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Psilocybin-assisted neurofeedback for the improvement of executive functions: a randomized semi-naturalistic-lab feasibility study

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Executive function deficits, common in psychiatric disorders, hinder daily activities and may be linked to diminished neural plasticity, affecting treatment and training responsiveness. In this pioneering study, we evaluated the feasibility and preliminary efficacy of psilocybin-assisted frontal-midline theta neurofeedback (NF), a neuromodulation technique leveraging neuroplasticity, to improve executive functions (EFs). Thirty-seven eligible participants were randomized into an experimental group (n = 18) and a passive control group (n = 19). The experimental group underwent three microdose sessions and then three psilocybin-assisted NF sessions, without requiring psychological support, demonstrating the approach's feasibility. NF learning showed a statistical trend for increases in frontal-midline theta from session to session with a large effect size and non-significant but medium effect size dynamical changes within sessions. Placebo effects were consistent across groups, with no tasks-based EF improvements, but significant self-reported gains in daily EFs—working memory, shifting, monitoring and inhibition—showing medium and high effect sizes. The experimental group's significant gains in their key training goals underscored the approach's external relevance. A thorough study with regular sessions and an active control group is crucial to evaluate EFs improvement and their specificity in future. Psilocybin-enhanced NF could offer significant, lasting benefits across diagnoses, improving daily functioning.

This article is part of the theme issue 'Neurofeedback: new territories and neurocognitive mechanisms of endogenous neuromodulation'.

1. Introduction

Cognitive impairments, particularly in executive functions (EFs), are a transdiagnostic characteristic common to all forms of psychopathology [1,2]. EFs orchestrate other cognitive abilities to facilitate goal-driven actions and adapt behaviour in novel demanding situations [3], thus EFs are pivotal for success in daily life [4]. Executive dysfunctions, on the other hand, are associated with reduced autonomy [5], impeded functional recovery (e.g. [6])

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and comprise the efficacy of both behavioural and pharmacological therapies across a spectrum of disorders [7–11]. At the same time, global mental health problems are on the rise, causing premature death and significant costs for individuals, families and society [12]. This highlights the need for better, accessible and scalable intervention and prevention programmes, with an additional focus on enhancing executive functioning. Unfortunately, treatments for these disorders do not adequately target cognition, leaving executive dysfunctions inadequately treated [13–15].

EFs rely on the intact neural functioning of the fronto-cingulo-parietal network [16] with frontal-midline (fm)-theta described as the brain communication mechanism of this network [17,18]. The midcingulate cortex and the dorsolateral prefrontal cortex are suggested to be the main generators of fm-theta [19,20]. An increase in fm-theta power is usually associated with improved cognitive processing and predicts successful performance in EFs [21–24]. The absence of fm-theta upregulation is associated with reduced task performance in EFs [25–28]. A neuroscientific method directly targeting cognitive processes by enabling participants to self-regulate the neural underpinnings is neurofeedback (NF).

During NF, real-time measurements of target neural activity are collected, analysed and provided as feedback to participants, allowing them to gradually acquire self-modulation over specific brain functions (e.g. [29–32]). Two critical aspects of NF hold potential for advancing treatment development. First, NF builds on learning mechanisms, such as procedural conditions and skill acquisition are involved [33]. Second, it promotes neuroplasticity through mechanisms like Hebbian mechanisms, homeostatic plasticity and structural plasticity [34–39]. This reflects the brain's capacity to adapt and reorganize itself in response to a changing environment, here also in the context of NF.

NF has shown promise in enhancing cognitive functions across various populations. Studies like Brito *et al*. [40] demonstrate moderate cognitive enhancements in athletes through EEG-based NF, leading to improved sports performance. Renton *et al*. [41] investigated NF's potential in cognitive rehabilitation among stroke survivors, hinting at a possible applicability in clinical recovery. Further extending NF's utility, Jackson *et al*. [42] observed a modest yet significant impact on episodic memory across both healthy and clinical groups, influenced by the type of memory and the effectiveness of self-regulation. The exploration deepens with Trambaiolli *et al.* [43] and Vilou *et al*. [44], who examined the effect of NF on dementia and other neurological conditions, confirming cognitive gains but also pointing out the methodological gaps in the research. These reviews and meta-analyses highlight current research of NF and its broad impact on cognitive effects across various domains and conditions.

Significantly, fm-theta NF, as demonstrated by Wang & Hsieh [45], Enriquez-Geppert *et al.* [46], Eschmann & Mecklinger [47], Brandmeyer & Delorme [48] and Marcos-Martínez *et al.* [49], has been identified as particularly effective in enhancing EFs in healthy individuals. Viviani & Velessi's [50] systematic review underscored that NF protocols targeting fm-theta are the most successful EEG protocols thus far regarding the improvement of EFs. Additionally, meta-analytic work on the specific EFs component working memory updating confirms a medium-sized effect through fm-theta NF [51].

However, NF encounters inherent challenges in training and treatment approaches. Notably, inter-individual variability in learning to self-regulate brain activity, along with the presence of 'non-responders' [52,53], demands focused attention and solutions. Recent advancements in NF methodology encompass real-time brain activity decoding [54], personalized NF tailored to individual anatomical and functional networks [55] and innovative NF techniques involving semantically guidance through mental states [56].

Regarding the application of fm-theta NF in (sub)clinical training, NF-specific improvements have been shown at six-month follow-up. A recent mega-analysis on fm-theta NF also suggests that NF non-responders report psychiatric disorders and EFs complaints more often than responders [57]. Additionally, recent advances indicate that impaired neuroplasticity plays a pivotal role in neuropsychiatric disorders (e.g. [58–60]), which might also negatively influence training and treatment outcomes.

Interestingly, psychedelics like psilocybin and LSD have shown rapid and long-lasting clinical benefits even after only a few doses, notably in conditions such as treatment-resistant depression [61–64]. The crucial effect of psychedelics on neuroplasticity involves both inter-cellular [65] and intra-cellular [66] activation of the 5HT2a receptor, initiating a signalling cascade that drive neuroplastic changes [67,68]. Moreover, psychedelics exhibit a strong affinity for binding directly to the BDNF receptor TrkB, making them potent psychoplastogens that create a critical period for activity-dependent effects [69].

One challenge in the widespread clinical use of psychedelics is their potent hallucinogenic properties, which require close monitoring during extended sessions in controlled environments. Recent studies indicate that repeated microdosing of psychedelics, involving sub-threshold doses (about 1/10th to 1/20th of a therapeutic dose, taken 3–4 times weekly), leads to biomarkers indicative of neuronal plasticity. This includes direct and indirect markers like elevated plasma BDNF levels [70], as well as subtle, long-term changes in functional connectivity [71–73]. For an overview, refer to Polito & Liknaitzky [74].

