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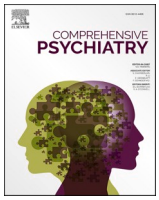

Single-dose (10 mg) psilocybin reduces symptoms in adults with obsessive-compulsive disorder: A pharmacological challenge study

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ABSTRACT

Background: Obsessive-compulsive disorder (OCD) is a common and disabling condition. A large proportion of patients fail to respond to first-line treatment with serotonin reuptake inhibitors either selective serotonin re-uptake inhibitors (SSRIs) or clomipramine. Preliminary evidence suggests psilocybin, a serotonin receptor agonist, might be efficacious. We conducted a pharmacological challenge study to investigate the efficacy and mechanisms of effect of psilocybin in OCD. This analysis reports the clinical outcomes only.

Methods: Participants with a diagnosis of OCD of at least moderate severity, received two single doses of oral psilocybin, 1 mg followed by 10 mg, administered in fixed order separated by 4 weeks. On the day of dosing, they were treated in a day-care facility in the presence of clinicians experienced in the use of psychedelics for treating mental disorders. Psychological support was provided before, during and after dosing. Participants and raters were blinded to the order of treatment. They were assessed on the day before each dose (baseline 1, 2), on the day of dosing and at intervals over a 4-week period afterward using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (primary clinical outcome) and secondary clinical outcomes including the Montgomery-Åsberg Depression Rating Scale (MADRS). Adverse effects were also recorded.

Results: Nineteen adult participants (aged 20–60) entered the study and 18 completed all assessments. Clinical outcomes following 1 mg and 10 mg psilocybin were compared using a linear mixed-effects model and ANOVA. A significant between-dosage effect favouring 10 mg psilocybin was found one-week after dosing on the Y-BOCS (Cohen's $d = 0.82$, $p = 0.002$). In particular, the effect one-week after dosing was statistically significant on the compulsion subscale of the Y-BOCS (Cohen's d: 0.74, $p = 0.003$), compared to obsession (Cohen's d: 0.50, $p = 0.06$). The effect diminished over the subsequent 3 weeks. No effect of psilocybin was detected on the MADRS. Psilocybin was well tolerated, with few adverse events reported at both dosages and no serious adverse events.

Conclusions: In this study, which was limited by a small sample size and the absence of randomisation, a 10 mg dose of oral psilocybin was found to be well-tolerated and potentially efficacious in patients with OCD. Psilocybin produced a rapid-onset, moderate to large effect on compulsive symptoms, which lasted up to one week after dosing. Future randomised placebo-controlled clinical trials investigating a longer course of multiple weekly

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doses of 10 mg psilocybin are indicated in OCD and in other obsessive-compulsive and related disorders characterised by compulsions.

1. Introduction

Obsessive-compulsive disorder (OCD) is a common, early-onset disorder affecting around 3 % of the general population [1–3]. OCD is characterised by compulsive rituals and obsessional thoughts [4]. With one of the longest duration of untreated illness among mental disorders [8,49] and linked to substantial impairments in both functioning and quality of life, OCD carries a major global disability burden and can even lead to suicide [5–8].

OCD responds to a relatively limited range of treatments. Most anxiolytics and antidepressants are ineffective, though the tricyclic clomipramine and the selective serotonin reuptake inhibitors (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) have all shown evidence of efficacy, suggesting enhancing serotonergic neurotransmission may be helpful [9]. Behavioural forms of cognitive behavioural therapy (CBT) involving exposure and response prevention (ERP) are also known to be efficacious; however, around 30–40 % of OCD patients do not respond to any of these treatments, underscoring the need for new alternative approaches [4]. Neurostimulation techniques hold promising efficacy, but they are still in an early stage in terms of clinical implementation [48,50,51].

Psilocybin, a 'classic psychedelic' with a strong affinity for serotonin receptors such as 5-HT2A and 5-HT1A [10], with additional downstream effects on glutamate receptors [11], might offer a novel approach to treating OCD. Research on this compound is encouraging, although only in its early stages. A recent systematic review of the use of psychedelics in obsessive-compulsive and related disorders (OCRDs) [12] identified one published small-sized open label clinical trial of psilocybin in patients with OCD [13] as well as a few case reports and preclinical studies. In the study by Moreno et al. [13], nine patients with OCD who had not responded to standard treatments (SSRIs) received different fixed doses of psilocybin, each separated by at least 1 week, according to a modified dose escalation protocol. The low (100 microg/kg), medium (200 microg/kg), and high (300 microg/kg) doses were assigned in that order, with an additional very low dose (25 microg/kg) inserted randomly and in double-blind fashion at any time after the first dose acting as a placebo. Marked decreases in OCD symptoms of variable degrees were observed in all individuals when taking active psilocybin, with a significant main effect of time, but no significant effect of dose or interaction of time and dose. According to Graziosi et al. [12], the existing evidence suggests that psilocybin is well-tolerated by patients with OCRDs, and as some individuals experience a reduction in symptoms over time, further investigation is warranted.

The most effective dosage of psilocybin for OCD remains a topic of investigation. Most studies assessing psilocybin in the context of mental health have explored a dose of approximately 25 mg [14–16]. Early evidence in depression suggests that psilocybin given at this dose may offer rapid and enduring symptom relief, potentially outperforming conventional pharmacotherapy [17–19]. However, in the context of OCD therapy, higher doses of psilocybin (of around 25 mg) have not so far shown greater effectiveness than lower doses [11]. Indeed, in the study by Moreno et al. [13], doses approximating to 7 mg, 14 mg and 21 mg seemed equally efficacious. Szafoni et al. [11] advocated tailoring psilocybin dosages based on specific therapeutic objectives and patient profiles. As well as being potentially preferred by patients (see below), advantages of studying a low dose of psilocybin in OCD include reduction in risk of adverse psychoactive effects and greater scope for achieving credible participant and rater blinding, thereby reducing expectation bias [11,13,20].

The most credible control agent for evaluating the efficacy of psilocybin remains another controversial topic [21]. Existing literature suggests that a very low dose of around 1 mg of psilocybin may serve as a valid control [14,22], since it does not produce significant physiological, perceptual, or emotional effects [13,23]. Importantly, by opting for a very low dose rather than an inert placebo, participants in controlled studies can be told that they will always receive at least some psilocybin, potentially further mitigating expectation bias in favour of the experimental treatment arm.

Despite emerging promising results, several challenges remain in the clinical application of psilocybin for OCD. It is crucial to consider the safety and tolerability of psilocybin in clinical settings. While psilocybin is generally regarded as safe when administered in controlled environments [24], there are concerns regarding its potential to induce adverse psychological effects, particularly in individuals with a history of bipolar disorder or psychosis [24–26]. Cases of severe OCD with comorbid bipolar disorder or psychosis are not uncommon [27,28] and may be particularly susceptible to adverse reactions. Indeed, the variability in individual responses to psilocybin, likely influenced by genetic, psychological, cultural, and environmental factors, suggests a personalised approach to treatment may ultimately be required [11,29]. Consultation, screening and monitoring of patients with OCD is essential to identify and thereby mitigate potential risks associated with its use.

In sum, emerging evidence suggests a need for further research into the effects of psilocybin in OCD, paying attention to careful participant screening and dosing strategies that balance efficacy and safety. Preliminary consultation between the authors and people with lived experience of OCD indicated that some would be willing to engage in a study of psilocybin (others would not) and that they would feel more comfortable taking a lower dosage to reduce the impact of any psychedelic experience or feelings of loss of control of their thinking. Based on the above critique and on the previous study by Moreno and colleagues (2006), demonstrating therapeutic effects of psilocybin at 10 mg dose in OCD, we decided to investigate the use of a moderate (sometimes called a mild-dose) dose of psilocybin (10 mg) as the active treatment to minimise adverse psychoactive effects, and a very low dose of psilocybin (1 mg) as control. We opted for a 10 mg dose of psilocybin to investigate the biological effect of the compound in the absence of a too intense psychedelic experience, which could be something patients with OCD might prefer to avoid. Another important point that guided us to this choice is the better blinding conditions: while giving a higher dose and therefore a full psychedelic experience would, by nature, determine unblinding, a small-to-moderate dose could still guarantee the biological effect with a more blunted psychedelic experience that could be easier to blind.

1.1. Aims

This investigation is part of a larger study investigating the efficacy and mechanisms of effect of psilocybin in OCD that included additional qualitative and cognitive measures (pre-registered on clinicaltrials.gov (NCT06258031)). We aimed to assess the effects of a single mild (10 mg) dose of psilocybin versus a very low (1 mg) dose when paired with encouraging, but non-interventional, therapeutic support. In this paper, we report the clinical outcomes only.

