psychological support might be safe and feasible in this patient population.

Keywords
psychedelics, psilocybin, functional neurological disorder, fMRI

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Any reports and responses or comments on the article can be found at the end of the article.

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Competing interests: M.J.E. does medical expert reporting in personal injury and clinical negligence cases, including in cases of functional neurological disorder (FND). M.J.E. has shares in Brain & Mind, which provides neuropsychiatric and neurological rehabilitation in the independent medical sector, including in people with functional neurological disorder. M.J.E. has received financial support for lectures from the International Parkinson's and Movement Disorders Society and the FND Society (FNDS). M.J.E. receives royalties from Oxford University Press for his book The Oxford Specialist Handbook of Parkinson's Disease and Other Movement Disorder. M.J.E has received honoraria for medical advice to Teva Pharmaceuticals. M.J.E. receives grant funding, including for studies related to FND, from the National Institute for Health and Care Research (NIHR) and the Medical Research Council (MRC). M.J.E. is an associate editor of the European Journal of Neurology. M.J.E. is a member of the international executive committee of the International Parkinson's and Movement Disorders Society and a board member of the FNDS. M.J.E. is on the medical advisory boards of the charities FND Hope UK and Dystonia UK. The study medication is provided by COMPASS Pathways Ltd who will receive adverse events information from the study practitioners.

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REVISED **Amendments from Version 1**

The manuscript was updated based on reviewer suggestions. We made some changes to the introduction, including removal of sections about the predicative processing theory of functional neurological disorder and psychedelics, and mention of the default mode network as being specifically implicated. We focus the introduction instead on particular brain regions. We updated the recruitment strategy to include targets for symptom subtypes (seizures and motor symptoms) and protected characteristics. We provided some clarifying information for the study schedule and justification for the dose of psilocybin used. We included additional scales (Short Suggestibility Scale, Watts Connectedness Scale, Psychedelic Predictor Scale, Challenging Experiences Questionnaire, Emotional Breakthrough Inventory, Psychological Insights Scale). We provided additional information on adverse event reporting. We updated our data sharing plans. We provided further detail on the planned analysis pipeline for the functional magnetic resonance imaging data. We made some other minor amendments for grammar or clarity.

Any further responses from the reviewers can be found at the end of the article

Introduction

Background

Functional neurological disorder (FND) produces a range of neurological symptoms and signs which have specific characteristics that positively separate them from those caused by neurological diseases and which implicate a specific malfunction of movement and perception[1]. Common phenotypes include functional motor disorders and functional seizures[2].

FND is common[3–5], with up to 100,000 in the UK living with the disorder[6]. Disability is similar to other neurological disease[7]. Symptoms are often found to persist or worsen over time[5], and prognosis can be poor[8,9]. Inpatient healthcare costs alone of FND in the United States are estimated to be around $1.2 billion per year[10]. A large survey of people with FND indicated that only 15% were able to work full-time[11].

Current best-available treatment options are psychological therapies (such as cognitive behavioural therapy), psychoeducation, physiotherapy, and multidisciplinary rehabilitation, however these are not always effective[5,12,13]. Although pharmacological therapies are not frequently used, there are specific cases in which psychoactive compounds may be effective as a single dose, particularly when used to augment psychological or physical therapy, for example in therapeutic sedation for functional dystonia[14] and historical cases of drug-facilitated abreaction[15].

Mechanistic evidence in FND

Functional neurological symptoms are varied, and their expression is likely to be underpinned by complex mechanisms. It may be that functional motor symptoms and functional seizures have distinct pathophysiological mechanisms; nevertheless, the two very commonly co-occur, indicating possible shared propensity mechanisms. Examples of overarching theoretical models of FND include aberrant predictive processing[16,17], the integrative cognitive model[18], and altered emotional processing[19].

Neurobiological theories of FND have been supported by neuroimaging[20,21]. People with FND have shown altered connectivity in brain regions such as the motor cortex[22–25], medial prefrontal cortex (mPFC)[22,26,27], dorsolateral prefrontal cortex (dlPFC)[26,28], inferior frontal gyrus[24,29], insula[24,25,27,29–33] posterior cingulate cortex[34], temporoparietal junction (TPJ)[25,35], anterior cingulate cortex[31,33,36]. Other neuroimaging studies have shown altered activation in regions such as the mPFC[37], anterior cingulate cortex[38], and inferior frontal gyrus[39], and insula[40]. Recently, some authors have suggested that the default mode network (DMN) is particularly implicated in FND[32,41].

FND is also associated with impaired sense of agency. Agency refers both to the subjective feeling of volitional control one's body, as well as the ability to enact such control[42]. Research incorporating an agency paradigm (Libet's clock test) has indicated that people with FND have a decreased awareness of the intention to move (motor agency) in comparison to healthy controls; attention to intention relative to attention to movement was associated with increased activity in the bilateral inferior parietal lobes, dlPFC-inferior frontal gyrus and pre-supplementary motor area-dlPFC[42], In addition, replicated functional imaging studies in FND have found hypofunction of the right TPJ, a key node in the network proposed to underpin agency[42–46].

Dysfunction of interoceptive processing may also contribute to the generation of functional symptoms[47]. People with FND may have poorer interoceptive awareness than healthy controls, as shown via interoceptive tasks such as heartbeat tracking[48–52]. Difficulties with interoceptive processing may be a correlate of the disorder or may represent a means by which symptoms arise via aberrant interpretation of somatic signals.

Finally, dissociation may be an additional mechanisms by which symptoms arise[49]. Dissociation can refer to the subjective feeling of disconnect from the self, others, or the environment (also known as depersonalisation and derealisation). It also has an additional specific definition as a psychological model which describes the splitting off of conscious awareness from attention[53]. In FND, this may manifest with the feeling of loss of volitional control over a neurological function.

Current psychedelic research

Classical psychedelics are agonists or partial agonists at the serotonin (5-HT) 2A receptors which induce states of acutely altered consciousness[54]. Prior to the 1970s, psychedelics were successfully investigated for a number of neurological and psychiatric indications[55–57]. A resurgence of research interest in psychedelics in recent years has led to investigation in neuropsychiatric disorders such as treatment-resistant depression[55], headache disorders[58,59], anorexia[60], post-traumatic stress disorder[61,62], alcohol use disorder[63], tobacco addiction[64], existential distress in life-threatening disease[65], and obsessive-compulsive disorder[66]. Psychedelics may have 'cross-diagnostic potential', and could

target core elements of a shared psychopathology across neuropsychiatric disorders, including FND[56].

Contemporary psychedelic research has emerged within an environment of lingering cultural stigma as well as premature and unjustified hype about their medical efficacy[67,68], however well-designed trials are attempting to address these issues[69]. Safety data from these trials is reassuring[57,70], and psychedelic drugs have been shown to be physiologically non-toxic and non-habit forming[55,71,72].

Modern psychedelic research involves non-directive psychological support[55,56,73,74], in which the therapeutic relationship between participant and therapist is thought to be of central importance[75]. This follows three phases: preparation, support during dosing and post-dose psychological integration[74]. At doses of 25mg psilocybin, participants may have transient psychologically-challenging experiences[76], however psychological preparation is argued to help mitigate these[77], and post-dose integration helps to process the experience and build upon insights gained[78].

Mechanistic effects of psychedelics

5-HT_{2A} receptors are densely distributed across the cerebral cortex, particularly in association cortices, with relatively scant expression in subcortical regions[79]. There have so far only a few primary neuroimaging studies with psychedelics[80]. Nevertheless, functional neuroimaging studies have shown indications of changes in within- and- between-network-connectivity in canonical brain networks including the DMN[81]. (85) The response to psychedelics (acute and longer-term) are likely to be mediated by multi-network changes[82].

Psilocybin may lead to network disintegration and desegregation in the acute phase[83]. Post-administration effects on resting state connectivity have shown heterogeneity, however may incorporate increase connectivity within the default mode network[84], with concurrent increases in inter-network connectivity[85,86].

Psychedelics have been shown to exert significant changes on the acute sense of body ownership[87,88]. Although direct research on psychedelic and agency is scarce, psychedelic users have been shown to have agency related measures which are no different to healthy controls[88]. Similarly direct research analysing the effects of classical psychedelics on interoception is lacking, however the psychoactive compound salvinorin-A has been shown to modify interoception[89]. Randomised trials of 3,4-Methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for treatment of chronic posttraumatic stress disorder showed non-significant reductions in dissociative experiences in the treatment arms[90].

Psychedelics in FND

Previous authors have suggested FND, including motor symptoms[91], and seizures[18] could representa target disorder for psychedelics[57,92]. Systematic reviews of 'pre-prohibition' case series of patients with FND administered psychedelics such as psilocybin and lysergic acid diethylamide (LSD) have found that side effects were minimal and transient in this population[93,94]. Nevertheless, as all relevant studies were conducted with insufficient experimental designs, further modern feasibility work is required.

In an international survey of people with FND, self-reported physical side-effects from recreational psychedelic use (n=10) were minimal at worst, and 46% of the >1,000 respondents reported that they would be willing to take part in medically-supervised psychedelic studies, with a further 20% undecided[95].

The proposed study

Taken together, this evidence suggests that psychedelics may target some of the mechanistic processes which underpin FND. Administering the psychedelic psilocybin to people with FND will allow us to probe theories of FND which postulate that it is a disorder typified by altered network connectivity across brain networks. Using a pre-post design, we will be able to test whether impaired sense of agency, changes in interoception, and dissociative phenomena are modifiable pathophysiological features of the disorder.

Protocol

Aim

The purpose of this study is to investigate the functional neuroimaging response to a single dose of psilocybin in patients with functional neurological disorder.

The study is pre-registered on clinicaltrials.gov (NCT05723276). The study and all relevant documents have ethical approval from the Health Research Authority Research Ethics Committee (23/WA/0213).

Objectives

We will administer a single 25mg oral dose of psilocybin in people with functional neurological disorder. This dose has been chosen as it is the most commonly-used in contemporary psychedelic trials[96], is sufficient to induce a recognisable but manageable acute psychedelic effect at a fixed dose[97], and evidence from other disorders indicates it has been more effective in comparison to lower doses[98]. Participants will undergo functional resting-state and task-based (Libet's Clock Test) fMRI one day prior to and one week following the psilocybin administration.

Exploratory objectives include assessment of the effect of psilocybin administration on mechanistic targets including interoceptive ability, dissociative phenomena, illness perceptions and self-compassion.

Endpoints

Primary endpoints

The primary endpoint of this study will be change in functional connectivity functional resting-state imaging via within-subjects region of interest connectivity analysis using a priori seed regions (medial prefrontal cortex, subgenual anterior cingulate cortex, posterior cingulate cortex, insula, temporo-parietal junction) and task-based magnetic resonance using Libet's clock test.

Additional exploratory functional neuroimaging analysis will likely take place with other methodologies (e.g. measures of modularity, entropy).

Exploratory endpoints

1. To assess any changes in the following outcomes following psilocybin administration (pre-post design):
    a. Interoceptive accuracy and confidence (as per the Heartbeat tracking task and the Multidimensional Assessment of Interoceptive Awareness – Version 2)
    b. Dissociation (Multiscale Dissociative Inventory Scale)
    c. Imaginative suggestibility (Creative Imagination Scale)
    d. Illness perceptions (Brief Illness Perceptions Questionnaire)
    e. Somatisation tendencies (Somatoform Dissociation Questionnaire)

    To explore the association of primary and exploratory outcomes with other measures, including:
    i. Expectancy (as per the Stanford Expectations of Treatment Scale)
    ii. Psychedelic preparedness (as per the Psychedelic Preparedness Scale)
    iii. Acute psychedelic experience intensity (as per the Ego Dissolution Inventory and the 5-Dimensional Altered States of Consciousness Rating Scale)
    iv. Self-compassion (as per the Self-Compassion Scale)
    v. Personality structure (as per the Short Assessment of Personality Scale)
2. To explore correlations of functional MRI connectivity with clinical outcomes (via the Clinical Global Impression; CGI) and assessment of associated symptoms (via the Revised Fibromyalgia Impact Questionnaire; FIQR).
3. To explore participants views on acceptability on psychedelic administration with psychological support via qualitative interviews.