Consequently, by promoting activity-dependent changes in the neuronal networks influenced by neuromodulators, microdosing could serve as a valuable adjunct to interventions like NF training. To fully optimize the capacity of cognitive improvement and ensure lasting impact of these improvements in daily life, we advocate for a novel, synergistic strategy that combines fm-theta NF with a powerful agent for neuroplasticity enhancement. Given the unprecedented nature of this strategy, a feasibility study is essential to assess the suitability of this intervention for further research. By identifying and addressing potential methodological adjustments, feasibility studies are instrumental in optimizing the design and efficacy of future randomized controlled trials [75–77].

The primary goal of this feasibility study was to assess the practicality of participants' ability to perform NF after taking microdoses and to test the preliminary efficacy of this psychedelic-assisted NF training. We employed a small-scale demonstration study using a brief three-session that integrates psilocybin microdosing with fm-theta NF, following a preparatory week of microdosing adaptation. Our study design adopts a semi-naturalistic lab setting, incorporating experimental assessments of EFs, self-reported EFs evaluations in participants' daily lives and considerations of their individual training goals. These were identified by asking participants before and after training about their goals to be achieved through psilocybin-assisted NF, their

initial and post-training levels of functioning in relation to these goals and their satisfaction with the outcomes regarding their goals. This multifaceted approach aims to improve the real-word applicability and ecological validity of NF training.

Our hypotheses are as follows:

H1: The inclusion of microdosing in the NF regime will not result in premature discontinuation of the training (feasibility aspect: practicality).

H2: The learning trajectories that will be observed in the experimental group will mirror those documented in existing literature, demonstrating an increase in fm-theta amplitude (preliminary efficacy).

H3: The experimental group, undergoing psilocybin-assisted NF, will exhibit significant improvement in both objective and subjective EF measurements compared to the passive control group (preliminary efficacy).

Additionally, we aim to explore whether the experimental group will show advancements in achieving their individualized training goals (external relevance).

2. Methods

Reporting of the methods follows the Consensus on the Reporting and Experimental Design of clinical and cognitive-behavioural NF studies (CRED-nf) checklist [78], and the Consolidated Standards of Reporting Trials of the reporting of randomized feasibility trials (CONSORT) [79] summaries of the checklists can be found in the supplementary material.

(a) Recruitment and inclusion criteria

Our semi-naturalistic study is aimed at individuals who decide to microdose independently of our research initiative. Given the nature of the feasibility study, a formal sample size calculation is not required, but we aimed for about 40 participants. Participants were recruited from an online microdosing workshop of the Dutch Microdosing Institute on two occasions, where the study was introduced as a general assessment of microdosing's impact on cognition. Informed consent was obtained, and participants were screened prior to participation to ensure that they met the following inclusion criteria: (i) no history of psychotic disorders (including family), (ii) normal or corrected vision, and (iii) three weeks of drug abstinence prior to the first measurement. Participants were randomly allocated (using the rand. Matlab function on the participant IDs) to either the experimental or passive control group by one of the authors. To minimize motivational differences, the passive control group was blind to the inclusion of NF from the experimental group. Participation in this study was voluntary, and no rewards were given. The study was not pre-registered.

(b) Procedure and materials

(i) Online and lab data collection

Data collection for both the pre- and post-assessment occurred online (§2b(ii)), enabling participants to be tested within their home environments. Fm-theta NF was performed with three sessions in a sound-attenuated EEG lab at the Heymans Institute at the University of Groningen, Netherlands.

Both groups followed an identical three-week schedule for pre- and post-measurements. In the initial week, pre-measurements were taken, and the experimental group began the microdosing adjustment week. During the second week, the experimental group engaged in three NF sessions alongside their microdosing regime. These psilocybin-assisted NF sessions took place on Mondays, Wednesdays and Fridays, adhering to a schedule of alternating dosing days. While the experimental group underwent the microdose adjustment and the psilocybin-assisted NF week, the passive control group had a two-week break. In the third week, both groups participated in the post-assessments. Following this, the experimental group completed their study participation, whereas the passive control group commenced microdosing. They began with the adjustment week and preceded by a week on a stable dose. This phase concluded with a final assessment, no longer falling within the study's scope (figure 1). Participants had the opportunity to receive on-call psychological support throughout the data collection period if they experienced side effects from microdosing.

(ii) Online pre-assessment and post-assessment

Measurements (pre and post) were performed online via Zoom in small groups with a maximum of three participants. After a common introduction, the measures were conducted in individual break-out rooms and monitored by one or two experimenters. The measurements had a uniform structure and lasted about 180 min, consisting of demographic questionnaires and cognitive assessment. Following three domains were assessed: (i) general placebo and expectancy (by general susceptibility and optimism, as well NF and psilocybin-assisted NF-specific experiences, attitudes and expectations), (ii) EFs (by self-rated EFs in daily life and four computerized experimental EF tasks), and (iii) functional abilities (by participant's priorities). The questionnaires were implemented through Qualtrics software (https://www.qualtrics.com). The EF tasks were programmed with OpenSesame software (v. 3.3.10), performed using the cross-platform graphical experiment builder [80] and hosted on MindProbe JATOS 3.7.2 server.