2. Methods

The study was designed as a pharmacological challenge study. The protocol was co-developed with patient advisors and underwent external peer review. The study investigational drug was COMP360, a proprietary pharmaceutical-grade synthesized psilocybin formulation developed by Compass Pathfinder Ltd., a subsidiary of Compass

Pathways plc ("Compass").

2.1. Research ethics and trial registration

The study received a favourable opinion on 14/12/2021 from the London Central Research Ethics Committee (REC) (registration number: 21/LO/0804) and was sponsored by Imperial College London's Research Governance and Integrity Team. The Medicines and Healthcare products Regulatory Agency (MHRA) confirmed its status as a non-clinical trial and waived the need for MHRA approval. The study was reviewed and approved by the Health Research Authority (HRA) and adopted by the National Institute of Health Research (NIHR) Clinical Research Network (CRN). It was pre-registered on clinicaltrials.gov (NCT06258031).

2.2. Study setting

The study took place at the CIPPRes (CNWL-Imperial Psychopharmacology & Psychedelic Research) Clinic, a research clinic facility founded by Imperial College London and Central and North West London NHS Foundation Trust, between October 2022 and July 2024. Researchers at the Clinic are experienced in the use of psychedelics for treating mental disorders. All study staff underwent Good Clinical Practice (GCP) training. For convenience, several study activities not requiring in person attendance took place online, via Microsoft Teams using a secure institutional account.

2.3. Recruitment

Recruitment occurred via flyers, word-of-mouth, and dissemination of a link to a standardised survey collecting information on key inclusion/exclusion criteria submitted via a secure centralised system using Qualtrics software. The study was also advertised on Imperial College London https://www.imperial.ac.uk/psychedelic-research-centre/participate-in-a-trial/ocd-study/ and Orchard websites (https://orchardocdregistry.org/studies/). Summarised participant information sheets were openly accessible on our study websites.

2.4. Consent

All participants provided written informed consent to be screened and, if relevant, to participate in this study.

2.5. Screening

2.5.1. Preliminary (remote) screening

Eligible self-referrals were invited to a remote preliminary online screening call where informed consent for the virtual screening interview was collected. Remote screening calls were conducted by an OCD-experienced psychiatrist to provide more specific information and determine eligibility, including a detailed Mini-International Neuropsychiatric Interview (MINI) to confirm diagnosis [30] and assessment against the study's inclusion and exclusion criteria (Table 1).

We selected participants with a primary DSM-IV diagnosis of OCD, at least moderate severity (Y-BOCS ≥16) who had OCD for at least 12 months. Key exclusion criteria were: Current or previous diagnosis of psychotic disorder, bipolar disorder or mania; having a first-degree relative with a diagnosed psychotic disorder; having a history of serious suicide attempts (requiring hospitalisation); being clinically depressed (MADRS>24); having borderline personality disorder. Participants taking medications that had the potential to interact with psilocybin, including lithium and serotonin-noradrenaline reuptake inhibitors (SNRIs), were also not included in the study. We did not exclude participants who had previously taken psychedelics and kept a record of prior use.

Table 1
Study inclusion and exclusion criteria.

Category	Inclusion criteria	Exclusion criteria
Demographics	- Aged 20 to 65 years - Any gender	- People who are pregnant, planning to get pregnant, or currently breastfeeding - People with inadequate understanding of English to participate in treatment or give informed consent
Mental Health	- Primary DSM-IV diagnosis of OCD - Y-BOCS ≥16 - Suffered from OCD for at least 12 months - MADRS ≤24	- Current or previously diagnosed psychotic disorder, bipolar disorder or personality disorder - Immediate family member with a diagnosed psychotic disorder - History of serious suicide attempts (requiring hospitalisation) - Y-BOCS <16 or MADRS >24
Physical Health	- Stable physical health - Able to engage in the physical demands of dosing session	- Unstable physical illness - Significantly abnormal clinical test result - Heavy smoker and/or unable to complete the dosing session without a smoking break
Medication	- Not currently using medication that could interact with psilocybin (antipsychotics, mood stabilisers, and serotonin-noradrenaline reuptake inhibitors, trazodone, mirtazapine) – only SSRIs are permitted	- Currently using medication (other than SSRIs) that could interact with psilocybin (antipsychotics, mood stabilisers, and serotonin-noradrenaline reuptake inhibitors, trazodone, mirtazapine)

2.5.2. Confirmatory (in-person) screening

If the participant was deemed eligible during the online screening call, they were invited to a second, in-person screening visit at the study centre. This consisted of an extended interview with the research doctor (with the second and definitive informed consent to sign). The goals of in-person screening were fourfold: 1) To provide a second opportunity for potential participants to be informed about the study goals and methodology by the study team and ask any remaining questions they may have had, to support the informed consent process, 2) To confirm that the information provided by participants on the video-call screening, in particular concordance with our inclusion and exclusion criteria, still applied, 3) To apply the remaining health checks requiring a physical examination to confirm eligibility, and 4) To familiarise them to the location where the psychedelic would be administered.

During this visit, demographics (such as date of birth, gender, race and ethnicity parameters) were captured, a full psychiatric history was taken and any medical or medication history was assessed. The severity of OCD and depression were assessed respectively using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) [31] and the Montgomery-Åsberg Depression Rating Scale (MADRS) [32]. The MADRS was also used to determine the presence of current suicidal ideation and/or intent.

Participants were asked to complete the Borderline Symptom List (BSL-23), as an extra aid to assess evidence of suspected personality disorder, which was an exclusion criterion. The National Adult Reading Test (NART) was also employed to assess premorbid intelligence levels (for the purposes of benchmarking the cognitive testing).

Subjects underwent weight and height measurement, physical examination, blood pressure (BP) and heart rate (HR), and electrocardiogram (ECG). A urine drug screen (UDS) for substances of abuse and an alcohol breathalyser test was performed for all participants, and a pregnancy test for female participants if applicable. Blood samples were collected for the following parameters (to screen out potential

participants with occult physical health problems that might have contra-indicated use of psilocybin): Full Blood Count, Urea and Electrolytes, and Liver Function Tests. We checked the participants' understanding of the procedure, requirements and commitments and answered any remaining questions the participant might have had before written informed consent to conditionally participate in the study, depending on the outcome of further final checks with their GP or other relevant health professional (see below), was taken.

To further strengthen the protection of participants' health and safety, primary healthcare providers and first-degree relatives were contacted in all eligible and consenting cases and informed of the patient's participation in our study. We additionally obtained a Summary Care Record (SCR) from their GP practice and contacted any mental healthcare practitioner actively involved in their care to confirm they were eligible in relation to our inclusion and exclusion criteria. As a final step, we required that each participant had in place a carer or dedicated support person who had agreed to provide them with support as required. We kept the contact details of such persons on file in case of need.

Once the screening and consent procedures were completed, participants were invited to start the study.

2.6. Preparation sessions

The preparatory sessions were designed to establish a reflective therapeutic foundation, foster trust and connection between participants and therapists, gather treatment history, and provide clear guidance on what to anticipate during dosing days. These sessions also offered an opportunity to begin exploring participants' relationships with their OCD symptoms. Any noticeable shifts in symptoms, overall well-being, or attitudes toward the study were carefully recorded. These sessions were held one week and one day prior to each dosing day to ensure readiness and alignment for the upcoming experience.

2.7. Dosing sessions

On each of the two dosing days, participants arrived at the clinic at around 9 am and left at around 5 pm. Dosing took place at about 9.30 am. Overnight onsite accommodation facilities were offered to all participants. Participants living some distance from the research centre were encouraged to take advantage of the onsite accommodation. Participants who did not wish to stay at the available accommodation were thoroughly assessed before leaving the research clinic by a research doctor and allowed to go home if no clinical issue was detected. Participants leaving the clinic on the day of dosing were not allowed to drive themselves (i.e., they were taken home by a trusted person, or they travelled by train or taxi booked by our research group). Details of the dosing-session procedures, including mental and physical health assessments are available in the supplementary materials (Table 1 in supplementary material).

2.8. Psychological support

Two therapists trained in psychedelic therapy provided support to participants throughout the study. The non-interventional model emphasised self-reflection and the processing of unconscious material, empowering participants to explore their relationship with OCD without directly targeting behavioural or cognitive changes. On dosing days, the therapists invited participants to engage in an "inner-directed" journey, offering the option to listen to music and use eyeshades. The therapists refrained from intervening or guiding participants but did ask participants to rate the intensity of their experience of psilocybin every 40 min. The dosing took place in a calm, relaxing and quiet room, with the participant lying on a bed (see Fig. 2 in the supplement). To maintain consistent conditions across dosing periods, participants received the same level of therapeutic support before, during and after both dosing sessions.