Hypotheses under investigation

- Hypothesis 1: Network connectivity from seed regions implicated in FND (including the medial prefrontal cortex, dorsolateral prefrontal cortex, inferior frontal gyrus, insula, posterior cingulate cortex, anterior cingulate cortex, and temporoparietal junction) will be altered post psilocybin.
- Hypothesis 2: Changes in in other mechanistic markers, including motor intentionality, interoception, dissociation, imaginative suggestibility, and somatisation will be observed.
- Hypothesis 3: There will be improvement in the FND core and associated symptom severity as measured by the CGI and FIQR.
- Hypothesis 4: Qualitative interviews will suggest acceptability for this form of therapy. Themes which emerge from these interviews will include changing relationships to their disorder, increased self-compassion, and meaningful experiences engendered by trial participation.

Study design

This study will be an open label within-subjects design in up to 24 participants (target 20 completers) who have a diagnosis of FND as per Diagnostic and Statistical Manual of Mental Disorders (5th Edition) (DSM-5) criteria[99]. They must have failed to respond to an FND-specific treatment (such as CBT, physiotherapy, or multidisciplinary rehabilitation).

Within the confines of the sample size, a representative sample of motor and seizure subtypes will be sought for inclusion:

- Functional seizures: 10 ± 3 completers
- Functional motor disorder 10 ± 3 completers

The sample will also seek to be representative of selected protected characteristics (gender, sexual orientation, and ethnicity) based on FND and population rates see Table 1.

Table 1: representative recruitment targets for ethnicity, gender identity, and sexual orientation. Ethnicity, sexual orientation, and transgender & non-binary data is taken from the national UK 2021 Census (https://www.nomisweb.co.uk/sources/census_2021).

Table 1. Recruitment targets by protected characteristics.

	UK	*London*	*Average*	Study target
Ethnicity				
White	81.70%	53.80%	67.75%	16
Asian	9.30%	20.70%	15.00%	4
Black	4.00%	13.50%	8.75%	2
Mixed	2.90%	5.70%	4.30%	1
Other	2.10%	6.30%	4.20%	1
Gender identity				
Women	-	-	70%	17
Transgender & non-binary	-	-	0.50%	0-1
Sexual orientation				
LGBT	-	-	3.50%	1

Ethnicity distribution varies across the country, and hence and average frequency was calculated between London and UK (as PsiFUND is a study based in London open to recruitment from the UK). The female prevalence data was taken from FND population data (https://jnnp.bmj.com/content/94/10/855). Anonymised socioeconomic status will also be presented descriptively using the UK Government indices of deprivation database (calculated by postcode).

Sample size calculation

We will recruit up to 24 participants for this study. The primary aim of the study is to assess resting-state and task-based functional neuroimaging changes. Based on a previous fMRI study of the effect of psilocybin on resting-state connectivity obtained by fMRI, a mean response in connectivity in the default mode network (a connectivity network of interest) of 2.48 (arbitrary units) and a standard deviation of 2.60[84] was found in pre versus post psilocybin within-subjects analysis; this signifies an anticipated minimum detectable effect size of 0.95. For a two-tailed test and an alpha of 0.01 (to account for multiple testing) and with a power of 0.90, a total sample size of n=20 is required. An additional four participants will be recruited given expected dropouts.

Recruitment

Recruitment will be via a number of methods, including referral from secondary and tertiary care services as well as established registries of patients who have consented to contact from study teams, word of mouth, and directly from advertising in the community and on social media. The public-facing study website (psifund.co.uk) will contain information about the study (including the participant information sheet), contact details for the study team, and frequently asked questions. All patient-facing information has been reviewed and approved by the Research Ethics Committee.

Screening

Potential study participants will be initially screened by online pre-screening survey. The online pre-screening will prompt potential participants to read the Participant Information Sheet and indicate their consent for providing information on their diagnosis, demographics and contact details. Pre-screening questions will include the inclusion and exclusion criteria in lay terms, which respondents will need to indicate with a check-box that they satisfy. We will also ask for a telephone contact number and an email address. Telephone or video pre-screening will then be undertaken to clarify inclusion and exclusion criteria and to arrange face to face screening if appropriate. Additionally, participants may be directly referred via contributing Participant Identification Centres.

Those who are deemed to be potentially eligible will be invited for a face-to-face screening assessment with a member of the study team. Final study inclusion and consent will be taken by a study medic.

The following inclusion criteria will apply:

1) Age 25 – 60 years.
2) Able to engage with face-to-face psychological support (undertaken in English without a translator)
3) A diagnosis of FND from a neurologist and/or neuropsychiatrist as per DSM-5 criteria
4) Moderate or severe symptoms (≥4 on Clinical Global Impression Severity (CGI-S) scale) which have been present for >12 months and have failed to respond to a recognised treatment.
5) Able to tolerate fMRI scanning procedures.

Failed to respond is defined as an inadequate (i.e. not complete) response to a full course of FND-specific therapy, such as CBT, physiotherapy, or inpatient treatment. Therapy must have been undertaken by a suitably trained expert in FND and must have been specifically targeted at FND symptoms.

The following exclusion criteria will apply:

1) Diagnosis of severe depression.*
2) Diagnosis of bipolar affective disorder.*
3) Diagnosis of a psychotic disorder, EXCEPT substance/medication induced psychotic disorder where the duration was limited to the acute period of direct intoxication with the substance/medication.*
4) Diagnosis of drug or alcohol dependence disorder.*
5) Diagnosis of a personality disorder.*
6) Diagnosis of any dementia based on clinical interview by a psychiatrist.
7) Diagnosis of any autistic spectrum disorder based on clinical interview by a psychiatrist.
8) Diagnosis of any learning disability based on clinical interview by a psychiatrist.
9) Significant suicidal behaviour in past 12-months defined using the Columbia-Suicide Severity Rating Scale (C-SSRS).*
10) Any other factor which would render the participant unsuitable for psilocybin and/or interfere with a supportive therapeutic relationship and/or preclude safe follow-up.
11) Those unable to give informed consent.
12) Medical diagnosis incompatible with psilocybin treatment (see *below*).
13) Inability to provide a screening blood sample, urine sample, or electrocardiogram.
14) Biochemical abnormalities (defined as falling outside the normal reference range) as evaluated by a full blood count, full biochemistry profile and thyroid function tests. Biochemical abnormalities must also be determined as clinically significant by a medical doctor to fulfil the criterion for exclusion.

15) Electrocardiographic abnormalities determined as clinically significant by a medical doctor.

16) Women of childbearing potential not using contraception.

17) Pregnant or breast-feeding women.

18) Non-registration with a GP or failure to consent to sharing of the GP summary care record and any psychiatric assessments held.

19) Those enrolled in another clinical or research study.

20) Use of any psychedelic substances >2 times in past 12 months.

21) Any factor which would exclude the participant from MRI scanning (e.g., presence of metal).

Diagnoses will be defined in each case as meeting DSM-5 criteria, where relevant.

*In all highlighted cases, diagnoses will be screened via appropriate tools (such as the Mini Neuropsychiatric Inventory v7.0 [MINI][100]) and will be subject to confirmation at clinical interview by a psychiatrist.

To be eligible for this study participants will need, in addition to satisfying the eligibility criteria, to agree to the following:

1) Provide contact details of a trusted friend or relative that the study team may contact in the event of an emergency.

2) To stay within the boundaries of the research centre during the Dosing Visit for at least six hours after the psilocybin is given, or until it is clinically determined that they are safe to leave, whichever is longer.

Exclusions for pre-existing medical conditions

Participants will be excluded if they have a current diagnosis of ≥1 of:

- Uncontrolled diabetes
- Hypertension (defined as a systolic blood pressure ≥ 160mm/Hg or a diastolic blood pressure ≥100mm/Hg on three separate readings). All readings of systolic blood pressure ≥ 140mm/Hg or diastolic blood pressure ≥ 90mm/Hg will be reviewed by a clinician. Hypertension ascertained prior to dosing will be subject to clinical confirmation via collateral information from the GP or other source.
- Cardiac failure, defined as class IV of the New York Heart Association classification
- Renal failure, defined as ≥ stage 4 (GFR ≤ 29mL/min)
- Liver failure, defined as a clinical diagnosis of liver fibrosis, cirrhosis of the liver, liver failure or advanced liver disease.
- Any cardiac arrhythmia, except atrial fibrillation.
- Any form of epilepsy

Past diagnosis of ≥1 of:

- Cerebrovascular accident or intracerebral trauma.
- Myocardial infarction within 1 year prior to the screening visit.

Women of childbearing potential

A female who is not of childbearing potential is considered to be postmenopausal (at least 12 consecutive months without menstruation) or permanently sterilized (e.g., hysterectomy and/or bilateral salpingectomy).

For females of childbearing potential who may participate in the study, the following methods of contraception, if used properly and used for the duration of the study, are considered sufficient:

- Oral contraceptives
- Patch contraceptives
- Injection contraceptives
- Diaphragm or cervical cap with spermicide
- Vaginal contraceptive ring
- Intrauterine device
- Surgical sterilization (hysterectomy and/or bilateral salpingectomy)
- Vasectomized partner
- Sexual abstinence
- Same-sex partners

Periodic abstinence, i.e., calendar, symptothermal, or post-ovulation methods, and tubal ligation/occlusion are not an acceptable form of contraception for this study.

The investigator and each participant will determine the appropriate method of contraception for the participant during the participation in the study. This will be documented at Screening (V1a).

Study phases

Please refer to the study flowchart (Figure 1) and breakdown of study visits (Figure 2).

Screening and preparation phase

Participants will be assessed by a study psychiatrist and enter a Screening & Preparation phase of between one to eight weeks. All participants will receive the same screening assessments and baseline psychological preparation session prior to receiving the dose. At screening assessment, participants will have baseline blood tests, electrocardiogram (ECG), urine drug tests, vital signs, and pregnancy test (if relevant).