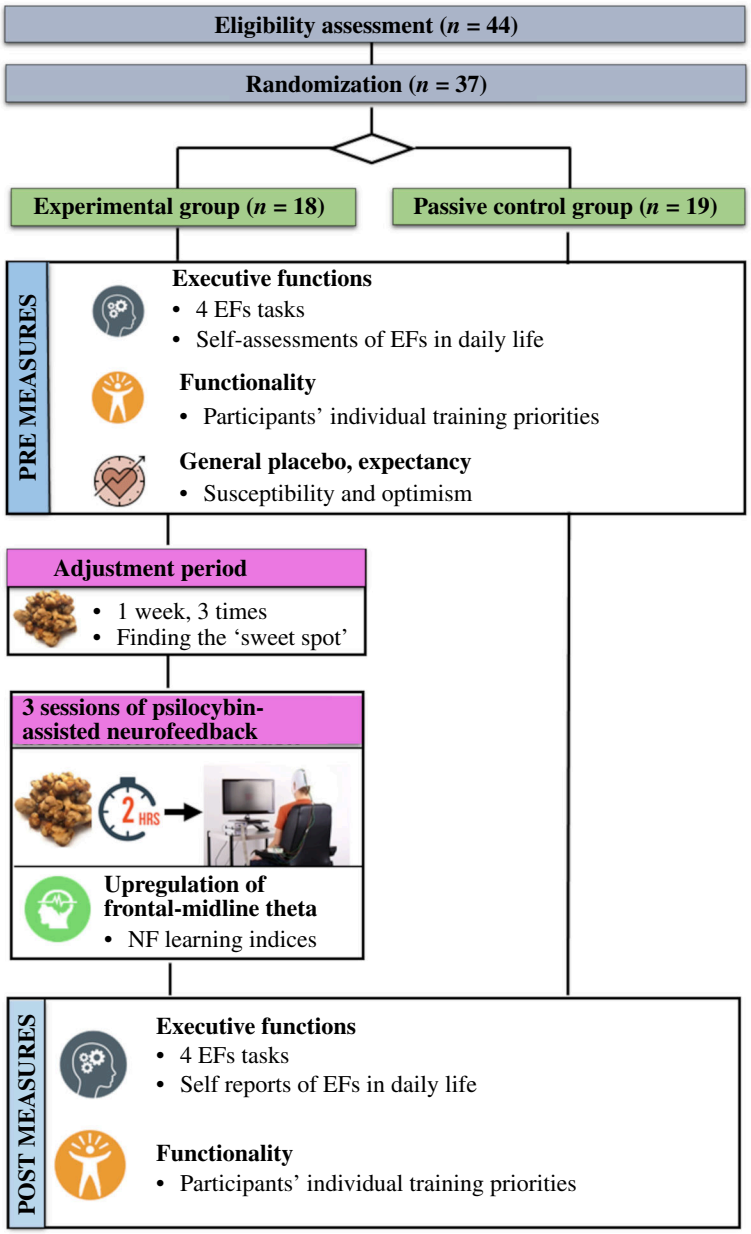

Figure 1. Flow diagram of progress, design and measures of the psilocybin-assisted NF study with two groups showing pre- and post-training assessments of main measures. It also illustrates the intervention, involving a microdosing adjustment period and three psilocybin-assisted NF sessions.

General placebo proxies and expectations regarding psilocybin-assisted neuropsychology

The Revised Life Orientation Task was used to assess dispositional optimism [81]. This questionnaire consists of ten questions that relate to the general outlook on life. Participants rated them on a five point Likert scale ranging from 'strongly disagree' to 'strongly agree' [82].

The Short Suggestibility Survey, a shortened version of the Multidimensional Iowa Suggestibility Scale, was used to assess trait susceptibility [83]. Questions assess susceptibility to suggestion in daily life, by determining the inclination to follow trends or others' opinions and arguments. This scale consists of 21 questions and was collected on a 100-point scale.

Psilocybin microdose expectancy was assessed using the adapted scale [84]. Participants rate their confidence in microdosing and its alignment in their daily routine. This questionnaire consists of four items, each scored on a 100 point scale.

The Experiences, Attitudes and Expectations regarding Neurofeedback Questionnaire [85] consists of six questions regarding their confidence and trust in NF in general, and with psilocybin-assisted NF specifically, each scored on a 100-point scale.

Measures of EFs

Experimental EF tasks

Four EF tasks gauged core functions: working memory updating, set-shifting, conflict monitoring and motor inhibition [3]. Tasks shared stimuli (animal pictures, animal words or letters) and trial structure and involved fast and accurate categorization of animal pictures or words/letter strings [86] into two categories (land or sea animals, or letter case). Word/letter strings were centrally presented above animal pictures and enclosed by a colour frame. We used blue and orange coloured frames

for conflict monitoring, task switching and memory updating tasks. For inhibition tasks, we used green and purple coloured frames. Each colour was prepared in 10 different shades, out of which one shade was randomly selected in each trial. The coloured frames indicated whether pictures or words/strings should be categorized; the colour was counterbalanced across participants. Each trial began with a 300–600 ms fixation cross, followed by a stimulus presentation up to 2000–2300 ms during which participants could respond. This was followed by the presentation of the fixation-cross presentation up to 2600 ms. Responses involved pressing the keyboard letters with index fingers ('X' for the left hand, and 'M' for the right hand). Each task began with the instructions and practice trials, giving the participant the opportunity to practise the task again. Tasks included four blocks, separated by short breaks, except the stop-signal task, which comprised eight blocks (see [87]).

The reference-back task [86] was used to measure working memory updating. The task consisted of sequences of reference and comparison trials. On the comparison trials, it had to be decided whether the animal category corresponds to the category of the last reference. Reference trials could change or remain the same (update versus no update) and were followed by a maximum of five comparison trials. Reference trials, comprising a 1:3 ratio to comparison trials, were marked by a distinct colour frame from comparison trials. The reference category of land and sea animals was presented randomly and equally often. There were 240 trials.

Set-shifting was measured with a switching task. Animal pictures were categorized as usual; however, instead of the words, this task presented letter strings on the animal pictures that had to be categorized into upper and lower case. Participants' current categorization task was indicated by the colour frame and could change or stay (switch versus stay). There were 172 trials; the first 32 trials served as baseline trials without changing the categorization. In the remaining 140 trials, switching between task categorization occurred with a 4 : 6 ratio.

A picture-word interference task was used to measure conflict monitoring. Here, animal pictures and words were either the same (e.g. a picture of a whale on which the word 'whale' was presented) or different (e.g. a picture of a whale on which the word 'rabbit') was shown (conflict versus no conflict). An equal number of congruent and incongruent trials was presented, with a total of 140 trials. Coloured frames indicated the categorization task.

A stop-signal task [88] was used to assess motor inhibition. While mostly categorizing animal pictures, participants had to stop when the stop signal was presented. A stop signal was indicated by a colour frame change and presented with a stop-signal delay (SSD) after the stimuli onset in stop trials (e.g. [88,89]). The SSD, set at 250 ms, was dynamically adjusted based on participants' performance success of stopping in 50% of the stop trials. After each correct stop trial, 50 ms were added; after an incorrect stop trial, 50 ms were subtracted. If a threshold of 90 or 910 ms was exceeded, SSD was reset to 250 ms. This task consisted of 400 trials in which 25% were stop trials. In the trial sequence, no two-stop trials could be presented after each other.

EF in daily life

The Behaviour Rating Inventory of Executive Function-Adult Version (BRIEF-A; [90]) was used to assess EFs in everyday life [91]. Participants self-assess their EF capabilities across a range of behaviours (e.g. 'I have difficulty moving from one task to another') via a three-point scale ('never', 'sometimes' and 'often'). BRIEF-A consists of nine subscales. For this study, we focused on four: working memory, shift, task monitor and inhibit. These subscales correspond directly to the four objective EF tasks.

Measures of functional ability in everyday life using participants' individual training goals

Participants were first asked to express their individual training goals, by using open-end questions, with the option to specify up to four priorities. They then rated their current functioning on a scale from 1 to 100 (pre-functioning) and the expected level of functioning they aimed to achieve post-psilocybin-assisted NF (expected functioning). Following the intervention, participants were then asked to re-evaluate their functioning (post-functioning) and indicate their satisfaction with the extent to which they had attained their expected outcomes (satisfaction).