2.9. Integration sessions

The participants engaged in four structured integration sessions with their assigned therapists. These sessions aimed to help the participant process and implement insights gained from the dosing days. Scheduled at intervals of one day, one week, two weeks, and four weeks post-dosing, the integration process began the morning following the dosing day. During this initial virtual meeting, participants shared their experiences with their guides, setting the foundation for deeper exploration in the subsequent sessions. Themes, whether related to OCD or not, were examined in greater detail over time. Given the four-week interval between dosing days, the final integration session following the 1 mg dose doubled as preparation for the upcoming 10 mg dose. During this session, the Y-BOCS and MADRS assessments were repeated, alongside the administration of exploratory self-reported questionnaires that assessed wellbeing and affective symptoms.

2.10. Study timetable

Participants underwent study activities at 15 different time points over a twelve-week study period (Fig. 1). There were two in-person dosing sessions involving attendance at the research facility, each lasting ~9 consecutive hours, as the anticipated drug effect would last for approximately 4–6 h (Table 1, supplementary materials). Dosing sessions (first 1 mg then 10 mg) were separated by at least four weeks, the drug being given orally. Each was preceded by at least one preparation session and followed by four integration sessions, with the final integration session taking place four weeks after the final dosing session.

2.11. Clinical outcomes

Observer-rated assessments took place one day pre-dose (baseline 1, 2), and then one week, two weeks and four weeks following each dose. These assessments were conducted by an assessor blinded to the dose (1 mg dose or 10 mg dose) and the order of dosing. They were performed remotely via Microsoft Teams using a secure institutional account. Outcomes included the Y-BOCS measuring OCD severity, including the total score (primary clinical outcome) and the obsession and compulsions sub-scale scores, and the MADRS measuring depression severity (secondary clinical outcomes).

A range of self-rated questionnaires was also delivered via a digital platform (Qualtrics), with different groupings of questionnaires administered at different study visits. Self-rated outcomes included two measures of depression, the Beck Depression Inventory (BDI) [52], which was delivered 1 day before each dosing session and at 2 and 4 weeks after, and the Patient Health Questionnaire (PHQ-9) [54], which was delivered 1 day before each dosing session and at 1, 2 and 4 weeks after, and a measure of functional disability, the Sheehan Disability Scale (SDS) [53], which was delivered 1 week before each dosing session and at 1, 2 and 4 weeks after. These outcomes were considered secondary clinical outcomes.

2.12. Adverse events

Adverse events were assessed by a blinded rater using a standardised form at baselines (form complying with Medical Dictionary for Regulatory Activities (MedDRA) terminology) (1 day before 1 mg and 1 day before 10 mg) and at 1 week, 2 weeks and 4 weeks after each dosing session.

2.13. Blinding

All staff in the study were unblinded apart from the blinded assessor. Participants were told they would receive a single dose of psilocybin on

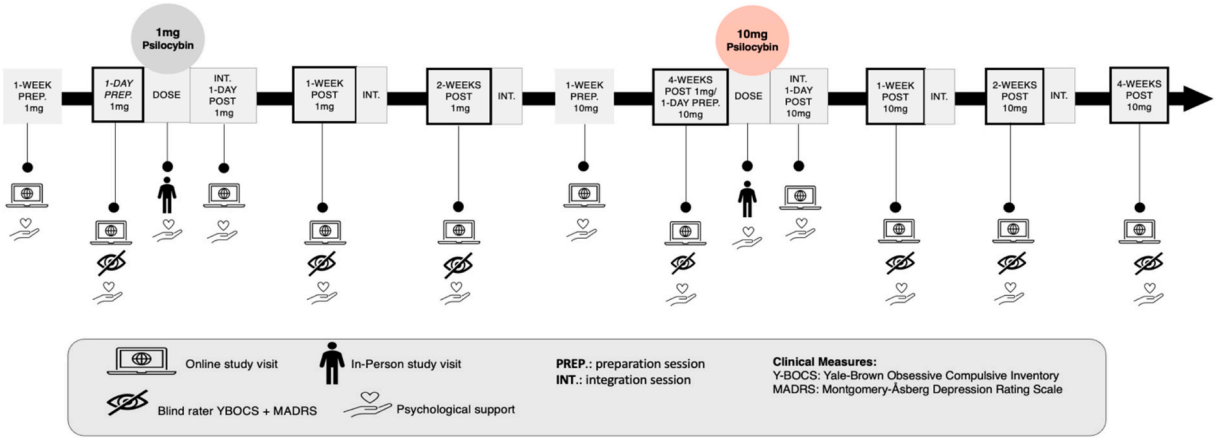

Fig. 1. Study timetable.

each dosing day and that one dose would be lower than the other. Participants were not informed about the two possible doses but they were told they would receive 'up to 10mg' psilocybin on each dosing day; no information on what the dose would be on the specific dosing session or the order of dosing was provided. Participant-blinding was evaluated by the study therapists, who were not blinded to the order of dosing, one day after each dosing session, by asking the study subjects to guess the dose they received (e.g., extremely small, small, small to moderate) and their confidence in this choice was assessed on a scale 0–100 %.

2.14. Expectancy

Expectation bias was evaluated using an adapted version of the Credibility/Expectancy Questionnaire [33,34] one day before each of the two dosing sessions. We used the following three faces to measure expectancy:

Expectancy_1. How confident are you that your upcoming psilocybin session will have a long-lasting positive effect?

1 2 3 4 5 6 7 8 9
1 = not at all confident
5 = somewhat confident
9 = very confident

Expectancy_2. At this point, how successful do you think the psilocybin session will be in improving your symptoms of OCD?

1 2 3 4 5 6 7 8 9
1 = not at all useful
5 = somewhat useful
9 = very useful

Expectancy_3. By the end of the experience, how much improvement in your overall well-being do you think will occur?

0 % - 10 % - 20 % - 30 % - 40 % - 50 % - 60 % - 70 % - 80 % - 90 % - 100 %

3. Additional measures

3.1. Cognition

We performed a series of cognitive tests investigating cognitive inflexibility, including the Intra Dimensional-Extra Dimensional Set Shift (ID-ED) [35], which was defined a priori as the primary cognitive outcome, and other executive functions known to be implicated in OCD [36]. Cognitive tasks were administered two days after each dosing session. These tasks are listed in Table 2 in the supplementary materials.

3.2. Additional self-rated questionnaires

We also included questionnaires measuring factors linked to cognitive functioning, including impulsivity, compulsivity, trait anxiety and personality (see Table 3 in supplementary materials for a full list of questionnaires and when they were applied).

Table 2
Demographic and clinical characteristics of participants at baseline ($N = 19$).

ID	Age	Gender	Ethnicity	YBOCS baseline	MADRS baseline	OCD medication (time of study)
OCD001	28	Male	Black British	17	9	100 mg sertraline
OCD002	40	Female	White British	28	8	None
OCD003	43	Female	Indo Caribbean + White	31	16	None
OCD004	33	Male	White British	18	4	None
OCD005	51	Male	White German	21	18	None
OCD006	43	Male	White British	24	7	40 mg fluoxetine
OCD007	42	Female	White British	25	15	10 mg escitalopram
OCD008	26	Male	White British	25	11	None
OCD009	37	Female	White British	25	21	15 mg escitalopram
OCD010	42	Female	White British	26	22	75 mg sertraline
OCD011	41	Female	White British	26	11	60 mg fluoxetine
OCD012	34	Male	White British	22	1	None
OCD013	26	Male	White British	27	17	None
OCD014	25	Male	White/Asian	20	5	200 mg sertraline
OCD015	32	Male	White British	25	11	100 mg sertraline
OCD016	54	Male	White British	30	15	None
OCD017	57	Male	White British	29	19	20 mg fluoxetine
OCD018	37	Male	Asian	25	19	80 mg fluoxetine
OCD019	32	Male	White British (Other)	22	5	50 mg sertraline

Table 3
Blinding assessment of participants.

Dose estimate options	1 mg placebo dose			10 mg active dose		
	Guess count	(n, %)	Mean confidence	Guess count	(n, %)	Mean confidence
Extremely small	**5**	**29 %**	**76 %**	0	0 %	
small	12	71 %	57 %	1	8 %	50 %
Small to moderate	0	0 %		**12**	**92 %**	**92 %**

3.3. Neural plasticity

We also performed an electroencephalogram (EEG), to investigate markers of neural plasticity, which was administered a total of three times: at screening, and at 1 h after each dosing session. Brain-derived neurotrophic factor blood levels were also taken pre- and post-dosing for 1 mg and 10 mg, to assess the association between BDNF and EEG markers of neuroplasticity.