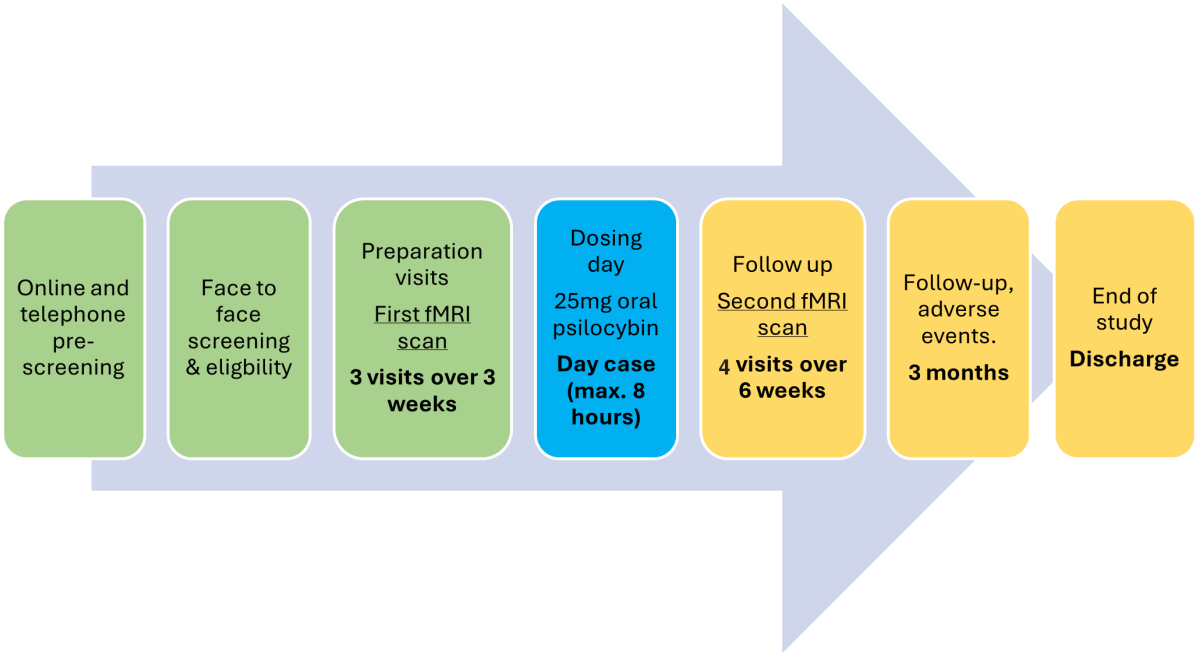

Figure 1. Study flowchart.

Withdrawal from relevant medications will be supervised by a clinician, flexible to the needs of the participant. This step is required because many medications, particularly those with serotonergic effects, may attenuate or block the effects of psilocybin. Participants will be allowed to continue to take medications for other medical illnesses throughout the study and on the Dosing Visit, provided they do not interact unfavourably with psilocybin.

We will allow the prescription of hypnotic medication (zopiclone, zolpidem or zaleplon within BNF dosage) for insomnia or a benzodiazepine (lorazepam or diazepam) or antihistamine (promethazine) for anxiety or withdrawal phenomena. Other over-the-counter remedies will be allowed, except for St John's Wort. Of note, a recent systematic review found no evidence to suggest significant interactions between psilocybin and psychiatric medications, including antidepressants[101].

During the Screening & Preparation Phase, participants will be reviewed weekly face to face (with the option for online in exceptional circumstance). We will extend the screening and preparation phase for a further period of up to eight weeks if participants require more time to withdraw from their medication, or if collateral history suggests a medical or personal problem that has not been adequately investigated, treated, or accounted for, or if participants require more preparation with their therapists prior to the dose. This would only be in extenuating circumstances in which an unforeseen event has rendered preparation sub-optimal.

During the screening phase, participants will be introduced to a therapist and a chaperone familiar with psilocybin and its effects. The therapist and/or chaperone will provide psychoeducation, establish rapport, and address anxieties prior to the dose; to provide appropriate care and support to participants during the dose; to provide an opportunity for psychological support and integration after the experience. Depending on participant needs we will arrange additional sessions for psychological preparation and integration as required. For further information on therapeutic support and principles please see overview in reference 102.

Baseline, dosing, and day one visit

One day prior to the Dosing Visit, participants will be invited to attend for the Baseline Visit. Final eligibility will be confirmed at this visit. We will perform baseline clinical procedures and measures of outcome and functioning (Figure 2). Participants will meet with their therapist and chaperone to prepare them for the Dosing Visit.

At this visit, participants will undergo the first fMRI scan. This scan will include structural, resting-state, and task-based (Libet's Clock) sequences. Outside of the scanner, participants will also undertake a heartbeat tracking test, a measure of interoceptive accuracy & awareness.

The Dosing Visit will take place 1–3 days after the Baseline Visit. Participants will receive 25mg of oral psilocybin. Neither participant nor study team will be blinded (i.e. the study is open label). The study team will perform a brief mental state exam, before allowing sufficient time for participants to relax and for any anticipatory anxieties or practical considerations to be addressed.

The environment within which the dose will be given will be a quiet, neutrally furnished room with adjustable lighting.

Visit	V1a	V1b	V1c	V2	V3	V4	V5a	V5b	V5c	V5d
Day	-21	-14	-7	-1	0	1	7	21	42	90
Location	Clinical Research Facility, King's College Hospital or The Centre for Mental Health Research and Innovation, Denmark Hill.									
Window (days)	+/- 14	+/- 3	+/- 3	-1	n/a	+1	+/- 3	+/- 3	+/- 5	+/- 5
Visit length (hrs)	4	2	2	6	8	2	6	2	2	2
Procedure	Time required for procedure (minutes)									
Informed consent	15									
Medical history	30									
Inclusion/exclusion criteria	30									
Prior & Concomitant Medications	15	5	5	5	5	5	5	5	5	5
Collateral History	30									
MINI	60									
Urine Drug Screen	15									
Urine Pregnancy Test (Females Only)	5			5						
Clinical laboratory investigations	15									
Electrocardiogram	15									
Urinalysis	15									
Vital signs (BP/HR/Temp)	15			15		15				
Weight	5									
Study drug					n/a					
Heartbeat tracking & discrimination task				60			60			
Neuroimaging task (Libet's Clock Test)				90			90			
Structured qualitative interview								(90)		
Psychological support		60	60	60	360	60	60	60	60	
C-SSRS	5									
CGI-S/I	5			5			5			
FIQR	5			5			5			
HAM-D	15									
CIS				20			20			
M3VAS	1									
GAD-7	5									
ACE	5									
TEC	10									
SETS	5			5						
SAPAS	1									
5D-ASC						15				
EDI						2				
MDI	10			10			10			
BIPQ	5			5			5			
SCS	10						10			
MAIA-2				5			5			
PPS				10						
SDQ	10			10			10			
SSS				5						
EBI						2				
PsyIS						5				
IPPS				2						
CEQ						5				
WCS	2						2			
	Nurse/RA		Psychologist		Participant		Medic			

Figure 2. Schedule of events. Estimated time needed for completion of each task indicated in the table in minutes.

Participants will lie or sit down on a bed, and easy access to the lavatory and light refreshments will be available. Participants will be given an eye mask and earphones through which they will be able to hear a curated playlist of relaxing music. The therapist and chaperone will be present in the room, with at least one person with the participant at all times during the Dosing Visit.

After the administration of the study drug, we will require participants to stay within the boundaries of the research facility until it is clinically determined that they are safe to leave. The subjective effects of psilocybin peak at approximately two hours and then wear off over approximately 2–4 hours. Inter-individual variation is, however, expected and participants will be accompanied for as long as necessary by the study team. If necessary, overnight hospital admission will be arranged for observation, with review by the study team the following morning and reporting of the event to appropriate pharmacovigilance authorities.

If necessary, and as a last resort, in the event of ongoing extreme distress unresponsive to therapist intervention, or in the event of threatened or actual violence unresponsive to de-escalation techniques, rescue medication will be given in liaison with the study medical and nursing staff. We will use oromucosal midazolam 2.5mg–5mg orally as a first line. Any further treatment will follow NICE guidelines. This will be given under the supervision of a psychiatrist.

Participants will attend the research facility the day following dosing. Participants will complete self-reported measures. Participants may meet with their therapist for up to 90 minutes to discuss their experience, and for example to process any difficult material that may have arisen.

Follow-up phase

The initial follow-up phase will last for six weeks post-dosing. During this time, the participant will attend three face-to-face follow-up visits which will include psychological integration sessions. The final three-month follow-up visit may take place online (via Microsoft Teams) if deemed appropriate by the participant and study team.

At one week post dose, participants will undergo follow-up fMRI imaging. The scanning protocol is the same as the first fMRI scan. An optional semi-structured qualitative interview about participants' experiences and opinions on the study and therapy will also take place during follow-up. We will ask participants to complete self-report measures and a member of the study team will perform study team-rated measures (Figure 2).

Psychological support

The psychological support used in this study will be based on a model that has been developed separately for COMPASS Pathways sponsored trials in depression. The psychological model is divided into three phases: preparation, dosing, and integration. This therapy is not specific to FND but will allow for the safe administration of psilocybin using a framework which has been successful in trials of psychedelics in other neuropsychiatric disorders. The therapists in this study have been trained as part of existing psilocybin studies and have experience of working with medical psychedelics.

Preparation focusses on building mutual trust, active listening, psychoeducation about the drug experience, and teaching methods of coping with difficult or unusual experiences that might arise. We will require participants to undergo a minimum of three hours of preparation, which will be delivered over several separate sessions. Satisfactory completion of this preparation will be assessed prior to dosing and the amount of preparation recorded in the case record form.

Neuroimaging task

Neuroimaging will take place on a Premier 3T MRI scanner. Scans will be clinically reviewed by a reporting clinician as routine. Participants will have a basic T1-weighted structural scan during which time they will be asked to lie back quietly with their eyes open or shut. This will be followed by a resting-state fMRI, in which patients will be asked to lie with their eyes open, staring at a fixation cross instead or an animation which encourages wakefulness[103]. Following this, participants will have functional MRI whilst they undertake Libet's clock test.

In Libet's Clock Test, participants will watch a ball revolving around a clock face and will press a button after a random time interval and will be asked (in 2x2 blocks of 15 trials) to note when they felt the urge to press (W judgement) or when they actually pressed the button (M judgement). The ball then appears at a random position, and participants are required to return it to the position it was in when they felt the urge to press the button, or actually pressed it depending on the block. Average latencies of the W and M judgements will be calculated as the differences between the final position of the ball and its position at the time of the recorded button press[104].

Interoception task

We will use a modified heart-beat tracking task to measure interoceptive accuracy and awareness. This is a version of the heartbeat tracking task developed by Schandry (1981)[105] and modified with previous successful use by Pick *et al.* (2020)[49] and Millman *et al.* (2023)[52]. Participants are advised not to wear any devices which would facilitate heartbeat tracking, and are asked not to explicitly measure their pule (e.g. via radial pressure).

Participants will be asked to sit comfortably and attend to and silently count their own heartbeats during four intervals of 25, 30, 35 and 40 seconds or 29, 34, 39 and 44 seconds.. The tracking trials will be interspersed with 20s rests in which participants fixated on the computer screen. The start and end of each heartbeat tracking, and rest period will be indicated on screen 'Start counting your heartbeats' in green, and 'Stop counting' in red. Immediately after each tracking period, participants will be cued to type in the number of heartbeats they

had counted, followed by a confidence rating (0–10, low-high certainty). Participants will be advised to indicate 0 if they could not feel any heartbeats at all.

Participants will be attached to a 2-lead ECG throughout the task to record actual heart beats, which will be recorded using a data acquisition system (PowerLab). Participants will be explicitly asked not to attempt to monitor the passing of time by counting seconds. A practice trial will be completed by all participants before starting the experimental procedures.

Following the heartbeat tracking task, participants will complete the time estimation task. This requires participants to count seconds during four randomised intervals (27, 32, 37 and 42 seconds, or 23, 28, 33 and 38 seconds). Otherwise, the trial will be conducted in the same manner as the heartbeat tracking task above.

Multidimensional Assessment of Interoceptive Awareness – Version 2 (MAIA-2)
In parallel, we will collect the Multidimensional Assessment of Interoceptive Awareness – Version 2 (MAIA-2) which is an 8-subscale trait self-report questionnaire to measure multiple dimensions of interoception (awareness of bodily sensations). The MAIA-2 is suitable for adults and has 37 items[106].