Participant goals were grouped qualitatively based on broad descriptives. Cognition (n = 17) describes goals that were focused on regulating mental processes. Presence (n = 18) refers to goals centred around mindfulness and bodily awareness. Mood (n = 13) refers to goals that target the upregulation of well-being or removal of anxiety. Connection (n = 5) refers to goals revolving around increased sociability. Other (n = 9) categories goals that do not fit the aforementioned descriptives.

(iii) EEG recordings and pre-processing

EEG measurements were conducted by trained research assistants. The EEG was recorded using a 15 Ag/AgCl electrodes Waveguard connect cap, an average reference Twente Medical Systems International (TMSI) REFA amplifier and Openvibe recording software [92]. Electrode placement followed the international 10–20 system. Electrode impedances were regularly checked to ensure they were below 10 kΩ. The amplifier provided 24-bit resolution EEG data at a sampling rate of 256 Hz.

(iv) Three-session psilocybin-assisted NF training

Substance description: psilocybin

Participants used 12 g of fresh *Psilocybe mexicana* truffles, portioned in 1 g vacuum packs. These were obtained via Microdose.nl (https://www.microdose.nl/en), a Dutch microdosing shop. Participants received a study participation discount code from the Dutch Microdose.nl shop that covered the truffle's costs if redeemed.

Psilocybin microdosing adjustment phase

In the adjustment phase of the first week, participants sought their optimal psilocybin dose, exploring on Tuesday, Thursday and Saturday with one varied dose until satisfied with their chosen amount. The Microdosing Institute advised a dosage range of 0.5–2 g.

Psilocybin-assisted NF training

The experimental group was advised to take their psilocybin dose 2 h before the NF appointment, which was scheduled in the morning. This time corresponds with the time of the so-called peak, where both psilocybin blood concentration and intensity of acute effects reach their peak (e.g. [93–95]).

Three 30 min NF sessions were performed for the upregulation of fm-theta. An NF session began with EOG calibration, which involves calculating the subject-specific artefact-associated frequency band. Each of the NF sessions comprised six 5 min blocks of NF, separated by self-paced breaks. Before and after the NF blocks, a 5 min resting-state measure with eyes open was taken (start/end baseline). In addition to the standard resting-state instructions (keep eyes open, think of nothing in particular, blink and breathe normally), we emphasized that the use of NF strategies should be avoided. During NF blocks, they aimed to upregulate their fm-theta power via feedback (see [46,96]). Participants received a NF logbook containing a list of strategies and a short questionnaire for each block and session and were asked about the strategies they used (§2b(iv)). Participants were motivated to find their own strategies and use their most effective ones.

Online feature extraction, feedback and instructions

CThe five steps of the real-time processing pipeline are described below. First, data acquisition was based on five electrodes covering the fm-brain region (Fz, FC1, FC2, FCz and Cz), the nose served as reference and Fp1 and Fp2 to monitor ocular activity. Second, online data processing was based on the computation of frequency spectra through fast Fourier transformation and a Hamming window for data segments of 2 s, shifting every 200 ms. Data underwent online detrending and rectification. The subject-specific artefact-associated frequency band was monitored for eye blink detection and rejection (see [97]). Third, for feature generation and selection, the raw power value of each 2 s segment in the fm-theta frequency range (4–8 Hz) was compared to the corresponding start baseline power. Fourth, real-time feedback was conveyed through a coloured square on the computer screen that exhibited a colour gradient from highly saturated red to grey to highly saturated blue (with 21 colour gradations). The colour saturation was updated every 200 ms. Red indicated an fm-theta power increase, blue indicated a decrease and grey indicated either an eye blink or no power change relative to the start baseline of the specific NF session. The feedback saturation scale covered 95% of the amplitude range, with values above 97.5% or below 2.5% indicated by maximum red or blue saturation. Fifth, participants were instructed to colour the square as red and as often as possible. For NF, the software NeuroFeedback Suite 2.0 was used. In all, the NF session took roughly 70 min.

Self-reports during psilocybin-assisted NF

At the start of the NF session, participants reported the dosage of their microdose and the time elapsed since consuming the truffles prior to the session in their NF logbook. To assess participants' readiness for NF, we measured their self-reported general fitness ('How fit do you feel today?') and their motivation ('How motivated are you to participate in the neurofeedback training today?'). In addition, we measured their sense of engagement and connection to the study with the question 'As participant, how connected do you feel to this study?'. The answers to these questions were documented on a seven-point Likert scale. They also indicated hours of sleep during the previous night and how many cups of coffee and tea they drank before taking part in NF.

After each NF block, participants briefly explained the strategy employed and rated its effectiveness on a seven-point Likert scale to assess the subjective efficacy of applied NF strategies.

At the end of each NF session, participants also indicated their perception of difficulty ('How difficult did you find this session?'). To assess participants' actual engagement with the NF sessions, we asked them about their level of commitment ('How committed were you to participating in this session?') using in both cases a seven-point Likert scale.

(c) Statistical analysis

(i) Feasibility outcomes

Feasibility outcomes regarding practicality will only be reported descriptively and narratively (discontinuation and need for psychological support).

(ii) NF effects

As with the online processing and feedback, the data were free of eye artefacts. Initially, the NF output was normalized to the overall power (1–40 Hz), and the theta band (4–8 Hz) was extracted. Two learning indices were employed to assess the

impact of fm-theta NF training on theta upregulation. Upregulation of fm-theta was assessed by determining the increase in fm-theta amplitude of a particular block to the session's start baseline. The first learning index reflects fm-theta across the training (i.e. changes between sessions). Mean relative theta amplitude across all six NF blocks was calculated for each session, and subsequently the training effects were analysed using repeated measures (RM) ANOVA with SESSION (1–3) as the within-subject factor. The second learning index represents the dynamical changes across the blocks (i.e. within sessions) [98]. The average relative theta amplitude was computed for the blocks in each session. Effects were analysed using RM-ANOVA with within-subject factor BLOCK (start baseline, NF blocks 1–6 and end baseline).

(iii) Experimental and self-rated EFs

Online experimental EF tasks

For each task, difference values were calculated for RTs (RTs pre substracted from RTs post) and accuracy (accuracy post substracted from accuracy pre), respectively, reflecting improvements for positive values. For each task, a two-way RM-ANOVA was calculated for RTs and accuracy as dependent variables with group (experimental and passive control) as between subject factor and condition (reference-back task: updating, no-updating; task switching: switch, no switch; picture-word interference task: conflict, no conflict) as within-subject factor. For the stop-signal task, only RTs were considered, since accuracy is dynamically adjusted to 50% during task performance. Assumptions of normality and homogeneity of variance were tested. In case of violation, non-parametric/robust tests were performed using Wilcox's paired and non-paired tests and robust ANOVA based on Wilcox [99].