These additional objective and subjective measures of cognition, neuroplasticity and study-related experiences will be reported separately in other papers.

3.4. Statistical analyses

Participant characteristics and outcome variables were subjected to conventional descriptive statistics. Statistical software R was used to carry out the statistical analyses described and to produce appropriate figures such as line plots. We employed linear mixed effects models using the lmer function to assess the impact of psilocybin on clinical scores, allowing us to separately assess cumulative change over time and compare magnitude of change after each dose. For the overall model assessing change across the entire study period, Timepoint was included as a fixed effect. For dose comparison models, Dose, Timepoint, and their interaction were included as fixed effects. Y-BOCS was the primary clinical outcome. Participant ID included as a random intercept in all models to account for within-subject dependency. Baseline symptom severity (1-day pre-1 mg) was included as a covariate in the overall model. For the dose comparison models, the corresponding pre-dose baseline score (either 1-day pre-1 mg or 1-day pre-10 mg) was included to adjust for individual variability and account for fixed-order design effects. Model structure (fixed and random effects) was pre-specified based on the experimental design and primary hypotheses.

Post-hoc pairwise comparisons were conducted using the emmeans package in R. For the overall models, we compared each timepoint to the baseline using the contrast() function with the 'trt.vs.ctrl' method and applied Bonferroni correction. For the dose models, we performed pairwise comparisons between dose conditions within each timepoint using the pairs() function, also applying Bonferroni correction for multiple comparisons.

Cohen's d effect sizes were calculated using the cohen.d function. For the overall models, effect sizes reflect the standardised mean difference between each post-treatment timepoint and the baseline (1-day pre-1 mg). For the dose comparison models, effect sizes were calculated based on the change from the corresponding pre-dose baseline (1-day pre-1 mg or 1-day pre-10 mg), allowing us to account for baseline differences introduced by the fixed-order dosing design.

A conservative, intent-to-treat (ITT) approach was chosen, which accounted for dropouts using the last observation carried forward (LOCF), to make results more generalisable to clinical settings.

To evaluate the impact of expectancy on clinical outcomes, we conducted separate analyses for each dosing condition (1 mg and 10 mg psilocybin) and for each of the three facets of expectancy assessed at baseline. For each analysis, the models included Visit, Expectancy Measure, and their interaction (Visit × Expectancy) as fixed effects. Participant ID was included as a random effect to account for within-subject variability. The outcomes of interest were the interaction terms between Visits and Expectancy. These interaction terms allowed us to determine whether the relationship between time and clinical outcomes was moderated by the level of expectancy. A significant interaction would indicate that changes in clinical outcomes over time differed depending on participants' expectancy levels prior to dosing.

4. Results

We recruited 19 participants with OCD, 18 of whom completed all study visits (see Fig. 2).

One patient withdrew from the trial after having received the 1 mg dose because of family issues not related to any study procedure. The mean age of the sample was 38.01 years, 68.4 % ($N = 13$) were male, 58 % ($N = 11$) were taking medication (all SSRIs) and 73.7 % ($N = 14$) were psychedelic naïve. The mean Y-BOCS at Baseline 1 was 24.5 (SD: 3.8), representing moderately severe OCD, and the mean MADRS was 12.3 (6.1). Baseline demographics are illustrated in Table 2.

4.1. Total Y-BOCS

First, we ran an ITT mixed linear effects model on all 19 enrolled participants' Y-BOCS scores, comparing the clinical outcome scores over the whole study period (all timepoints) to the first baseline (1 mg). A last observation carried forward (LOCF) correction was applied. Subsequent ANOVA analysis revealed a significant effect of time on scores ($F = 13.23$, $p < 0.0001$), demonstrating that changes over time were statistically meaningful (see Fig. 3). Pairwise comparisons indicated that the Y-BOCS scores at 1-week, 2-weeks, and 4-weeks post-10 mg dose were significantly lower (all p-values <0.0001) compared to the chosen baseline, 1-day pre-1 mg. The timepoint with the greatest reduction from baseline was 1-week post-10 mg psilocybin ($\beta = -3.63$, Cohen's $d = 1.12$).

Next, we conducted an analysis to examine the effect of dose on the change in Y-BOCS scores over time, controlling for experimental baseline scores (1-day pre-1 mg and 1-day pre-10 mg; i.e. the day before each psilocybin dose). We used a linear mixed-effects model with Time and Dose as fixed effects and experimental baseline values as a covariate and then ran an ANOVA on the model to check for significance. This revealed significant main effects for dosage ($F = 23.11$, $p < 0.0001$) and Time ($F = 6.33$, $p < 0.0001$), indicating that both the dosage and the passage of time contributed to the observed changes in Y-BOCS scores. However, the interaction between dose and time was not significant ($F = 1.59$, $p = 0.20$) (see Fig. 4). Given the significant main effect of dose, pairwise contrasts were performed to identify where differences between 1 mg and 10 mg emerged. Pairwise comparisons revealed a significant dose effect was observed at 1 week post-treatment, with the 10 mg dose resulting in more pronounced reductions in Y-BOCS scores compared to the 1 mg dose with a moderate-large effect size ($\beta = -4.49$, Cohen's $d = 0.82$, $p = 0.002$). At 2 weeks, the difference between doses showed only trend-level significance ($\beta = -3.34$, Cohen's $d = 0.45$, $p = 0.06$), and by 4 weeks, the difference was no longer statistically significant ($\beta = -2.28$, Cohen's $d = 0.19$, $p = 0.45$).

Fig. 5 shows the obsessions and compulsions Y-BOCS subscales, where we found a statistically significant difference only in compulsions ($\beta = -2.44$, Cohen's $d = 0.74$, $p = 0.003$) and not in obsessions ($\beta = -1.78$, Cohen's $d = 0.50$, $p = 0.06$) at one week post-dosing. Therefore, improvements in compulsions may play a relatively greater role in driving the significant reduction in total Y-BOCS scores.

4.2. MADRS

To explore the effect of psilocybin on depression scores, we ran a linear mixed-effects model including participants' baseline scores as a