Semi-structured qualitative interview

Participants will be offered an optional semi-structured interview at a visit following the dosing. The interview will be conducted by a clinician in the trial team and will principally focus on the experience of the psilocybin dosing session as well as on any subsequent positive or negative effects on FND symptoms. The first stage of the interview will focus on illness background and perceptions, whilst the second stage will focus on participant's own appraisal of the effects (if any) of the experience of the dosing session. The sessions will be audio recorded using Microsoft Teams and stored on a secure cloud server.

Clinician reported outcome measures

The Columbia Suicide Severity Rating Scale (C-SSRS)
The C-SSRS is a clinician- and participant-rated scale that includes definitions of suicidal behaviour adapted from the Columbia Suicide History Form[107]. The purpose of this scale is to exclude participants with significant suicidal thoughts or behaviour where necessary. The CSSRS will be administered at screening.

17 Item Hamilton depression rating scale (HAM-D-17)
The HAM-D-17 is a 17-item scale used to measure the degree of symptom severity in depressed patients[108]. The HAM-D-17 will be administered at screening and follow-up. The purpose of including this scale is to exclude severe depression in potential participants.

Clinical Global Impressions Scale (CGI)
The CGI severity and improvement scales offer a readily understood, practical measurement tool that can be administered by a clinician in clinical trial settings. The Scale has two sections: Severity of illness, and (relative) Improvement[109]. We will undertake the CGI as part of the screening process as well as at follow-up visits. For patients with functional seizures, simple average numbers of seizures will be recorded in other to help clarify CGI scores. Likewise, brief descriptive information on FND symptom frequency and severity will be noted.

Participant reported outcome measures

Stanford Expectations of Treatment Scale (SETS)
The SETS is used in clinical trials to improve statistical sensitivity for detecting responses to interventions. The six-item SETS contains two subscales: positive expectancy and negative expectancy. The SETS is simple to administer, score, and interpret[110]. We will use the SETS score to investigate whether expectancy is associated with any outcome changes following psilocybin.

Psychedelic Preparedness Scale (PPS)
The PPS is a 20-item self-report measure of the degree to which respondents feel prepared for a psychedelic experience. It measures four domains: Knowledge-Expectation, Psychophysical-Readiness, Intention-Preparation, and Support-Planning. Participants rate their agreement with statements on a seven-point scale from 'not at all' to 'completely'[111].

5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC)
The 5D-ASC is a 94-item self-report measure of the acute effects of psychoactive drugs using 5 primary dimensions. Participants are given a statement pertaining to an element of conscious experience then asked to mark a point on a line between 'No, not more than usually' and 'Yes, much more than usually'. The 5 dimensions are 'oceanic boundlessness', 'anxious ego dissolution', 'visionary restructuralisation', 'auditory alterations', and 'reduction of vigilance'[112,113]. We will use the 5D-ASC score to investigate whether subjective intensity of experience is a associated with any outcome changes following psilocybin.

Ego Dissolution Inventory (EDI)
The EDI is a short 8-question visual analogue scale aimed to assess the extent to which participants felt they had lost their sense of self ('ego dissolution') during an experience. The scale has been validated and demonstrates a close relationship between ego-dissolution and the psychedelic experience; it was explicitly designed to facilitate the study of the neuronal correlates of ego-dissolution[114].

Short Suggestibility Scale (SSS)
The Short Suggestibility Scale is a 21-item subset of the Multidimensional Iowa Suggestibility Scale[115]. Suggestibility is a personality trait that reflects a general tendency to internalise and accept messages, including those from healthcare practitioners. The SSS has been used in previous psychedelic studies[116].

Emotional Breakthrough Inventory (EBI)
The Emotional Breakthrough inventory is a short six item questionnaire which assesses emotional breakthroughs during the psychedelic experience[117], Emotional breakthrough is

an important and distinct component of the acute psychedelic experience that appears to be a key mediator of subsequent longer-term psychological changes.

Psychological Insight Scale (PsyIS)
The Psychological Insight Scale is a six- to seven-item questionnaire that enquires about psychological insight after a psychedelic experience (PIS-6) and accompanying behavioural changes (PIS item 7)[118]. Insight has been found to be a key mediator of long-term psychological outcomes following a psychedelic experience.

Imperial Psychedelic Predictor Scale (IPPS)
The Imperial Psychedelic Predictor Scale is a short 9-item scale measuring factors which may be predictive of acute features of the psychedelic experience in a broad range of contexts[119]. The scale helps assess knowledge of psychedelic preparedness in controlled settings.

Challenging Experiences Scale (CEQ)
The Challenging Experience Questionnaire is a 26-item questionnaire which assesses difficult aspects of a psychedelic experience, such as feelings of unpleasant emotions[76].

Watts Connectedness Scale (WCS)
The Watts Connectedness Scale is a 19-item Likert scale questionnaire which measures three separable subscale factors pertaining to a felt connection to 'self', 'others' and 'world'[120]. Changes in total and subscale WCS scores have been correlate with outcomes post psychedelic use.

Creative Imagination Scale (CIS)
The Creative Imagination Scale is a measure of imaginative suggestibility. It does not require a hypnotic/trance induction procedure[121]. The CIS will be split in half, as per previous studies, with five questions administered pre-dose and five post-dose (this will attenuate the practice effect)[122].

Multiscale Dissociation Inventory (MDI)
The MDI is a 30-item self-report test of dissociative symptomatology. It is fully standardized and normed, and measures six different type of dissociative response[123]. We will use the MDI score to investigate whether measures of dissociation change following psilocybin administration.

The 20-item Somatoform Dissociation Questionnaire (SDQ)
The 20-item Somatoform Dissociation Questionnaire evaluates the severity of somatoform dissociation[124]. We will investigate whether any alterations in neuroimaging measures (fMRI functional connectivity) are linked to changes in dissociation measures following psilocybin.

Brief Illness Perceptions Questionnaire (BIPQ)
The Brief Illness Perception Questionnaire is a 9-item questionnaire designed to rapidly assess cognitive and emotional representations of illness[125]. The Brief IPQ uses a single-item scale approach to assess perception on a 0–10 response scale. It is developed by forming one question that best summarises the items contained in each subscale of the Illness Perception Questionnaire-Revised which has over 80 items. The Brief IBQ comprises five items on cognitive representation of illness perception: consequences, timeline, personal control, treatment control, and identity.

Self-Compassion Scale (SCS)
The Self Compassion Scale is 26-item scale comprising 6 subsections that tend to load together. Self-compassion entails being kind and understanding toward oneself in instances of pain or failure rather than being harshly self-critical; perceiving one's experiences as part of the larger human experience rather than seeing them as isolating; and holding painful thoughts and feelings in mindful awareness rather than overidentifying with them[126].

Maudsley 3-Item Visual Analogue Scale (M3VAS)
The Maudsley Visual Analogue scales indicate the quality of mood, experience of pleasure and experience of suicidal thoughts or feelings during a preceding interval of time that can be varied according to study need[115]. The MVAS will be administered at screening.

Generalised Anxiety Disorder Scale (GAD-7)
The GAD-7 is a self-rated screening and symptom severity measure covering 7 of the most commonly occurring anxiety symptoms[127]. Participants choose one of four severity scores and also indicate the degree to which these problems caused functional and/or social difficulties. Scores are derived from the values for each of the 7 domains. The GAD-7 will be collected at screening.

Adverse Childhood Experiences (ACE)
The ACE is a 10 item questionnaire that collects data about childhood traumatic life events[128]. The CTQ will be collected at screening.

Traumatic Experiences Checklist (TEC)
The Traumatic Experiences Checklist is a self-report measure addressing potentially traumatising events. It is a reliable and valid self-report instrument that can be used in research. Scores can be calculated for emotional neglect, emotional abuse, physical abuse, sexual harassment, sexual abuse, and bodily threat from a person[129]. The TEC will be collected at screening.

Short Assessment of Personality Scale (SAPAS)
The SAPAS is a very short assessment of personality designed to capture indicative elements of personality that may further indicate personality structures captured within the ICD-10 and DSM-IV constructs of personality disorder. Eight items are rated 'yes' or 'no'[130]. We will collect the SAPAS at screening to assess whether answers to any particular question are indicative of positive or negative response to psilocybin. The SAPAS will be collected at screening.

Revised Fibromyalgia Impact Questionnaire (FIQR)
The FIQR is an instrument used in the evaluation of fibromyalgia patients. It assesses three domains: function, overall impact, and symptoms[131]. There is significant overlap between the domains assessed by the FIQR and the 'associated' symptoms of FND, which are found at high rates and are found to be just as functionally impairing as the primary FND symptoms[11]. We will undertake the CGI as part of the screening process as well as at follow-up.

Creative Imagination Scale (CIS)
The Creative Imagination Scale is a measure of imaginative suggestibility. It does not require a hypnotic/trance induction procedure[121]. The CIS will be split in half, as per previous studies, with five questions administered pre-dose and five post-dose (this will attenuate the practice effect)[122].

Adverse events reporting

Data on adverse events will be collected and reported via the Health Research Authority safety reporting for non-CTIMP studies guidance[132]. We will specifically enquire about adverse events at each of the participant visits. All adverse events will be recorded. Participants will be asked to contact the study team about any adverse events they experience in-between face to face visits. Serious adverse events will be reported to the Sponsor and REC within 24 hours.

In addition to reporting all adverse events in line with the requirements of this protocol, the study team will be recording adverse events separately. These AEs will be transferred to Worldwide Clinical Trials for adding into a safety database, managed by both Worldwide Clinical Trials and COMPASS Pathways, allowing for the continued development of safety data around psilocybin.

We require consent from any participants to additionally share anonymised adverse event information with COMPASS Pathways, who will provide the study drug.

Analysis

Statistical measures
Pre-post changes analysed using paired t-tests. Alpha will be set at 0.05. Any clinical data will be presented descriptively without comparison. Multiple comparisons will be post-hoc corrected.

Qualitative analysis
Free text transcriptions from the qualitative interviews will be thematically analysed. Each transcript will be independently coded by two researchers. The agreed codes will be aggregated using NVivo 14.0. An inductive method will be employed to establish emergent themes from the codes. Coverage (% of total data) for each theme will be calculated.

Functional neuroimaging
Analysis of the neuroimaging data will take place using the KCL Neuroimaging Network and the Rosalind cluster. fMRI analysis will be carried out within Statistical Parametric Mapping software using a seed-based approach implemented in the CONN-fMRI Functional Connectivity toolbox. For each seed we will conduct a seed to voxel analysis using permutation-based multiple comparisons correction at the cluster level as implemented within the CONN toolbox with white matter and CSF (but not grey matter) regressors. The primary analysis will not include global signal regression.

Resting state region of interest connectivity analysis will be performed using a priori seed regions (medial prefrontal cortex, dorsolateral prefrontal cortex, inferior frontal gyrus, insula, posterior cingulate cortex, anterior cingulate cortex, and temporoparietal junction.). Additional exploratory functional neuroimaging analysis may take place with other methodologies (e.g. measures of modularity, entropy).

Libet clock task
Judgment data
Average latencies of the W and M judgements relative to the recorded button press will be calculated for each participant. Outliers (greater than two standard deviations from participants' mean values) will be excluded.

fMRI correlates
A windows of 1 second prior to the recorded button press will be selected as events of interest for the fMRI analysis. Intention versus movement trials will be contrasted at the participant level, and then qill be subsequently inputted into a paired-sample t-test to compare pre and post effects. Pre-selected ROIs will include the pre-SMA, inferior parietal lobule, and dorsolateral prefrontal cortex (see Baek *et al.*[42]).