Self-reports of EFs in daily life

A difference score (pre substracted from post) was calculated for the four subscales: working memory, shift, task monitor and inhibit. Based on the hypothesis of improved self-reports for the experimental group, the difference between groupS (experimental and passive control) was assessed using one-sided *t*-tests for independent samples for each subscale, and assumptions of homogeneity and normality were tested.

Participant's individual training goals

Functionality differences in the different priority areas that participants reported as their individual training goals were assessed using a series of paired-sample *t*-tests. Assumptions of normality were assessed using a Shapiro–Wilk test.

(iv) Data preparation and interpretation

Participants whose overall and subtasks' accuracies were below 60% were excluded.

The conflict monitoring task exhibited significantly poorer performance, with 12 out of 37 participants scoring below the threshold. Consequently, we opted to exclude the task from the analysis. The poor performance in this task could be attributed to its placement as an initial task in the online assessment, with participants being less familiar with the environment and the novel tasks.

In the inhibition task, we excluded participants whose overall SSRT was outside the range ±2.5 s.d. from the mean and whose overall accuracy was below 60%. After accuracy checking, 31, 35 and 33 out of 37 participants were included in the analysis of the reference back, switching and stop-signal task, respectively.

For statistical tests, a *p*-value of ≤0.05 was used to determine significant differences. In some analysis, assumptions were slightly violated. Since the effects remained significant in the non-parametric test, we report the results of the parametric tests.

The effect size for RM-ANOVA was indicated by partial eta squared (η^2p) and interpreted as small (<0.06), medium (≥0.06) or large (≥0.14). Confidence intervals (CI) are also given. Statistical analyses were performed using software R (v4.1.0).

3. Results

(a) Participant characteristics

In total, 44 people were assessed for eligibility. Of these, 37 participants met the inclusion criteria and took part in this study (20 female, 16 male and 1 other) with a mean age of 24 years (s.d. = 4.3). Eighteen participants were randomized into the experimental group and 19 into the passive control group. All randomly assigned participants were assessed for each objective, and every member of the experimental group underwent psilocybin-assisted NF (figure 1). Recruitment started in May 2022, and data collection was completed in December 2022.

Of the total, 31 were right-handed (five left-handed and one ambidexter). Most were students (28 students, five employed, three unemployed and one other), with 21 completing a secondary school and 16 a university degree. Most spoke German (n = 12), followed by Dutch (n = 6), and the remainder spoke other languages as their mother tongue.

Most of the participants did not take medication regularly (n = 33). Two participants reported taking either antihistamine or vitamins B12 and D. The majority (n = 28) had no psychiatric disorders beyond those in the exclusion criteria, nine

indicated comorbidities and two reported medication for corresponding disorders (either citalopram or methylphenidate and escitalopram). The study allowed the use of medication to avoid participants having to go without potential medical treatment for an extended period of time.

Half of the participants (19 out of 37) reported regular drug use, and half of this subgroup used multiple drugs (10 out of 18). Among those using regular drugs, most exclusively consumed cannabis (n = 8). Additionally, the majority of the participants mentioned previous psychedelic use (n = 20) (electronic supplementary material), ranging from 5 to 20 times. In this subgroup, the last time of use was more than half a year ago (n = 11), followed by more than three weeks within the last month (n = 10).

(b) Dosing and further self-reports in psilocybin-assisted NF

Participants took on average a microdose of 1.14 g (s.d. = 0.52; minimum: 0.29 g, maximum: 2 g) of Psilocybin mexicana truffles, which they consumed an average of 2.2 h (s.d. = 0.35; minimum: 1.5 h, maximum: 2.83 h) before visiting the lab. The night before the NF sessions, they slept an average of 7 h (s.d. = 0.68; minimum: 5.67 h, maximum: 8 h), drank before coming to the labs an average of 0.64 cups of coffee or tea (s.d. = 0.43; minimum: 0 cups, maximum: 1.5 cups).

At the start of the NF session, participants stated that they felt relatively fit (mean = 5, s.d. = 1.1; minimum: 3.3, maximum: 6.7). In general, they reported being highly motivated (mean = 6, s.d. = 0.03; minimum: 4.3, maximum: 7), feeling very connected to the study (mean = 5.7, s.d. = 0.66; minimum: 4.7, maximum: 6.7), all on a scale from 0 to 7. After the end of the NF blocks, participants rated their strategies for increasing fm-theta as moderately good (mean = 4.2, s.d. = 1; minimum: 3.3, maximum: 5.6) on a scale from 0 to 7. After each NF session, participants rated their commitment to attending the relevant NF session as high (mean = 6, s.d. = 0.88; minimum: 4.33, maximum: 7). The NF sessions were perceived as moderately difficult (mean = 4.2, s.d. = 1.24; minimum: 1.7, maximum: 6), both on a scale from 0 to 7.

(c) Feasibility outcomes

No participant dropped out, no participant requested psychological support throughout the study and no adverse effects were reported.

(d) NF learning outcomes

Figure 2 illustrates the learning trajectory, showing both session-to-session effects (learning index 1) and dynamical changes within sessions (learning index 2). The RM-ANOVA of the first learning index (averaged changes per session relative to the start baseline) showed a trend for significance $F(2,34) = 3.185$, $p = 0.054$, $\eta^2p = 0.158$ (95% CI: 0.00–0.36″), and upregulation of theta was observed with a large effect size. Similarly, the RM-ANOVA of the second learning index (changes relative to baseline and averaged change per block) $F(2.457, 41.765) = 1.303$, $p = 0.285$, $\eta^2p = 0.071$ (95% CI: 0.00–0.23) after applying Greenhouse–Geisser correction) indicated no significant differences within the sessions, upregulation of theta was observed with a medium effect size.

(e) General placebo proxies and expectations regarding psilocybin-assisted neuropsychology

The results of the two placebo effect assessment questionnaires assessing suggestibility ($p = 0.968$) and dispositional optimism ($p = 0.344$) revealed no significant differences between the experimental and passive control groups. Additionally, expectations related to microdosing did not exhibit any significant differences between both groups ($p = 0.761$). Notably, participant expectations for microdosing were lowest, slightly higher for psilocybin-assisted NF, and highest for NF alone (see table 1).

(f) Measures of EFs

(i) Online experimental EF tasks

Main effects group, condition and their interaction of the RM ANOVAs assessing pre–post difference of RTs and ACC of the objective EF tasks were not significant, except for two. However these were not specific for a group and for the EFs condition (figures 3 and 4). A summary of the statistical results as well as interpretation of effect size is given per task in the following section.