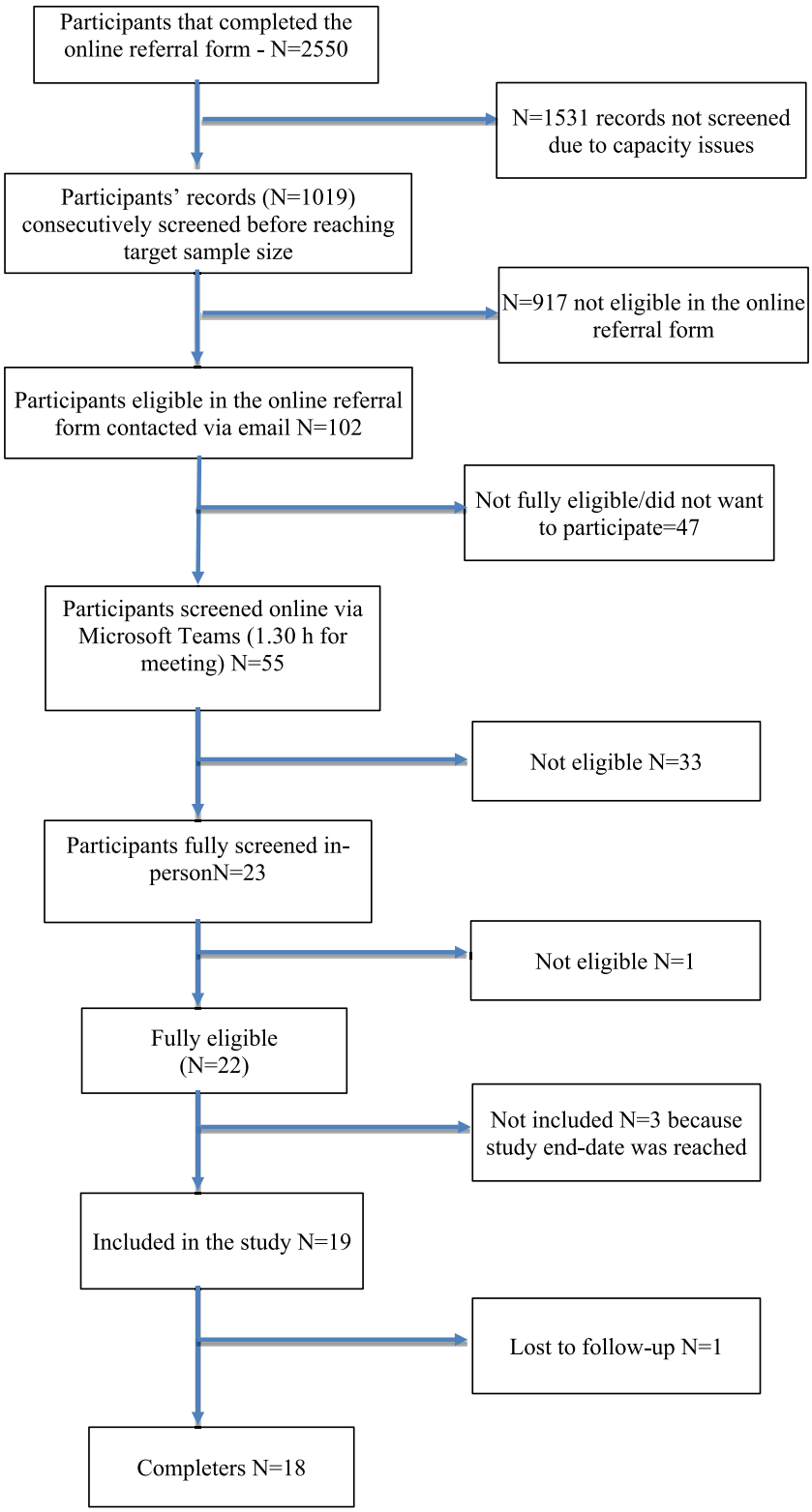

Fig. 2. Participant flow through the study.

covariate to account for initial differences in depression severity among participants (as we did before, for Y-BOCS scores). The ANOVA results from this model revealed that the main effect of time was not significant ($F = 2.00$, $p = 0.07$) (see Fig. 6).

The next analysis focused on understanding the effect of the different doses of psilocybin on changes in MADRS scores over time controlling for participants' experimental baseline scores (1-day pre-1 mg and 1-day pre-10 mg). The ANOVA results from this model indicated that neither the dose effect ($F = 1.44$, $p = 0.23$) nor the time effect ($F = 1.37$, $p = 0.26$) reached statistical significance. Moreover, the interaction between dose and time was also not significant ($F = 0.82$, $p = 0.49$), suggesting that the changes in depression scores over time were similar regardless of the dose administered Fig. 7.

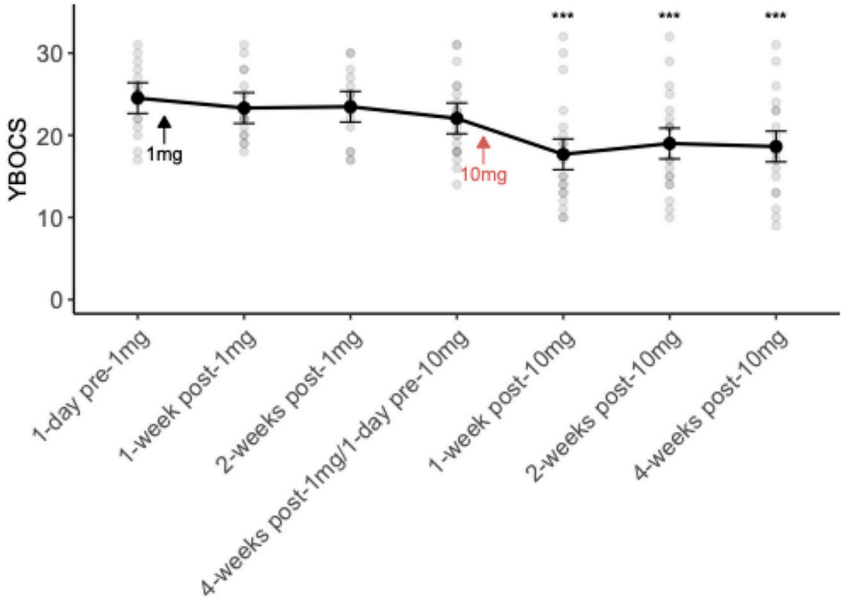

Fig. 3. Reduction in OCD symptoms over time after psilocybin treatment. The graph illustrates changes in Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) scores over time following psilocybin treatment, analysed with a linear mixed-effects model. Baseline scores (1-day pre-1 mg dose) were used as a covariate. A significant main effect was found for Time ($F = 13.23$, $p < 0.0001$). Pairwise tests revealed significant reductions in OCD scores at 1-week, 2-weeks, and 4-weeks post-10 mg compared to baseline ($p < 0.0001$ for all). $n = 19$, data shown as estimated marginal mean ± 95 % CI. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

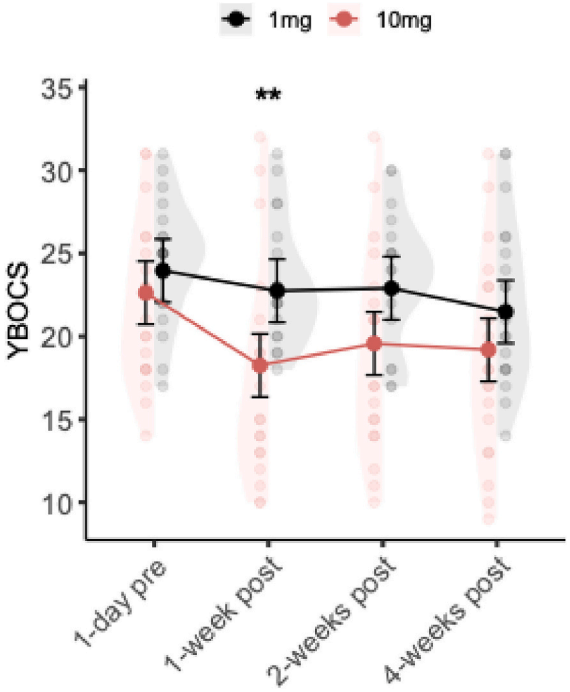

Fig. 4. This graph displays Y-BOCS scores over time to evaluate the individual effects of psilocybin doses (1 mg vs 10 mg); $n = 19$, data shown as estimated marginal mean ± 95 % CI. A linear mixed-effects model was used, with respective baseline values prior to each dose used as a covariate. ANOVA indicated significant effects for Dose ($F = 23.11$, $p < 0.0001$) and Time ($F = 6.33$, $p < 0.0001$), but the interaction between Dose and Time was not significant ($F = 1.59$, $p = 0.20$). Pairwise comparisons showed a significant Dose effect at 1 week ($p = 0.002$) but not at 2 weeks ($p = 0.06$) or 4 weeks ($p = 0.45$).

4.3. Demographic analysis

We explored whether treatment response differed by SSRI use or gender, focusing on percentage change in Y-BOCS scores between −1 day and 1-week post-10 mg, the peak response timepoint. The participants not taking SSRIs showed a mean reduction of −23.6 % ± 19.9 % ($n = 8$), compared to −17.0 % ± 23.4 % among those on SSRIs ($n = 11$). Female participants showed a mean reduction of −10.2 % ± 20.6 % ($n = 6$), while male participants showed a mean reduction of −24.2 % ± 21.4 % ($n = 13$).

Linear mixed-effects models including SSRI use or gender and their interaction with time revealed no significant SSRI × Time interactions, suggesting no substantial moderation by medication status. For gender, while the Gender × Time interaction was not significant at 1-week post 10 mg, a significant difference between males and females was observed at the 4-week post-10 mg timepoint ($\beta = -6.22$, $p = 0.009$), with males showing a slightly greater sustained response. These findings should be interpreted with caution due to limited sample size and exploratory nature. Figures presenting change in Y-BOCS by medication status and sex are presented in the supplementary materials.

4.4. Expectancy analysis

Our analyses to evaluate the impact of expectancy on clinical outcomes revealed no significant interactions between any of the expectancy measures and changes in clinical outcomes from baseline to any visit across both dosing conditions. Specifically, for both the total Y-BOCS scores and the MADRS scores, no significant Visit × Expectancy interactions were found prior to any correction for multiple comparisons (see Supplementary Table 4 and Supplementary Fig. 1).