Heartbeat tracking task
Time estimation accuracy will subsequently be calculated using the following formula:

$$1/4 \sum [(1 - (|\text{actual seconds} - \text{perceived seconds}| / \text{actual seconds})$$

Interoceptive accuracy will subsequently be calculated using the following formula:

$$1/4 \sum [(1 - (|\text{actual heart-beats} - \text{perceived heart-beats}| / \text{actual heart-beats})$$

Study and intervention feasibility parameters
Feasibility parameters will be assessed using descriptive statistics and confidence intervals. We will assess the rate of consent of eligible patients, study retention, loss to follow-up, the acceptability of psilocybin and deviations from study protocol. Confidence intervals will be estimated where appropriate.

Participant demographic and clinical characteristics will be summarised at baseline. Patterns of missing data or nonattendance will be described for the outcome at measurement time- points and reasons for drop-out. Statistics derived will be means and standard deviations or medians, minimum, maximum, and interquartile range for continuous measures.

End of study
The study is expected to be open for recruitment for two years. The total duration of a participant's involvement in the study will vary between 15 and 22 weeks, dependent on the length of the (clinically flexible) Screening & Preparation Phase. The follow up of participants will last for 3 months after the Dosing Visit. Ongoing care for participants will be handed over to primary or secondary care teams after this time.

Data sharing
All shareable study data, including sharable neuroimaging data, will be uploaded to an online sharing platform hosted by King's College London.

Discussion
This study will likely be the first in the modern era to administer psychedelics to people with FND. The primary aim is to assess functional neuroimaging changes following psychedelic administration. This may help us to further understand the complex pathophysiology underpinning FND, which is currently poorly understood[5]. Additional putative mechanistic aspects of FND, such as dissociation, interoception, and agency will also be explored, and administration of psilocybin will allow us to probe whether these are modifiable targets.

Drug-facilitated therapy is current under review for a number of neuropsychiatric disorders, and there has been some emerging evidence that people with FND may respond to (es)ketamine therapy, which sometimes includes a psychotherapeutic component[133–135]. Response may be based on the ability of ketamine to disrupt brain networks or modify the top-down priors implicated in the disorder.

Pharmacological therapies are generally not specifically recommended for FND, however drug facilitated psychological[15] and physiotherapeutic[14] interventions do have a small evidence base in the disorder. The present study is not equipped to answer clinical questions about the efficacy of psychedelics; however, it may offer preliminary information about whether drug-facilitated psychotherapy is safe and feasible in this patient population.

Data availability
No data are associated with this article.

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Open Peer Review

Current Peer Review Status: ✔ ✔ ? ✔

Version 2

Reviewer Report 10 May 2025

https://doi.org/10.21956/wellcomeopenres.26488.r122471

✔ **Manesh Girn**
Department of Neurology, University of California San Francisco, San Francisco, CA, USA

The authors have thoughtfully addressed my comments. I believe the manuscript is now suitable for indexed.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: functional neuroimaging/fMRI, large-scale brain networks, static and dynamic functional connectivity analyses, psychedelic neuroimaging, default mode network

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 24 April 2025

https://doi.org/10.21956/wellcomeopenres.26488.r122474

✔ **Manoj Doss**
Department of Psychiatry and Behavioral Sciences, The University of Texas at Austin Dell Medical School, Austin, USA

The authors have addressed my concerns, and I approve it now.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 02 October 2024

https://doi.org/10.21956/wellcomeopenres.24838.r96127

Rayyan Zafar
Imperial College London, London, UK

This protocol justifies and sets out the rationale for investigating psilocybin's effects on Functional Neurological Disorder (FND). The justification is warranted and comes off the back of a mechanistically informed hypothesis linked to proposed amelioration of neurobiological deficits found in FND.

There are a few minor points/suggestions that could be incorporated which I list below:

Additional biomarker integration
While the study primarily focuses on neuroimaging and behavioral measures, additional biomarkers may be considered. Current research suggests that biomarkers such as inflammatory markers, or hormonal fluctuations could offer additional insights into how psilocybin affects systemic processes. For example, psychedelics have been shown to modulate immune system activity, including reductions in inflammatory cytokines, which may have relevance to FND's psychoneuroimmunology model. Including exploratory biomarker analyses could provide a more holistic understanding of psilocybin's effects. Additionally, inclusion of digital wearables that measure heart rate variability and other autonomic functions may also provide additional insight into the systemic mechanisms of action of psilocybin therapy which may also be core to FND symptomology. Integrating EEG alongside fMRI, could also be done at the same time points and under acute administration to understand effects related to entropy (which was discussed as an exploratory endpoint)

Gender-specific responses
Emerging evidence suggests that gender and hormonal fluctuations may influence responses to psychedelics. This could be particularly important in FND, which disproportionately affects women. Hormonal differences, including those related to menstrual cycles or menopause, could impact serotonergic activity, which plays a crucial role in psilocybin's effects. The study would benefit from incorporating exploratory analyses of gender-specific responses, potentially tracking hormonal phases in female participants. This could contribute to more personalized treatment approaches for FND.

Longer follow-up for clinical and fMRI observations
The current follow-up period of one week for fMRI scanning may miss long-term functional/structural changes induced by psilocybin. Research indicates that neuroplasticity, particularly in network connectivity, can occur up to 4 weeks post-dosing. Extending the follow-up to 4 weeks or further would allow for a more comprehensive understanding of psilocybin's longer-term effects on brain connectivity/function in FND. Also extending clinical follow up beyond 3 months is also important to understand the longer-term effects on core clinical symptoms. Expanding neuroimaging targets to include networks beyond the DMN, such as the salience network and central executive network, which have been implicated in both FND and psychedelic studies. Also to include DTI analysis as additional to resting state connectivity as Imperial College have data to suggest structural brain changes 4 weeks following a single administration of psilocybin is psychedelic naïve healthy participants in the thalamocortical tracts.

Psychological support
'Depending on participant needs we will arrange additional sessions for psychological preparation and integration as required.' This could induce variability if the primary outcome is powered for imaging, it would be useful to know the parameters under which additional psychological support would be administered. Additionally, there is very limited detail of what will happen in the 3 preparation session and 4 integration session, you mention these are nonspecific to FND but could you clarify in more detail what the aims/objectives of these sessions are. Also, what is the plan for the patients post study, if you are to follow them up would they be receiving treatment as usual?

Additional scales to consider:
- Watts connectedness scale
- BEAQ (brief experiential avoidance questionnaire)
- EBI (Emotional breakthrough inventory)
- Psychological Insight scale (PIS) Peill et al
- STAR – Scale to assess therapeutic relationships
- Unpleasant Psychedelic Experience Scale (UPES) score
- Geneva Emotional Music Scales (GEMS) scores
- Early Prognostic Predictor Scale (EPPS) total score
- Imperial psychedelic predictor scale (IPPS)
- Setting questionnaire

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Partly

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Neuropsychopharmacology, Psychedelic research, fMRI

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 19 Mar 2025

Matt Butler

Many thanks for your helpful comments which we think have improved the quality of the protocol. We have addressed your suggestions below:

1.While the study primarily focuses on neuroimaging and behavioral measures, additional biomarkers may be considered. Current research suggests that biomarkers such as inflammatory markers, or hormonal fluctuations could offer additional insights into how psilocybin affects systemic processes. For example, psychedelics have been shown to modulate immune system activity, including reductions in inflammatory cytokines, which may have relevance to FND's psychoneuroimmunology model. Including exploratory biomarker analyses could provide a more holistic understanding of psilocybin's effects. Additionally, inclusion of digital wearables that measure heart rate variability and other autonomic functions may also provide additional insight into the systemic mechanisms of action of psilocybin therapy which may also be core to FND symptomology. Integrating EEG alongside fMRI, could also be done at the same time points and under acute administration to understand effects related to entropy (which was discussed as an exploratory endpoint) Thank you for these suggestions, which are all pertinent to the neurobiology of FND. Whilst analysis of serum biomarkers would certainly be interesting, we do not feel we have the expertise as a study team to complete these. We have not included wearable technologies due to previous difficulties we have had in securing institutional approval for their use. The addition of EEG would be interesting, but perhaps not feasible both in terms of study cost and participant burden.

2. Emerging evidence suggests that gender and hormonal fluctuations may influence responses to psychedelics. This could be particularly important in FND, which disproportionately affects women. Hormonal differences, including those related to menstrual cycles or menopause, could impact serotonergic activity, which plays a crucial role in psilocybin's effects. The study would benefit from incorporating exploratory analyses of gender-specific responses, potentially tracking hormonal phases in female participants. This could contribute to more personalized treatment approaches for FND. We agree with the suggestion to conduct exploratory analyses of gender-specific responses. The sample size is likely too small to render any hormonal or cycle tracking useful. We do however support the notion in general that gender and hormonal factors are likely to be fruitful avenues of exploration in both FND and psychedelics in future.

3. The current follow-up period of one week for fMRI scanning may miss long-term functional/structural changes induced by psilocybin. Research indicates that neuroplasticity, particularly in network connectivity, can occur up to 4 weeks post-dosing. Extending the follow-up to 4 weeks or further would allow for a more comprehensive understanding of psilocybin's longer-term effects on brain connectivity/function in FND. Also extending clinical follow up beyond 3 months is also important to understand the longer-term effects on core clinical symptoms. Thanks for the helpful suggestions. We considered (and had originally planned) a third fMRI at a later follow-up date, however due to time and financial constraints of this project, we will be unable to do this. Likewise with clinical follow-ups after 3-months.

4. Expanding neuroimaging targets to include networks beyond the DMN, such as the salience network and central executive network, which have been implicated in both FND and psychedelic studies. Also to include DTI analysis as additional to resting state connectivity as Imperial College have data to suggest structural brain changes 4 weeks following a single administration of psilocybin is psychedelic naïve healthy participants in the thalamocortical tracts. Based on this suggestion and those from other reviewers, we have expanded our neuroimaging regions of interest beyond the DMN to include e.g. some implicated in the salience network, such as the insulae and anterior cingulate cortices.

5. 'Depending on participant needs we will arrange additional sessions for psychological preparation and integration as required.' This could induce variability if the primary outcome is powered for imaging, it would be useful to know the parameters under which additional psychological support would be administered. Additionally, there is very limited detail of what will happen in the 3 preparation session and 4 integration session, you mention these are nonspecific to FND but could you clarify in more detail what the aims/objectives of these sessions are. Also, what is the plan for the patients post study, if you are to follow them up would they be receiving treatment as usual? Although full discussion of the details of the therapy is beyond the scope of the paper, we have included an additional reference for further reading. We have included a sentence to qualify that additional sessions would only be used in unforeseen extenuating circumstances. The plan for patients post-study is mentioned in the 'End of Study' section.

6. Additional scales to consider: Watts connectedness scale BEAQ (brief experiential avoidance questionnaire) EBI (Emotional breakthrough inventory) Psychological Insight scale (PIS) Peill et al STAR – Scale to assess therapeutic relationships Unpleasant Psychedelic Experience Scale (UPES) score Geneva Emotional Music Scales (GEMS) scores Early Prognostic Predictor Scale (EPPS) total score Imperial psychedelic predictor scale (IPPS) Setting questionnaire Thanks for these suggestions. After discussion with our PPI panel, we have now included: Watts Connectedness Scale Emotional Breakthrough Inventory (also suggested by another reviewer) Psychological Insight Scale Imperial psychedelic predictor scale We were unable to find the unpleasant psychedelic experiences scale, the early prognosis predictor scale, and the setting questionnaire. We felt the Geneva Emotional Music Scale went beyond the scope of this protocol. We have also decided not to include the STAR-C scale.

Competing Interests: No competing interests were disclosed.