Reference-back task RT: group $F(1,29) = 1.473$, $p = 0.235$, $\eta^2p = 0.05$ (0.00, 0.26 95% CI); condition $F(1,29) = 1.060$, $p = 0.312$, $\eta^2p = 0.04$ (0.00, 0.24 95% CI); group × condition $F(1,29) = 1.707$, $p = 0.202$, $\eta^2p = 0.06$ (0.00, 0.27 95% CI) with a medium effect size. Reference-back task ACC: group $F(1,29) = 1.204$, $p = 0.282$, $\eta^2p = 0.04$ (0.00, 0.25 95% CI) was not significant. The main effect of condition was significant $F(1,29) = 5.551$, $p = 0.025$, $\eta^2p = 0.16$ (0.00, 0.40 95% CI), having no switch condition bigger improvement than switch condition $M = 0.021$, SE = 0.0089, $t(29) = 2.356$, p(adj. holm) = 0.025. The interaction group × condition was not significant $F(1,29) = 0.718$, $p = 0.404$, $\eta^2p = 0.02$ (0.00, 0.21 95% CI) with a small effect size. Task-switching RT: group $F(1,33) = 1.098$, $p = 0.302$, $\eta^2p = 0.03$ (0.00, 0.22 95% CI); condition $F(1,33) = 0.045$, $p = 0.833$, $\eta^2p = 0.001$ (0.00, 0.10 95% CI); group × condition $F(1,33) = 1.791$, $p = 0.190$, $\eta^2p = 0.05$ (0.00, 0.25 95% CI) with a small effect size). Task-switching ACC: group $F(1,33) = 1.676$, $p = 0.205$, $\eta^2p = 0.05$ (0.00, 0.24 95% CI); condition $F(1,33) = 1.595$, $p = 0.215$, $\eta^2p = 0.05$ (0.00, 0.24 95% CI), group × condition $F(1,33) =$

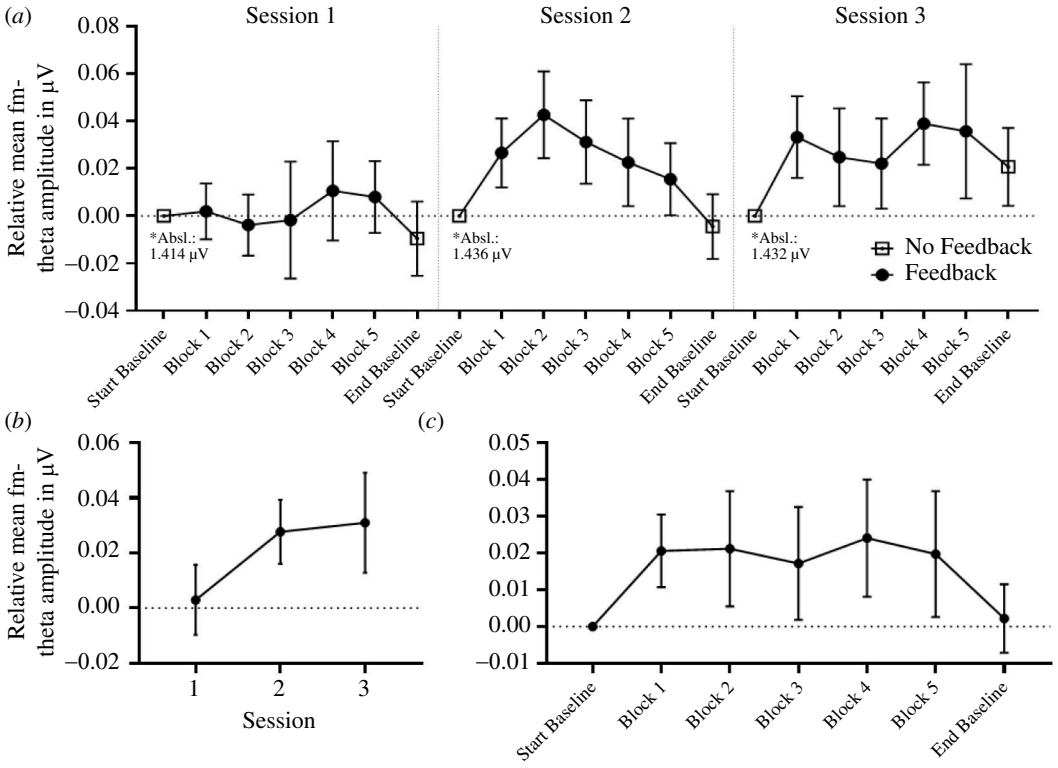

Figure 2. NF learning in the experimental group. This figure illustrates the modulation and learning indices of fm-theta amplitude in the 18 participants. (*a*) Depicts the relative mean fm-theta amplitude for each block per session, with each starting baseline per block's absolute value marked with an asterisk (*) next to the corresponding starting baseline. (*b*) Learning index 1: Mean fm-theta amplitude relative to the respective start baseline per session, averaged across the six NF blocks, elucidating session-to-session changes. (*c*) Learning index 2: Mean fm-theta amplitude relative to the respective start baseline per block, averaged across sessions, revealing dynamical changes within sessions. Error bars represent the standard error of the mean.

Table 1. Expectancy scale results. EXP, experimental group; PCG, passive control Group; SSS, short suggestibility scale; LOT-R, life orientation task; microdosing, microdosing specific expectancy; NF-XP, neurofeedback-specific expectancy; PANF-XP, psilocybin assisted neurofeedback expectancy.

	group				
	EXP (*n* = 18)		PCG (*n* = 19)		
scale	*M*	*SD*	*M*	*SD*	*p*
SSS	32.91	13.73	32.72	14.47	0.968
LOT-R	60.28	16.87	65.526	16.43	0.344
microdosing	57.347	20.64	59.158	14.991	0.761
NF-XP	68.11	21.58	—	—	—
PANF-XP	61.49	16.03	—	—	—

0.430, $p = 0.517$, $\eta^2 p = 0.01$ (0.00, 0.17 95% CI) with a small effect size. Stop-signal task: group $F(1,31) = 0.159$, $p = 0.693$, $\eta^2 p = 0.005$ (0.00, 0.15 95% CI); condition $F(1,31) = 1.866$, $p = 0.182$, $\eta^2 p = 0.06$ (0.00, 0.27 95% CI). The interaction of group × condition was significant $F(1,31) = 5.736$, $p = 0.023$, $\eta^2 p = 0.16$ (0.00, 0.39 95% CI) with a large effect size. Planned comparison revealed changes in RTs in go trials between the groups ($M = 65.0$, SE = 31.7, $t(31) = 2.053$, $p = 0.049$); however, no changes were seen for SSRTs between groups ($M = -41.3$, SE = 42.0, $t(31) = -0.982$, $p = 0.334$). In general, the presence of statistically non-significant *p*-values alongside practically significant effect sizes indicates that the sample size was insufficient [100].