4.5. Blinding analysis

The same blinded rater assessed all the participants across the whole project. While her blinding status was unfortunately not formally assessed, she was interviewed by a principal investigator at the end of the study, before the blind was broken. She reported that she had been

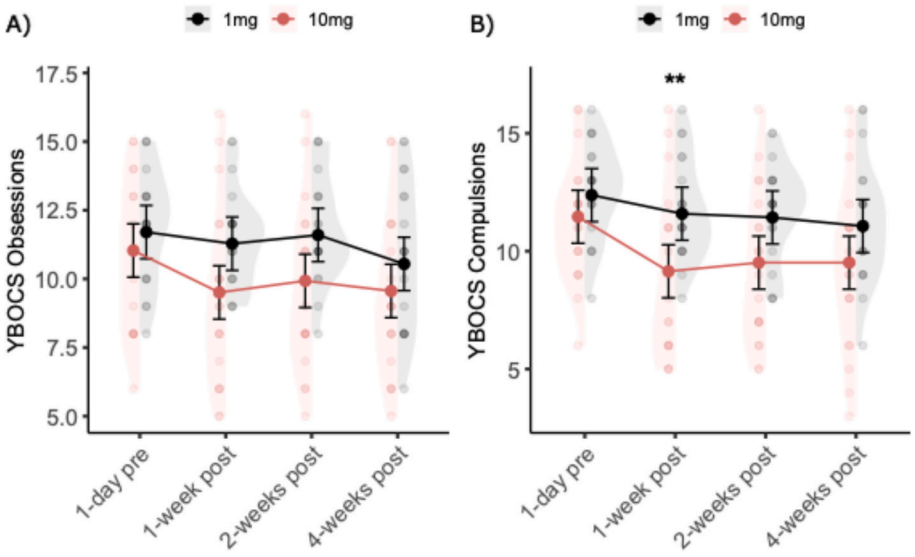

Fig. 5. Dose-dependent changes in Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) obsessions (a) and compulsion (b)scores over time. This graph displays Y-BOCS scores over time to evaluate the individual effects of psilocybin doses (1 mg vs 10 mg); n = 19, data shown as estimated marginal mean ± 95 % CI. Pairwise comparisons showed a significant Dose effect at 1 week for compulsions: Cohen's d = 0.74, $p = 0.003$, with a trend level effect for obsessions: Cohen's d = 0.50, $p = 0.06$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

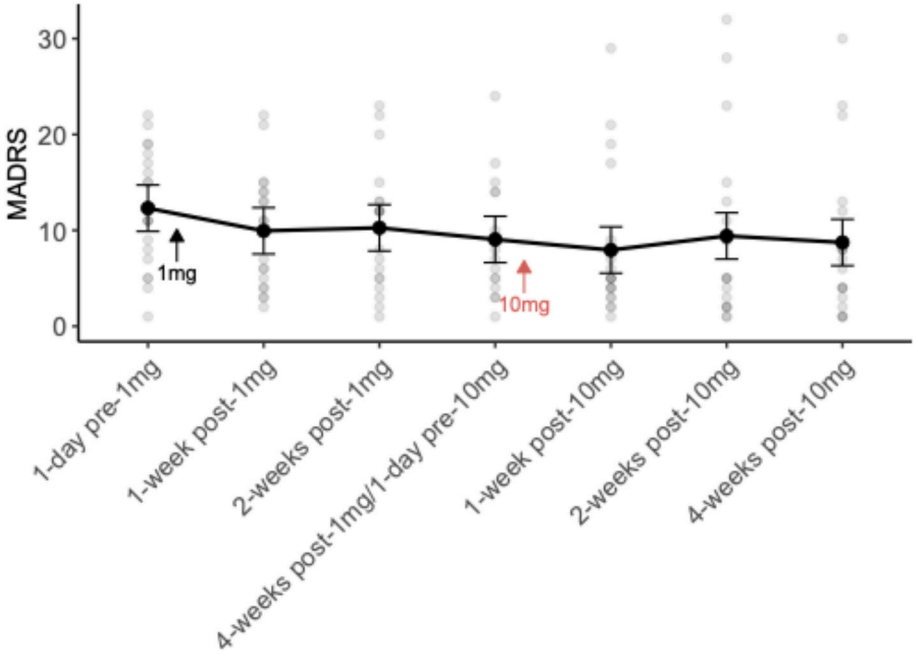

Fig. 6. Total Montgomery-Asberg Depression Rating Scale (MADRS) score over time. This figure illustrates the effect of a 10 mg psilocybin dose on depression symptoms as measured by MADRS scores (n = 19, data shown as estimated marginal mean ± 95 % CI). A linear mixed-effects model was used, with participants' baseline scores (1-day pre-1 mg) included as a covariate. ANOVA results indicated that Time was not significant (F = 2.00, $p = 0.07$).

unable to confidently say which dose was active (and which inactive) for any case. She had assumed randomisation had occurred and was surprised to discover the fixed order regimen.

Blinding was evaluated among the participants by asking them to guess how high the dose of psilocybin was after dosing sessions. This data was incomplete due to technical errors, with data from 17 participants recorded after the 1 mg dose and 13 participants following the 10 mg dose. For the 1 mg (small) dose, only 5 participants (29 %) guessed correctly with a moderate level of confidence (76 %), while for the 10 mg dose (small to moderate) all but one participant (92 %) guessed correctly, with a confidence of 92 % (see Table 3).

4.6. Adverse events

Adverse events were few and mild in nature with no clear between-arm differences. No adverse perceptual experiences were reported. Only one event, although not serious, required attention by the lead psychiatrist, in which a participant experienced an anxiety attack a few hours after the 1 mg dose. No serious adverse events were recorded (see Table 4).

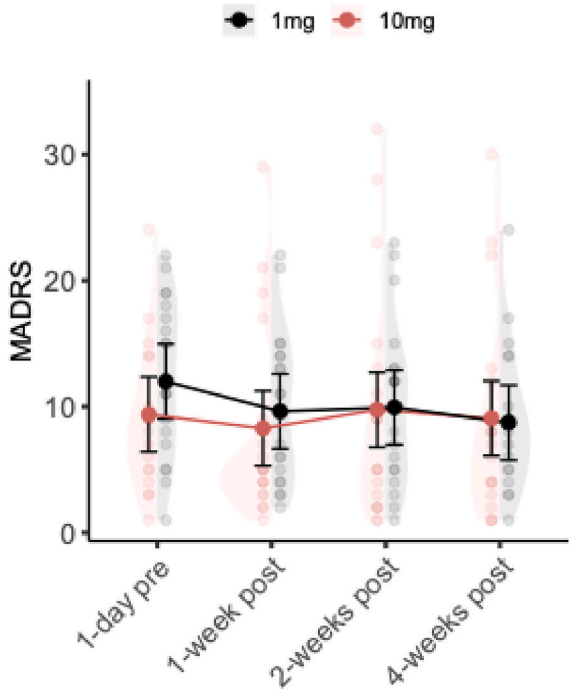

Fig. 7. This figure examines MADRS scores from baseline, comparing the effects of 1 mg versus 10 mg doses of psilocybin (n = 19, data shown as estimated marginal mean ± CI). A linear mixed-effects model was applied, with respective baseline values prior to each dose used as a covariate. ANOVA results showed that neither the Dose effect (F = 1.44, $p = 0.23$) nor the Time effect (F = 1.37, $p = 0.26$) were significant. The interaction between Dose and Time was also not significant (F = 0.82, $p = 0.49$).

4.7. Self-report measures

Secondary analyses of self-report scales assessing depression and functional impairment (PHQ-9, BDI, and SDS) are detailed in the Supplementary Materials.

As for depressive symptoms measured through the BDI, in the dose comparison model, a significant main effect of time was found (F = 5.41, $p = 0.007$), while both the main effect of dose (F = 0.06, $p = 0.80$) and the Time × Dose interaction (F = 0.12, $p = 0.88$) were not significant. These findings indicate a gradual but consistent reduction in self-reported depressive symptoms over time, with no evidence that the 10 mg dose produced greater reductions than 1 mg at matched timepoints (Supplementary Fig. 1).

In the model assessing changes in the PHQ-9 dose effects (with Time and Dose as fixed effects and baseline values as covariates), the main effect of time approached significance (F = 2.56, $p = 0.06$), while the main effect of dose (F = 0.48, $p = 0.49$) and the Time × Dose interaction (F = 1.07, $p = 0.36$) were again not significant. There was no evidence that changes differed significantly between the two doses (Supplementary Fig. 2).

In terms of functional impairment measured as scores on the SDS, the dose comparison model revealed a significant main effect of time (F = 14.28, $p < 0.0001$), as well as a significant Time × Dose interaction (F = 3.05, $p = 0.03$), whereas the main effect of dose was non-significant (F = 0.0004, $p = 0.98$). However, none of the pairwise dose comparisons at individual timepoints reached significance (all $p > 0.05$), suggesting that the interaction reflects differing trajectories over time rather than a consistent between-dose effect at specific timepoints (Supplementary Fig. 3).