Reviewer Report 22 September 2024

https://doi.org/10.21956/wellcomeopenres.24838.r95501

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Lorenzo Pasquini
Department of Neurology, University of California, San Francisco, USA

Butler and colleagues propose an open-label clinical in 24 patients with FND to explore potential medium-term mechanisms as well as clinical improvements of 25 mg psilocybin. Overall, the relevance of the problem is clear, and the study design is well described.

I have following comments which I would like to bring to the attention of the authors:

1. Altered interoception is a potential mechanism proposed to be involved in FND and impacted by psilocybin. In this case, the neuroimaging analyses should not only focus on the DMN, but also on the Salience Network, which has been shown to play an important role in interoceptive processes (see Critchley Nat Neurosci 2004 and Seeley JNuerosci 2019).

2. A rationale for using a single dose of 25 mg psilocybin should be provided (vs for example, multiple dosing or lower doses).

3. I would strongly encourage the authors to also acquire multi-shell DTI to map structural connectivity (see also Perez Neuroimage Clinical 2021)

4. The heart beating counting task has several important limitations, notably that participants know they should have about 60 beats/min. A more sophisticated experimental design is needed to accurately measure interoception, where participants are asked to press a button or to blink each time they think they are having a heartbeat. This behavior should be recorded in sync with the EKG. See for example work by Sarah Garfinkel and Hugo Critchley, as well as by Agustin Ibañes

5. Will the interviews be recorded?

6. A description of the planned statistical analysis is needed (e.g., paired t-test, significance level, correction for multiple comparisons for fMRI, etc.).

7. For fMRI analyses, if interoception is of interest, it may help to add the insula

8. I have a major concern regarding the documentation of adverse events. It is unclear from

the study description how adverse events will be collected and how often. For example, it is unclear at which precise time points EKG and pulse will be collected. More details are needed.

9. Another important point is related to screening procedures. Since common symptoms in FND include movement/loss of balance and non-epileptic seizures, it would be important to screen and longitudinally follow participants for fall risk (e.g. using STEDI), as well as ensure through an EEG the absence of epileptic seizures.

10. A final important point relates to the assessment of comorbidities. More details are needed on how patients will be screened for severe depression (threshold used), but also for anxiety and fibromyalgia, to accurately describe the heterogeneity of the disorder

11. Will only psychedelic-naïve participants be recruited? If not, how many previous psychedelics experiences are allowed and how close to screening?

12. The authors should specify whether fMRI analyses will involve global signal regression or not (or both) and describe approaches to mitigate the effects of head movement in the scanner. Levels of sleepiness and anxiety should be assessed after each scan.

13. Will any data be publicly available, e.g. on neuroimaging repositories?

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Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

No

Are the datasets clearly presented in a useable and accessible format?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Neuroimaging, autonomic physiology, psychedelics, interoception, fMRI, neurodegenerative diseases

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 19 Mar 2025

Matt Butler

Many thanks for your helpful comments which we think have improved the quality of the protocol. We have addressed your suggestions below:

1.Altered interoception is a potential mechanism proposed to be involved in FND and impacted by psilocybin. In this case, the neuroimaging analyses should not only focus on the DMN, but also on the Salience Network, which has been shown to play an important role in interoceptive processes (see Critchley Nat Neurosci 2004 and Seeley JNuerosci 2019). Based on this comment, and those of other reviewers, we have now included regions which constitute the salience network, for example the insula and the anterior cingulate cortex.

2. A rationale for using a single dose of 25 mg psilocybin should be provided (vs for example, multiple dosing or lower doses). An expanded rationale for choosing 25 mg psilocybin has been included.

3. I would strongly encourage the authors to also acquire multi-shell DTI to map structural connectivity (see also Perez Neuroimage Clinical 2021) While we agree that structural connectivity is a potentially sensitive metric, in this particular study we have decided not to include it for the following reasons: We do not have a non-FND control group to compare to There is little information of short-term psychedelic (or any drug effects) on streamlines Our scan time is limited by feasibility and it will not be possible to add in a full multi-shell DTI sequence for structural connectivity.

4. The heart beating counting task has several important limitations, notably that participants know they should have about 60 beats/min. A more sophisticated experimental design is needed to accurately measure interoception, where participants are asked to press a button or to blink each time they think they are having a heartbeat. This behavior should be recorded in sync with the EKG. See for example work by Sarah Garfinkel and Hugo Critchley, as well as by Agustin Ibañes We accept that the HTT does have its limitations, some of which have been pointed out here. Of note, this version of the HTT is a quick and acceptable measure that involves minimal burden on the patient. In the context of this study, this is a benefit, given everything else the participants are being asked to do. Of note, I don't think we can take it for granted that most people assume their heartrate is

around 60 bpm. There is a likely to be a larger range in both true heartbeat and estimation which ranges from say 50-100bpm. In this HTT we will explicitly remind participants not to count seconds, and the trials are varied in length. We will also include the TET which will allow us to see how accurate people are at estimating the passage of time.

5. Will the interviews be recorded? We have clarified that the sessions will be audio recorded using Microsoft Teams and stored on a secure cloud server. 3.06 A description of the planned statistical analysis is needed (e.g., paired t-test, significance level, correction for multiple comparisons for fMRI, etc.). This section has now been updated.

7. For fMRI analyses, if interoception is of interest, it may help to add the insula We have now included plans to focus on the insula based on this comment and those from other reviewers.

8. I have a major concern regarding the documentation of adverse events. It is unclear from the study description how adverse events will be collected and how often. For example, it is unclear at which precise time points EKG and pulse will be collected. More details are needed. We have added further context to the recording and reporting of adverse events. Recording of all adverse events will take place at every participant contact/visit. Please note this has been approved by a REC review. The frequency of e.g. ECG and vital signs are in Fig 2. We have also expanded in the main text which tests are to be undertaken at screening.

9. Another important point is related to screening procedures. Since common symptoms in FND include movement/loss of balance and non-epileptic seizures, it would be important to screen and longitudinally follow participants for fall risk (e.g. using STEDI), as well as ensure through an EEG the absence of epileptic seizures. All participants with functional seizures will have their diagnosis confirmed by a neurologist or expert neuropsychiatrist (this is a requirement for the study). Often this will have included a video EEG. The falls risk point does not to use represent something that needs to be covered specifically for this study, but of course is something clinicians will take into account when screening.

10. A final important point relates to the assessment of comorbidities. More details are needed on how patients will be screened for severe depression (threshold used), but also for anxiety and fibromyalgia, to accurately describe the heterogeneity of the disorder Psychiatric disorders will be screened for via The Mini-International Neuropsychiatric Interview. We will record co-morbid diagnoses at screening.

11. Will only psychedelic-naïve participants be recruited? If not, how many previous psychedelics experiences are allowed and how close to screening? Please see exclusion criterion 20: “Use of any psychedelic substances >2 times in past 12 months.” In practice we would not be recruiting participants with frequent or very recent psychedelic use. And our data on self management (Butler et al. 2022)

12. The authors should specify whether fMRI analyses will involve global signal regression or not (or both) and describe approaches to mitigate the effects of head movement in the scanner. Levels of sleepiness and anxiety should be assessed after each scan. The primary

analysis will not include global signal regression because of the issues raised and its covariance.

13. Will any data be publicly available, e.g. on neuroimaging repositories? We have now stated that all shareable study data, including sharable neuroimaging data, will be uploaded to an online sharing platform hosted by King's College London.

Competing Interests: No competing interests were disclosed.

Reviewer Report 17 September 2024

https://doi.org/10.21956/wellcomeopenres.24838.r96124

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Manoj Doss
Department of Psychiatry and Behavioral Sciences, The University of Texas at Austin Dell Medical School, Austin, USA

Butler et al. describe the procedures for a future study on the effects of psilocybin on brain function (as measured with fMRI), as well as clinical outcomes, in functional neurological disorder (FND). The overall design and methods are fairly straightforward. My main concern is that some of the background literature doesn't really support the hypotheses proposed here, which seem to be more specific to narratives in psychedelic research rather than a bridge between idiosyncratic psychedelic effects and abnormalities in FND.

Below are my specific points:

1) Fourth paragraph of the Introduction, the predictive processing section is rather non-specific. In general, the predictive processing framework has become a bit of a catch-all for every disorder and every drug effect.

2) First paragraph of Mechanistic evidence in FND, "*People with FND have shown increased connectivity in brain regions which comprise the default mode network (DMN), such as the medial prefrontal cortex and posterior cingulate cortex (PCC), both in resting-state and task based paradigms* [19–25]." I only skimmed these references, but I think this claim is largely unsupported. Reference 19 didn't find increased FC within the DMN but rather increased FC between motor cortex and DMN regions. Reference 20 didn't look at FC. Reference 21 didn't find increased FC among DMN regions. Reference 22 also didn't look at FC. Reference 23 yet again didn't look at FC. Reference 24, which was a SPECT study (and thus difficult to look at FC), didn't look at FC, and they found *less* activity in the DMN. Reference 25 didn't look at FC. Given that much of this proposal relies on the DMN, the lack of DMN evidence is rather problematic. Some (but not all) of the studies above found changes in vmPFC activation (though they might not all have been directionally consistent), so it might be

easier to focus on vmPFC or other specific brain areas (that may not necessarily be part of the DMN).

3) Third paragraph of Current psychedelic research, "*Modern psychedelic research involves non-directive psychological support[39,40,56,57], in which the therapeutic relationship between participant and therapist is of central importance[58].*" The importance of the patient-therapist relationship to psychedelic therapy is currently conjecture, and reference 58 is not exactly the most evidence-based text. Likewise, "*At doses of 25mg psilocybin, participants may have transient psychologically-challenging experiences[59], however psychological preparation can mitigate these…*" Again, I'm not sure there's good evidence yet for the degree to which preparation can influence challenging experiences. I think more nuanced language is needed for these assumptions that are at times taken as fact in psychedelic research.

4) First paragraph of Mechanistic effects of psychedelics, "*The extent of reduction in connectivity correlates with self-reported degree of loss of selfhood ('ego-dissolution')[63].*" This effect has yet to replicate, and in a study with a larger *N* and less motion artifacts, the correlation between attenuated DMN FC and ego dissolution was basically non-existent at r = .06 (https://doi.org/10.1016/j.nicl.2018.03.005)[1]. Moreover, "*Functional neuroimaging in psychedelics have shown relatively consistent effects of decreases in within-network-connectivity and increases in between-network-connectivity in canonical brain networks including the DMN[64].*" These findings are not really that consistent when one considers the specific networks impacted (again see https://doi.org/10.1016/j.nicl.2018.03.005[1] for the lack of agreement between which 2 specific networks increased their FC across 3 studies).

5) Second paragraph of Mechanistic effects of psychedelics, "*Loosened global network connectivity may enable improvement of neuropsychiatric symptoms by reducing the influence of top-down processing and loosening established prediction errors[66].*" I'm not sure what is meant by "*loosening established prediction errors*." Moreover, while within-network FC under psychedelics is reduced (under resting-state conditions), there are increases in between-network FC with at least one study finding increases between the DMN and SM networks (https://doi.org/10.1073/pnas.2218949120)[2]. Given that reference 19 mentions that there are increases in FC between motor cortex and the DMN in FND, I'm not sure how to reconcile these two sets of findings.