(ii) Self-reports of EFs in daily life

Raw scores of the scales shifting, monitoring and inhibit were in the normal functioning rate. Before psilocybin-assisted NF, both groups exhibited an excess of the threshold for self-rated working memory in daily life, indicating cognitive deficits in this domain.

Self-reports of EFs in daily life showed significantly greater improvements in the experimental group after participating in psilocybin-assisted NF compared to the passive control group in all four subscales (working memory: $t(35) = 2.69$, $p = 0.0054$, $d = 0.885$ (0.31, Inf 95% CI) with large effect sizes; shifting: $t(35) = 2.08$, $p = 0.0226$, $d = 0.683$ (0.12, Inf 95% CI) with medium

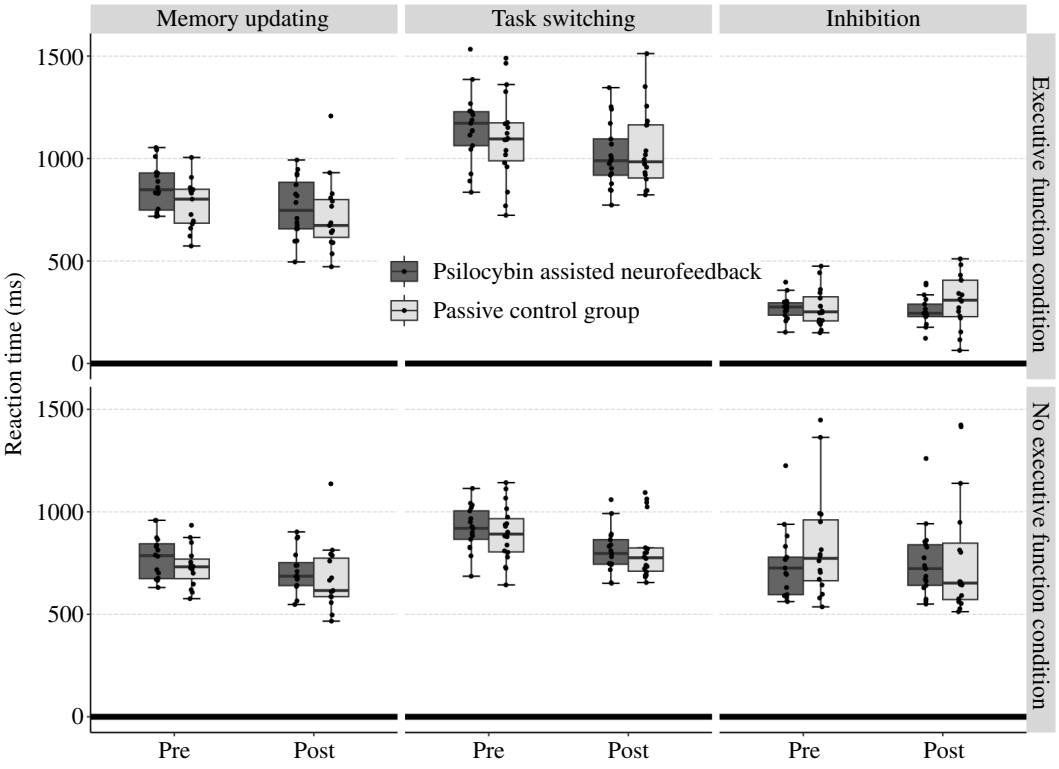

Figure 3. Box plots of RTs for all three EF tasks. This graphic displays RTs across all conditions of the three tasks, both pre and post, for both the experimental and passive control groups. The upper row represents RTs for the conditions involving EFs (update, switch and stop), while the lower row illustrates conditions that do not require EFs (update, stay and go).

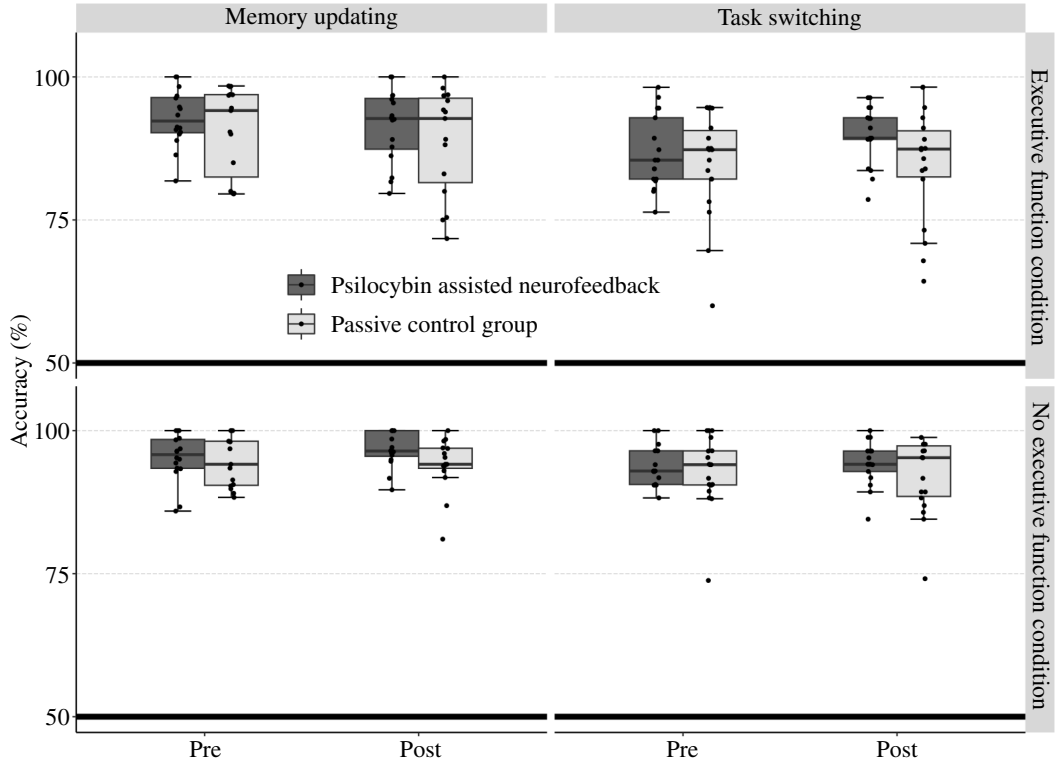

Figure 4. Box plots showing accuracies for two EF tasks. This graphic illustrates accuracy across all conditions of the three tasks, both pre and post, for both the experimental and passive control groups. The upper row shows accuracies for the conditions requiring EFs (update and switch), while the lower row illustrates conditions that do not involve EFs (update and stay).