In summary, all three measures showed significant main effects of time, with the largest and most consistent changes observed on the SDS. Pairwise comparisons revealed that improvements in depressive symptoms were most apparent following the 10 mg dose, although dose comparisons did not show statistically significant differences at individual timepoints. These findings suggest modest improvements in self-reported mood and functioning took place, with no between-dose difference, i.e. no significant effect of dose on subjective measures of depression, or functional impairment.

5. Discussion

In this study, a single 10 mg dose of oral psilocybin was found to be effective in reducing obsessive-compulsive symptoms (specifically compulsions) at the one-week time point after dosing compared with a control treatment session comprising a single 1 mg dose of psilocybin. The statistical significance of the effect was lost by week 2. Therefore, we can infer that a 10 mg dose of psilocybin can achieve a rapid onset of a relatively short-lived improvement in OCD symptomatology. Our results align with those of the single published study of psilocybin in OCD, which found improvement with a range of dosages [13]. Despite the absence of OCD-specific psychotherapy, the therapeutic dyad fostered a supportive environment that helped participants process their experiences and integrate the insights gained during the psilocybin session. Considerable effort and attention were deployed preparing patients and supporting them throughout the study but given that no specific OCD-directed psychotherapy was administered, the results might directly relate to the effects of the drug. Moreover, we should point out the unexpectedly high application rate for the study, which means there is a

Table 4
Adverse events in the sample.

Reported adverse event	Participants: *n* (%)	Number of reports	Dose					
			1 mg			10 mg		
			Mild	*Moderate*	*Severe*	*Mild*	*Moderate*	*Severe*
Headache	2 (10.5)	2	–	–	–	1	1	–
Anxiety	2 (10.5)	2	–	–	–	–	–	2
Nightmares	2 (10.5)	2	–	–	–	–	–	2
Coughing	2 (10.5)	2	1	–	–	1	–	–
Low mood	1 (5.3)	1	–	–	–	–	–	1
Insomnia	1 (5.3)	1	–	–	–	–	–	1
Nausea	1 (5.3)	1	–	–	–	–	1	–
Fatigue	1 (5.3)	1	–	–	–	–	–	1
Light-headedness	1 (5.3)	1	–	–	–	–	–	1
Visual disturbances	1 (5.3)	1	–	–	–	1	–	–
Stomach ache	1 (5.3)	1	–	–	–	1	–	–
Panic attack	1 (5.3)	1	–	–	1	–	–	–
Sore throat	1 (5.3)	1	1	–	–	–	–	–
Nasal congestion	1 (5.3)	1	–	–	–	1	–	–
Total	7/19 (36.84 %)	18	3 (16.7 %)			15 (83.3 %)		

significant interest for psilocybin in the OCD community.

OCD is usually a chronic condition and has a different response pharmacological profile compared with depression and anxiety [9]. In the context of OCD, treatment responses are often gradual and progressive, with a propensity for rapid relapse upon cessation of therapy. We obtained a significant improvement in the Y-BOCS for compulsions just one week after dosing, however the effect was lost afterward. Intriguingly, a significant improvement was detected for compulsions and not for obsessions, hinting at the possibility that psilocybin might act specifically on the altered executive functions in OCD that drive the performance of repetitive compulsive behaviours.

Furthermore, we did not find improvement in depressive symptoms in OCD, which contrasts with previous findings in patients with depression [14], though with a 25 mg dose. We also note that the level of depression in our sample was not high (mean baseline MADRS: 12.32, SD: 6.07), suggesting a possible 'floor effect' which may have prevented significant changes in depression to be seen. Nevertheless, our finding indicates that the improvement in obsessive-compulsive symptoms was not mediated by an improvement in depression, i.e., psilocybin does not exert its actions via depressive symptoms but seems to specifically target the obsessive-compulsive machinery.

Importantly, our study suggests that a single 10 mg dose of psilocybin combined with psychological support produces core OCD symptom improvements with a moderately large effect size in individuals with the disorder. Our results also show that baseline expectancy for response to psilocybin did not substantially influence this response, consistent with prior work [33]. One could argue that a 10 mg dose would offer certain advantages for future research (versus 25 mg, for example) by allowing greater potential for blinded treatment allocation, at least for raters, if not for participants, who, in our study, tended to recognise when they had received the 10 mg dose. Nevertheless, given the very few and minor adverse events caused by psilocybin at the 10 mg dosage, we infer that, at the very least, a single-blinded evaluation is possible and implementable in future work.

In this context, a mild, lower (i.e., 10 mg) dose of psilocybin, compared to the standard dose for depression (i.e., 25 mg), could be particularly useful in the clinical treatment of OCD, since clinical experience suggests patients with OCD, for who harm avoidance is a core motivational dimension [37], might fear experiencing loss of control of their thoughts and prefer not to have an intense psychedelic experience. In our study, the 10 mg dose was not associated with any troubling/distressing perceptual abnormalities. If meaningful improvements in OCD symptoms could arise from the administration of a mild psychedelic dose, this may be preferable for many patients. The use of a lower dose could also be expected to have advantages for study design e.g., by reducing blinding being broken and perhaps expectation bias. Although we did not directly assess this, there is further preliminary evidence hinting that this strategy (using a low dose) may have a notable clinical potential [11].

Another important finding was the acute onset of effect. A moderately large and significant improvement in OCD symptomatology was seen one week after the 10 mg dose, which could be extremely clinically useful and stands apart from the SSRI effect in OCD, which usually takes many weeks to fully develop. The mechanisms by which psilocybin may be effective in treating OCD are not yet elucidated [38,39]. Psilocybin is thought to act primarily as a serotonin receptor agonist, particularly at the 5-HT2A receptor. This interaction may lead to alterations in brain connectivity and neuroplasticity, potentially addressing the neurobiological underpinnings of OCD. Acute reductions in activity within the anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC) have been observed during [40] and after psilocybin treatment [41], suggesting it may facilitate therapeutic effects by modulating hyperactive neural circuits known to be implicated in OCD. Preliminary studies have also suggested that psilocybin may lead to improvements in the flexibility or openness of brain network dynamics [42,43] that may relate to improved cognitive flexibility and emotional processing, which are often impaired in individuals with OCD [44] and improved with psilocybin-therapy [45].

The notable tolerability of the 10 mg dose also hints that longer, multiple-dose studies of psilocybin may be feasible in OCD as a rational next research step. Importantly, we found limited evidence of any negative effect of being on SSRI in terms of treatment response (visualisation available in the supplement, Fig. 3). OCD is a chronic, relapsing disorder and a single dose, albeit with significant acute benefit, is unlikely to be that clinically useful. Integration of psilocybin with established therapeutic techniques such as cognitive-behavioural therapy (CBT) and exposure and response prevention (ERP), may offer yet another novel avenue for enhancing treatment outcomes in this clinical population. For instance, combining psilocybin with CBT and ERP could potentially facilitate deeper emotional processing and cognitive restructuring, leading to yet more significant symptom relief [46]. Alternatively, consideration of a higher doses as an effort for extending clinical effect could be considered in future work.

In the context of this pharmacological challenge study, we opted to use a very low dose of psilocybin (1 mg) as an active control. This strategy was chosen for several reasons: (1) it supports partial blinding and enhances acceptability among patients who may be reluctant to receive no treatment at all; (2) it allows participants to be told they are receiving psilocybin at all dosing sessions, which may help mitigate expectation bias; and (3) alternatives like lorazepam or niacin, though used in other trials, are distinguishable from psychedelics in both subjective experience and potential side effects, potentially compromising blinding and introducing confounds unrelated to the psychedelic state. However, considering the scarcity of prior psychedelic research in OCD, we could not be certain that our very low dose (1 mg) would be clinically inert. Indeed, in the study by Moreno et al. 2006, a low dosage of psilocybin [25 μg/kg (equivalent in a 70 kg person to 1,75 mg)], albeit probably higher in most cases than our 'placebo' dosage, was used as a control and induced a reduction in symptoms in seven patients with OCD. While our study showed that 1 mg of psilocybin also produced a minor clinical effect, this effect was significantly less than the effect produced by the 10 mg dose. This result provides some validation for the use of 1 mg psilocybin as an active control treatment in OCD. However, given the imperfect blinding achieved in the current study, it is arguably not an ideal choice. The use of placebo, effective blinding and placebo-controlled study design in psychedelic research remains a topic of active debate [55].