Another issue is that these are acute effects. If one turns to the literature on persisting resting-state effects of psychedelics on FC, then it is unclear what the implications are for FND, as the effects are rather unreliable such as increases in DMN FC (https://doi.org/10.1038/s41598-017-13282-7)[3], decreases in DMN FC (https://doi.org/10.1177/0269881120909409[4], https://doi.org/10.1016/j.neuroimage.2019.04.009[5]), no impact on DMN FC (https://doi.org/10.1038/s41398-021-01706-y)[6], and even both increase and decreases in DMN FC dependent on the analysis (https://doi.org/10.1038/s41591-022-01744-z)[7], though perhaps these inconsistencies in DMN FC have little bearing on FND considering the above cited studies in which DMN FC is rarely impacted in FND.

6) If the researchers' interest is in the DMN, why not probe function known to be supported by the DMN such as episodic memory, semantic memory, future simulation, theory of mind, or even attentional tasks with inappropriate DMN engagement that is thought to support mind wandering?

7) Regarding the endpoints, if one's interest is in intrinsic FC (i.e., what resting-state neuroimaging aims to capture), then resting-state analyses of the task-based data should produce similar results. That is, if one is attempting to capture a general scaffolding of functional brain activity, then it should be largely insensitive to task manipulations, and if these effects are abolished by some stimuli and button presses, then what was being measured wasn't intrinsic in the first place. It's possible that the variability in cognitive operations of the resting-state is a likely culprit for the unreliable acute and post-acute effects of psychedelics, as well as the unreliability in various disorders (e.g., large studies finding both increases and decreases in DMN FC in depression, https://doi.org/10.1001/jamapsychiatry.2015.0071[8], https://doi.org/10.1073/pnas.1900390116[9]). Finding similar post-acute effects of psychedelics on FC under diverse cognitive constraints would provide stronger support that these FC changes are reliable markers. Analyzing task-based data with resting-state analyses is something that has been done (e.g., https://doi.org/10.1073/pnas.1608819113)[10], can improve predictive models (e.g., https://doi.org/10.1038/nn.4179)[11], and has been advocated for (e.g., https://doi.org/10.1016/j.tics.2021.09.005)[12].

8) First bullet point of Hypotheses under investigation, "*The direction of change will be towards that of healthy controls (Figure 1).*" Without a matched control group, it'll be hard to determine this. Moreover, I'm not sure how Figure 1 is related to this point.

9) It's a bit odd that this manuscript discusses how DMN FC is increased in FND, yet the effect that is used to justify the sample size is an increase in FC following psilocybin therapy (i.e., reference [76]).

10) Resting-state scans with eyes closed can be problematic, as participants might fall asleep. In a fairly large study with eyes open conditions, >40% of participants reported falling asleep (https://doi.org/10.1016/j.jad.2019.07.066)[13], a number that could be potentially larger when one considers that people do not always realize that they fall asleep, and some participants may have not wanted to upset researchers. Thus, with eye-closed conditions, it's not impossible that up to 50% of participants could fall asleep. I'd recommend a fixation cross instead or even the Inscapes video, as it better standardizes the perceptual input (though not necessarily the cognitive operations) across participants.

11) There doesn't seem to be much information on the plan for analyzing the task-based data.

12) Regarding the follow-up, it might be worth examining a later time-point (e.g., 1 year) for clinical assessments, as one issue raised in regarding the recent rejection of MDMA therapy was that the trials didn't have longer term follow-ups.

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Is the rationale for, and objectives of, the study clearly described?

Partly

Is the study design appropriate for the research question?

Partly

Are sufficient details of the methods provided to allow replication by others?

Partly

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Psychedelics

I confirm that I have read this submission and believe that I have an appropriate level of

expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 19 Mar 2025

Matt Butler

Many thanks for your helpful comments which we think have improved the quality of the protocol.

We have addressed your suggestions below:

Comment: 2.01 Fourth paragraph of the Introduction, the predictive processing section is rather non-specific. In general, the predictive processing framework has become a bit of a catch-all for every disorder and every drug effect.

Response: Thank you. Based on this comment and those from other reviewers we have removed mention of the predictive processing framework.

Comment: 2.02 First paragraph of Mechanistic evidence in FND, “People with FND have shown increased connectivity in brain regions which comprise the default mode network (DMN), such as the medial prefrontal cortex and posterior cingulate cortex (PCC), both in resting-state and task based paradigms19–25.” I only skimmed these references, but I think this claim is largely unsupported. Reference 19 didn’t find increased FC within the DMN but rather increased FC between motor cortex and DMN regions. Reference 20 didn’t look at FC. Reference 21 didn’t find increased FC among DMN regions. Reference 22 also didn’t look at FC. Reference 23 yet again didn’t look at FC. Reference 24, which was a SPECT study (and thus difficult to look at FC), didn’t look at FC, and they found less activity in the DMN. Reference 25 didn’t look at FC. Given that much of this proposal relies on the DMN, the lack of DMN evidence is rather problematic. Some (but not all) of the studies above found changes in vmPFC activation (though they might not all have been directionally consistent), so it might be easier to focus on vmPFC or other specific brain areas (that may not necessarily be part of the DMN).

Response: Based on this comment and those from other reviewers we have removed explicit mention of the DMN and are instead focussing on specific regions from the FND and psychedelic literature (such as the mPFC).

Comment: 2.03 Third paragraph of Current psychedelic research, “Modern psychedelic research involves non-directive psychological support39,40,56,57, in which the therapeutic relationship between participant and therapist is of central importance58.” The importance of the patient-therapist relationship to psychedelic therapy is currently conjecture, and reference 58 is not exactly the most evidence-based text. Likewise, “At doses of 25mg psilocybin, participants may have transient psychologically-challenging experiences59, however psychological preparation can mitigate these…” Again, I’m not sure there’s good evidence yet for the degree to which preparation can influence challenging experiences. I think more nuanced language is needed for these assumptions that are at times taken as fact in psychedelic research.

Response: Thanks for bringing up this discussion, which is an active topic in the psychedelic research literature at the moment. Although we agree conclusive evidence for the psychological component is currently not available, it is, in our opinion, the safest course of action for a study such as this. We'd welcome further exploration in other studies. We have toned down the language as suggested.

Comment: 2.04 First paragraph of Mechanistic effects of psychedelics, "The extent of reduction in connectivity correlates with self-reported degree of loss of selfhood ('ego-dissolution')63." This effect has yet to replicate, and in a study with a larger N and less motion artifacts, the correlation between attenuated DMN FC and ego dissolution was basically non-existent at r = .06 (https://doi.org/10.1016/j.nicl.2018.03.005)1. Moreover, "Functional neuroimaging in psychedelics have shown relatively consistent effects of decreases in within-network-connectivity and increases in between-network-connectivity in canonical brain networks including the DMN64." These findings are not really that consistent when one considers the specific networks impacted (again see https://doi.org/10.1016/j.nicl.2018.03.0051 for the lack of agreement between which 2 specific networks increased their FC across 3 studies).

Response: We have now removed the sentence on correlation with ego dissolution and have toned down the language on the DMN.

Comment: 2.05 Second paragraph of Mechanistic effects of psychedelics, "Loosened global network connectivity may enable improvement of neuropsychiatric symptoms by reducing the influence of top-down processing and loosening established prediction errors66." I'm not sure what is meant by "loosening established prediction errors." Moreover, while within-network FC under psychedelics is reduced (under resting-state conditions), there are increases in between-network FC with at least one study finding increases between the DMN and SM networks (https://doi.org/10.1073/pnas.2218949120)2. Given that reference 19 mentions that there are increases in FC between motor cortex and the DMN in FND, I'm not sure how to reconcile these two sets of findings.

Response: Given we have now removed mention of the predictive processing theory of FND, we have also removed the parts quoted in this suggestion.

Comment: 2.06 Another issue is that these are acute effects. If one turns to the literature on persisting resting-state effects of psychedelics on FC, then it is unclear what the implications are for FND, as the effects are rather unreliable such as increases in DMN FC (https://doi.org/10.1038/s41598-017-13282-7)3, decreases in DMN FC (https://doi.org/10.1177/02698811209094094, https://doi.org/10.1016/j.neuroimage.2019.04.0095), no impact on DMN FC (https://doi.org/10.1038/s41398-021-01706-y)6, and even both increase and decreases in DMN FC dependent on the analysis (https://doi.org/10.1038/s41591-022-01744-z)7, though perhaps these inconsistencies in DMN FC have little bearing on FND considering the above cited studies in which DMN FC is rarely impacted in FND.

Response: We agree there is a lot of inconsistency in these findings and this is part of our

reasoning to move away from limiting our hypotheses to the DMN. As a caveat, however, these studies generally pertain to the acute effects of psychedelics, something that we are not looking at in this study.

Comment: 2.07 If the researchers' interest is in the DMN, why not probe function known to be supported by the DMN such as episodic memory, semantic memory, future simulation, theory of mind, or even attentional tasks with inappropriate DMN engagement that is thought to support mind wandering?

Response: Thanks for these suggestions. We have now toned down our emphasis on probing the DMN. Many of these functions would only be indirectly associated with FND (except perhaps for measures of attention).

Comment: 2.08 Regarding the endpoints, if one's interest is in intrinsic FC (i.e., what resting-state neuroimaging aims to capture), then resting-state analyses of the task-based data should produce similar results. That is, if one is attempting to capture a general scaffolding of functional brain activity, then it should be largely insensitive to task manipulations, and if these effects are abolished by some stimuli and button presses, then what was being measured wasn't intrinsic in the first place. It's possible that the variability in cognitive operations of the resting-state is a likely culprit for the unreliable acute and post-acute effects of psychedelics, as well as the unreliability in various disorders (e.g., large studies finding both increases and decreases in DMN FC in depression, https://doi.org/10.1001/jamapsychiatry.2015.00718, https://doi.org/10.1073/pnas.19003901169). Finding similar post-acute effects of psychedelics on FC under diverse cognitive constraints would provide stronger support that these FC changes are reliable markers. Analyzing task-based data with resting-state analyses is something that has been done (e.g., https://doi.org/10.1073/pnas.1608819113)10, can improve predictive models (e.g., https://doi.org/10.1038/nn.4179)11, and has been advocated for (e.g., https://doi.org/10.1016/j.tics.2021.09.005)12.

Response: While we take into account the comments on the connectivity patterns across a task, which may yield similar results as the resting state, we would see this as a post-hoc analysis of the task fMRI data. To this end, we will conduct an exploratory replication analysis of the task data, but analysed in the same manner as the resting state (including task regressors).

Comment: 2.09 First bullet point of Hypotheses under investigation, "The direction of change will be towards that of healthy controls (Figure 1)." Without a matched control group, it'll be hard to determine this. Moreover, I'm not sure how Figure 1 is related to this point.
Response: Apologies, we mentioned fig 1 in error. Reference has been removed from the sentence.

Comment: 2.10 It's a bit odd that this manuscript discusses how DMN FC is increased in FND, yet the effect that is used to justify the sample size is an increase in FC following psilocybin therapy (i.e., reference 76).

Response: Thanks for this point which further illustrates the complexities of the literature. The narrative we had been building was around acute effects on DMN connectivity (not longer-term effects, as shown in this paper). Nevertheless, this narrative has now been removed, We have stuck with this measure as an (imperfect) means of calculating sample size given our ongoing desire to assess network connectivity of the mPFC.

2.11 Resting-state scans with eyes closed can be problematic, as participants might fall asleep. In a fairly large study with eyes open conditions, >40% of participants reported falling asleep (https://doi.org/10.1016/j.jad.2019.07.066)13, a number that could be potentially larger when one considers that people do not always realize that they fall asleep, and some participants may have not wanted to upset researchers. Thus, with eye-closed conditions, it's not impossible that up to 50% of participants could fall asleep. I'd recommend a fixation cross instead or even the Inscapes video, as it better standardizes the perceptual input (though not necessarily the cognitive operations) across participants.