Accepting the constraints of design and sample size, the findings indicate a potential acute benefit of psilocybin for OCD that merits additional investigation. As discussed, the pharmacological pathways by which 10 mg psilocybin may facilitate anti-OCD effects remain uncertain. Although participants tolerated the treatment well, and there was little effect on mood, it is nevertheless possible that non-pharmacological effects also played a part in the positive clinical outcome. Subjects in psychedelic trials may experience a general reduction in symptoms due to the influence of mindset and setting; the contextual anticipation of improvement; or simply the distracting effects of the psychedelic or a "pleasurable experience [13].

5.1. Limitations to the study

Our study has several limitations, many of them inherent to trials on psychedelic compounds.

First, we should acknowledge the small sample size and the fixed-order design, where all participants received the 1 mg dose first, followed by the 10 mg dose, as limitations, as they introduce biases that undermine the ability to draw definitive conclusions and limit the generalizability of the findings. Based on our crossover design, rather than randomise the dose order, we decided to fix the dose order and administered the 1 mg dose before the 10 mg one, to avoid a potential carry-over effect whereby if the 10 mg psilocybin were given first, and had a sustained effect, it might confound the validity of the placebo dose

given afterward. While there is no evidence that prior dosing with psilocybin induces pharmacological sensitisation, and we ensured at least 4 weeks elapsed between the dosages for the effect of the first dose to wear off, we additionally cannot fully exclude a carry-over effect of the first dose on the clinical outcomes.

Additionally, the lack of randomisation and the absence of a satisfactory placebo, an integral issue in the study of psychedelic drugs when administered above micro dosages, notwithstanding our attempt to target this issue by using a moderate dose (10 mg) as active treatment and 1 mg dose as control treatment, resulted in imperfect blinding among the participants, and means caution is required in interpreting the results. On the other hand, we found limited evidence of an expectation bias effect on our results; although we note that causal expectancy effects are not "a given" with psychedelic-therapy. Indeed, the lack of a relationship between baseline expectancy and response is consistent with prior work [33].

Although a significant dose-related reduction in Y-BOCS scores was observed one week after the 10 mg dose, this finding occurred in the absence of a statistically significant dose × time interaction. This means the overall pattern of symptom change over time did not differ significantly between the two doses, and the time-specific difference should therefore be interpreted cautiously. Nonetheless, the timing and direction of the observed effect align with our pre-specified hypothesis and support further investigation in a larger, fully powered trial.

The finding that psilocybin specifically reduced compulsions, without significantly affecting obsessions, and therefore a hypothetical compulsions-specific effect, should be interpreted with caution due to limited statistical power. A larger sample size and methods such as Bayesian statistics would be required to more definitively determine whether psilocybin differentially impacts these two distinct facets of OCD.

While all participants were found to have a structured diagnosis of OCD, we cannot exclude the possibility of a selection bias toward those individuals willing to undertake treatment with a psychedelic. Indeed, in designing our study, we consulted with patients with OCD on their reservations about undergoing psychedelic treatment and adapted our protocol accordingly to make it as acceptable as possible for them. Furthermore, unlike other researchers (Moreno et al., 2006; Schneier et al., 2023), we did not prioritize participants who had previously done well on psilocybin. However, we must accept that this treatment may only be suitable for a proportion of patients with OCD willing and motivated to take this medication. As the use of psychedelics in psychiatry becomes more acceptable, it is possible that this proportion will grow.

Another limitation of our study is the fact that the design does not test whether the 10 mg dosage is superior to a higher dose, such as the standard that is used in depression. A trial to test the relative efficacy and tolerability of different dosages within the same study would be a logical step in the development of psilocybin for OCD. Future research into the use of psilocybin as a treatment for OCD also needs to take into account implementational barriers [47]; one such potential barrier is the induction of side effects such as distressing perceptual experiences that may potentially be mitigated by use of the 10 mg dosage.

6. Conclusions

Our study, which was limited by a small sample size and the absence of randomisation, demonstrated that a single fixed dose of 10 mg psilocybin was well tolerated by people with OCD and outperformed an ultra-low comparator dose of 1 mg psilocybin to produce a specific, fast-onset, moderately large reduction in OCD symptoms. The effects lasted for a week after which they lessened and were no longer significant by week 2. Intriguingly, a significant drug-effect was found for compulsions and not for depressive symptoms, hinting at a potential role for psilocybin as a treatment for a broader range of disorders characterised by compulsive behaviour. An adequately powered, randomised controlled trial represents a feasible next step to establish the efficacy and tolerability of 10 mg psilocybin in OCD with greater certainty.

CRediT authorship contribution statement

Luca Pellegrini: Validation, Conceptualization, Visualization, Methodology, Writing – original draft, Formal analysis, Supervision, Resources, Project administration, Investigation, Data curation, Software. **Naomi A. Fineberg:** Investigation, Writing – review & editing, Visualization, Validation, Data curation, Supervision, Methodology, Writing – original draft, Conceptualization. **Sorcha O'Connor:** Data curation, Writing – review & editing, Visualization, Investigation, Methodology, Conceptualization, Writing – original draft, Formal analysis. **Ana Maria Frota Lisboa Pereira De Souza:** Data curation, Investigation, Writing – original draft, Writing – review & editing, Methodology. **Kate Godfrey:** Formal analysis, Validation, Writing – original draft, Writing – review & editing, Visualization, Methodology, Data curation, Investigation, Conceptualization. **Sara Reed:** Writing – original draft, Visualization, Writing – review & editing, Investigation. **Joseph Peill:** Methodology, Investigation. **Mairead Healy:** Conceptualization, Writing – review & editing, Writing – original draft, Investigation, Software. **Cyrus Rohani-Shukla:** Data curation, Investigation, Conceptualization. **Hakjun Lee:** Investigation. **Robin Carhart-Harris:** Data curation, Conceptualization, Methodology, Formal analysis, Investigation. **Trevor W. Robbins:** Conceptualization, Investigation, Formal analysis, Funding acquisition, Data curation, Methodology. **David Nutt:** Writing – review & editing, Validation, Conceptualization, Methodology, Formal analysis, Supervision, Investigation, Writing – original draft, Funding acquisition, Data curation. **David Erritzoe:** Writing – review & editing, Software, Funding acquisition, Writing – original draft, Supervision, Resources, Methodology, Formal analysis, Data curation, Investigation, Conceptualization, Project administration.

Ethics statement

The study received a favourable opinion on 14/12/2021 from the London Central Research Ethics Committee (REC) (registration number: 21/LO/0804). The patients/participants will provide their written informed consent to participate in this study.

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Declaration of competing interest

NAF has recently held research or networking grants from the NIHR, COST Action, Orchard, UKRI, Compass Pathways; accepted travel and/or hospitality expenses from the BAP, ECNP, RCPsych, CINP, World Psychiatric Association; received payment from Elsevier for editorial duties and the Mental Health Academy and Children and Screens for lecturing. She leads an NHS treatment service for OCD. She holds Board membership for various registered charities linked to OCD.

TWR consults for Cambridge Cognition and Supernus. He also currently receives a research grant from Shionogi & Co. Editorial honoraria from Elsevier and Springer-Nature.

LP reports a relationship with European Cooperation in Science and Technology, the University of Hertfordshire, Orchard, ECNP-OCRN International College of Obsessive-Compulsive Spectrum Disorders (ICOCS), that includes: funding grants.

DN In the past 3 years he has received lecture fees from Takeda, Lundbeck, Otsuka and Janssen plus consulting fees from Algernon, Beckley Psytech, Leith Pharma and Amitis partners. He is a director of

Gaba Labs and Chief Research Officer of Awaknlifesciences. He has shares/options in Psyched Wellness and Neurotherapeutics. DN is currently Head of the Imperial College Centre for Psychedelic Research that has received support in kind from both COMPASS Pathways and USONA (psilocybin) and Beckley Psytec (5-MEO-DMT) studies.

DE is acting as a paid scientific advisor for Aya Biosciences, Lophora Aps, Clerkenwell Health, Mindstate Design Lab and is paid for delivering teaching on MMA's CPAT Course.

SR receives honoraria for speaking engagements and consultations related to psychedelic therapy. She was an inaugural board member of the Board of Psychedelic Medicines and Therapies (USA), designed to bring certification standards for future psychedelic-assisted therapists. She currently lectures internationally on culturally responsive practices in psychedelic therapy with Mind Medicine Australia, the Psychedelic Liberation Training, and Vital (Psychedelics Today).

RCH is a scientific advisor to TRYP Therapeutics, Journey Colab, Osmind, MindState, Entheos Labs, and Otsuka. These relationships did not influence the design of the proposed study or its interventions. These and other commercial entities may stand to indirectly benefit from any positive research on psychedelic therapies but will not benefit directly, such as by receiving intellectual property or privileged access to research results.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.comppsych.2025.152619.

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