Response: We have updated the methods to specify that we will be using a fixation cross or the animation video during the rs-fMRI.

Comment: 2.12 There doesn't seem to be much information on the plan for analyzing the task-based data.

Response: This section has been updated to include further information on analysing the task-based data (both the timings and the fMRI results).

Comment: 2.13 Regarding the follow-up, it might be worth examining a later time-point (e.g., 1 year) for clinical assessments, as one issue raised in regarding the recent rejection of MDMA therapy was that the trials didn't have longer term follow-ups.

Response: Thanks for this suggestion, which has also been raised by other reviewers. Given the time and financial constraints of this study, a 1-year follow-up unfortunately won't be feasible. As this study is not a clinical trial, the results cannot form part of any licencing decisions.

Competing Interests: No competing interests were disclosed.

Reviewer Report 12 September 2024

https://doi.org/10.21956/wellcomeopenres.24838.r93854

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The present manuscript proposes a study protocol for a mechanistic study that applies functional magnetic resonance imaging (fMRI) and a battery of psychometric assessments to assess the mechanisms by which psilocybin might help treat functional neurological disorders (FND). It aims to both help illuminate the mechanisms underlying FND and its potential alleviation, while simultaneously assessing whether psychedelic administration is safe and well-tolerated by this patient population. Resting-state fMRI analyses are centered primarily on regions of interest that overlap with the default mode network, and task-based fMRI analyses are aimed at assessing changes in the neural underpinnings of motor agency.

Overall, this an important preliminary study on a novel indication for psilocybin therapy and has strong potential to yield valuable mechanistic and clinical insights. That said, there are a few things the authors might want to consider in terms of their specific analyses and hypotheses.

- The authors state that "a representative sample of motor and seizure subtypes will be sought for inclusion". However, the majority of the narrative, cited research, and focus seems to be biased towards functional motor disorders. Indeed, there is no explicit mention of functional seizures throughout. Moreover, there is no explicit mention of existing overarching theoretical models for the neurobiology of either.
    - Do the authors assume that the pathophysiology is the same for both of these conditions?
    - Might it be better to have distinct theoretically and empirically motivated hypotheses for each?
    - For example, in our recent paper (https://doi.org/10.1177/02698811241248395) Lewis *et al*.(2024[1]) we outline hypotheses and fMRI empirical directions for functional seizures in particular based on past theoretical models and findings (e.g., the Integrated Cognitive Model).
- Relatedly, the authors describe predictive processing but don't clearly offer an explanation as to why the intended analyses/hypotheses are consistent with or might shed light on this perspective on FND.
- Moreover, the mechanistic hypotheses as currently articulated are relatively non-specific and not clearly motivated. More specific hypotheses and explicit rationales for the regions of interest chosen for the seed-based analyses, and for the analyses conduced for the motor agency task, would be ideal.
    - Greater explicit reference to previous theoretical models (of FND mechanisms and/or psilocybin therapeutic mechanisms) to support the hypotheses/ROI selection would also be a strength.
- The authors could have also provided much more detail on the specific statistical/analytical approaches that will be conducted for the seed-based analyses (e.g., as pertains to cluster correction/multiple comparison correction, how the coordinates of ROIs will be determined, etc.).
- Furthermore, the papers cited in support of the idea that the DMN is of central importance for FND (15, 19-25) do not clearly support focusing on this network over others. Several papers highlight the ventromedial prefrontal cortex in particular, but I do not see compelling evidence that the DMN per se is critical. A large literature highlights the VMPFC's role in action selection and decision making – might that role be of particular importance, as opposed to its membership in the DMN per se?
    - It also should be emphasized that the link between the DMN and psychedelic ego

dissolution is far from unequivocal, and psychedelic mechanisms cannot be primarily attributed to the DMN based on existing empirical evidence, strictly speaking. A more distributed, dynamic, multi-network explanation is likely more apt (e.g., as we have argued in Girn *et al.* (2023[2]), *Trends in Cognitive Science*).
    - In addition, given the emphasis on interoceptive awareness, somatic signalling, and agency/body ownership, the insula presents itself as an essential region of interest for seed-based analyses.
    - Motor cortex functional connectivity would also presumably be of particular interest, as it has been previously implicated in FND (e.g., *J Neurology Neurosurgery Psychiatry,* Diez *et al. (*2019[3]); *Molecular Psychiatry,* Diez *et al*. (2021[4])).
- Although perhaps more advanced and exploratory, the authors might consider dynamic functional connectivity analyses, such as those which seek to estimate brain states and their dynamic evolution to characterize neural changes related to FND (e.g., see *Network Neuroscience,* Lurie *et al.* (2020[5])).
    - Indeed, FND is a dynamic condition in which symptoms seem to occur in a quasi-periodic fashion (e.g., seizure episodes or dystonic movements), and which therefore might exhibit pathophysiology particularly in the way in which the brain traverses dynamic interactions between networks (i.e., in the dynamic changes within a scan rather than the average across the scan as a whole).
        - E.g., there may be less time spent in patterns exhibiting strong connectivity between the VMPFC, motor cortex, and/or the insula for those with a functional movement disorder - and/or there might be cyclic/recurring transient patterns of motor cortex (dis)connectivity in such patients that would not be detectable with time-averaged analyses.
        - We also touch on the importance of dynamic, systems-level analyses in our functional seizures paper linked above.
- The authors selected a strong comprehensive suite of non-neural measures to assess relevant psychological and clinical constructs at pre, immediately post-acute, and follow-up timepoints.
    - One suggestion for measures of the acute experience is to consider using the Emotional Breakthrough Inventory, (Roseman *et al*. 2019[6]), *Journal of Psychopharmacology*) especially given the potential role of emotional abreaction in such conditions.
    - The authors might also consider a simple measure of seizure occurrences/frequency in the case of functional seizure patients.

All in all, with more clearly and cogently motivated hypotheses and analytic approaches, this study has potential to provide an important contribution that expands the breadth of psilocybin therapy, and which may also shed valuable light on the mechanisms of FND and its treatment.

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Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Partly

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: functional neuroimaging/fMRI, large-scale brain networks, static and dynamic functional connectivity analyses, psychedelic neuroimaging, default mode network

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 19 Mar 2025

Matt Butler

Many thanks for your helpful comments which we think have improved the quality of the protocol. We have addressed your suggestions below:

Comment: 1.01 The authors state that “a representative sample of motor and seizure subtypes will be sought for inclusion”.

Response: We have specified that this will be a roughly 50/50 split between functional seizures and functional motor disorder, with allowed variance to account for the small sample size.

Comment: 1.02 The majority of the narrative, cited research, and focus seems to be biased towards functional motor disorders. Indeed, there is no explicit mention of functional

seizures throughout. Moreover, there is no explicit mention of existing overarching theoretical models for the neurobiology of either. Do the authors assume that the pathophysiology is the same for both of these conditions? Might it be better to have distinct theoretically and empirically motivated hypotheses for each? For example, in our recent paper (https://doi.org/10.1177/02698811241248395) Lewis et al.(20241) we outline hypotheses and fMRI empirical directions for functional seizures in particular based on past theoretical models and findings (e.g., the Integrated Cognitive Model).

Response: We have suggested that whilst there may well be distinct underlying pathophysiology between FND subtypes (particularly between motor and seizure subtypes), that their common co-occurrence suggests that there may also be overlap. Although future research can and should look at mechanisms underlying subtypes in more granular detail, this is not possible within the scope of this study. We have made reference to the integrated cognitive model in our discussion and have cited the helpfully suggested relevant paper.

Comment: 1.03 Relatedly, the authors describe predictive processing but don't clearly offer an explanation as to why the intended analyses/hypotheses are consistent with or might shed light on this perspective on FND.

Response: This section has been removed to improve clarity.

Comment: 1.04 Moreover, the mechanistic hypotheses as currently articulated are relatively non-specific and not clearly motivated. More specific hypotheses and explicit rationales for the regions of interest chosen for the seed-based analyses, and for the analyses conduced for the motor agency task, would be ideal. Greater explicit reference to previous theoretical models (of FND mechanisms and/or psilocybin therapeutic mechanisms) to support the hypotheses/ROI selection would also be a strength.

Response: We have now updated our ROI specification to bring it up to date with the current FND functional neuroimaging literature. A theoretical justification for each region is probably beyond the scope of this protocol paper, particularly as the analyses are exploratory.

Comment: 1.05 The authors could have also provided much more detail on the specific statistical/analytical approaches that will be conducted for the seed-based analyses (e.g., as pertains to cluster correction/multiple comparison correction, how the coordinates of ROIs will be determined, etc.).

Response: We have updated the analysis methods to explain that for each seed we will conduct a seed to voxel analysis using permutation-based multiple comparisons correction at the cluster level as implemented within the CONN toolbox with white matter and CSF (but not grey matter) regressors.

Comment: 1.06 Furthermore, the papers cited in support of the idea that the DMN is of central importance for FND (15, 19-25) do not clearly support focusing on this network over others. Several papers highlight the ventromedial prefrontal cortex in particular, but I do

not see compelling evidence that the DMN per se is critical. A large literature highlights the VMPFC's role in action selection and decision making – might that role be of particular importance, as opposed to its membership in the DMN per se?

Response: Based on this suggestion and from those made by other reviewers, we have decided to move focus away from the default mode network in general, and move instead towards the specific regions in particular.

Comment: 1.07 It also should be emphasized that the link between the DMN and psychedelic ego dissolution is far from unequivocal, and psychedelic mechanisms cannot be primarily attributed to the DMN based on existing empirical evidence, strictly speaking. A more distributed, dynamic, multi-network explanation is likely more apt (e.g., as we have argued in Girn et al. (20232), Trends in Cognitive Science).

Response: We agree with this suggestion that it is more complicated than simply the DMN. We have updated the introduction to reflect this and have included the helpful reference.

Comment: 1.08 In addition, given the emphasis on interoceptive awareness, somatic signalling, and agency/body ownership, the insula presents itself as an essential region of interest for seed-based analyses.

Response: Motor cortex functional connectivity would also presumably be of particular interest, as it has been previously implicated in FND (e.g., J Neurology Neurosurgery Psychiatry, Diez et al. (20193); Molecular Psychiatry, Diez et al. (20214)). We agree and have added these regions to the analysis plan.

Comment: 1.09 Although perhaps more advanced and exploratory, the authors might consider dynamic functional connectivity analyses, such as those which seek to estimate brain states and their dynamic evolution to characterize neural changes related to FND (e.g., see Network Neuroscience, Lurie et al. (20205)).

Response: We agree with the reviewer that dynamic connectivity would be an interesting analysis and the data will be suitable for this, but the study plan does not currently include any hypotheses for such an analysis and after reflecting on this we are not sure what they would be. We could certainly derive some from the psychedelic literature, but the link to FND is exploratory. Therefore, we have decided not to include this as part of our protocol but recognise the value of exploratory analyses. We also note our data will be shared.

Comment: 1.10 One suggestion for measures of the acute experience is to consider using the Emotional Breakthrough Inventory, (Roseman et al. 20196), Journal of Psychopharmacology) especially given the potential role of emotional abreaction in such conditions.

Response: This has now been included.

Comment: 1.11 The authors might also consider a simple measure of seizure occurrences/frequency in the case of functional seizure patients.

Response: We have clarified that we will be recording participant reports of average number of seizures in intervening period when undertaking the CGI. Likewise, simple descriptions of motor/other symptoms will be recorded. Any further formal recording will be beyond the scope of this study, which is not a clinical trial.

Competing Interests: No competing interests were disclosed.