effect sizes; monitoring: $t(35) = 2.63$, $p = 0.0063$, $d = 0.865$ (0.29, Inf 95% CI) with large effect sizes; inhibition: $t(35) = 2.61$, $p = 0.0067$, $d = 0.857$ (0.28, Inf 95% CI) with large effect sizes). These changes reflected more efficient EFs experienced in daily activities with high effect sizes. In terms of working memory, the experimental group receiving psilocybin-assisted NF showed

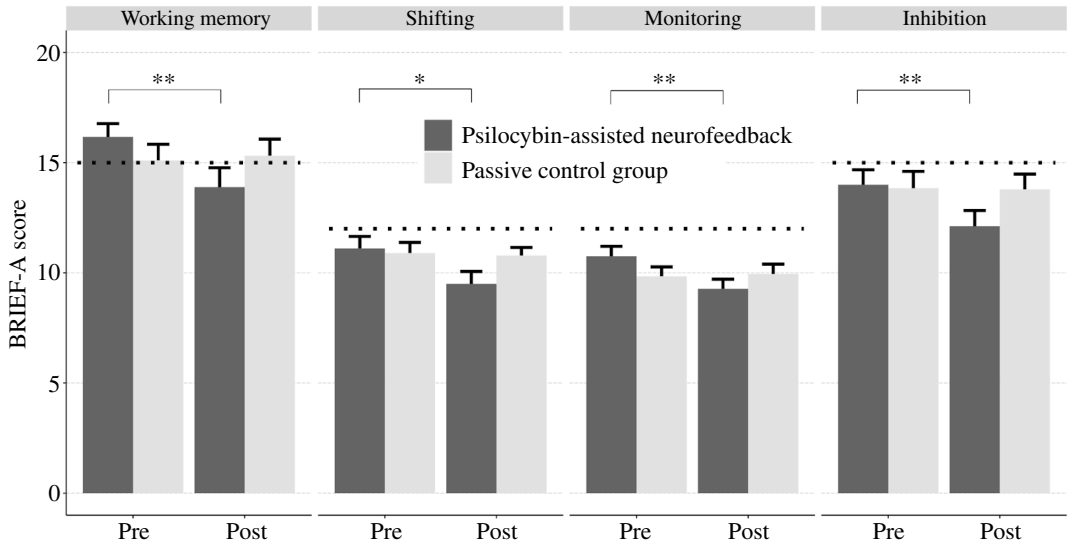

Figure 5. Self-rated EFs in daily life. This figure presents BRIEF-A raw scores before and after the experimental group underwent psilocybin-assisted NF, comparing them to the passive control group. Dotted lines represent scores in the 90th percentile or higher on specific subscales, indicating dysfunctions. A lower score corresponds to better daily life functioning. Significant levels are marked: *$p < 0.05$, **$p < 0.01$.

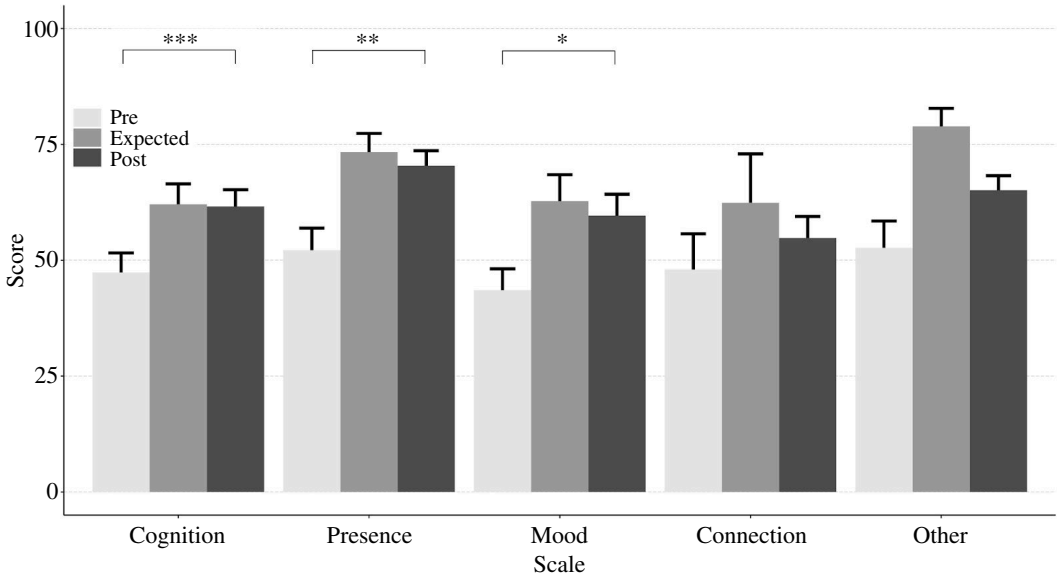

Figure 6. Functionality ratings of participants' priorities. This graphic illustrates the rating in the experimental group after undergoing psilocybin-assisted NF. It displays individual training goals in five domains, with functional scores assessed for pre-functioning (light grey), excepted functioning (medium grey) and post-functioning (dark grey). Significant levels are marked: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

an improvement in their scores and reached a range indicating normalized functioning after training, while the passive control group continued to show deficits (figure 5).

(g) Measures of functional ability in everyday life using participants' individual training goals

Before engaging in psilocybin-assisted NF, the 18 participants of the experimental group rated their functioning in their respective goals as moderate, with mean scores around 50 on a 0–100 scale. They expected slightly improved functioning, with expected scores ranging between 62 and 73 after training. The following findings were yielded, which include also the achieved scores (figure 6).

Significant differences were observed for cognition, presence and mood when comparing functioning ratings before and after undergoing psilocybin-assisted NF. These differences mean notable improvements in these three areas (pre- versus post-functioning cognition $t(16) = 3.895$, $p = 0.001$, $d = 0.945$ (0.36, 1.51 95% CI) with large effect sizes; pre- versus post-functioning presence $t(17) = 3.566$, $p = o.002$, $d = 0.840$ (0.29, 1.37 95% CI) with large effect sizes; pre- versus post-functioning mood $t(12) = 2.520$, $p = 0.027$, $d = 0.699$; 0.08, 1.30 95% CI) with large effect sizes. Their satisfaction with these results can be regarded as medium for cognition and mood, and as good for presence.

However, considering connection, there was no significant difference between functioning before and after psilocybin-assisted NF (pre- versus post-functioning $t(4) = 0.634$, $p = 0.560$, $d = 0.284$ (−0.63, 1.16 95% CI) with small effect sizes). Connection illustrated a non-significant difference between expected and post-functioning ($t(4) = 0.562$, $p = 0.604$, $d = 0.251$ (−0.66, 1.13 95% CI) with a small effect size).

4. Discussion

EF deficits are pervasive across psychiatric disorders and significantly worsen daily functioning. Particularly in people with EF deficits and psychiatric disorders, responsiveness to fm-theta NF seems reduced [57] and a potential reason might be impaired neural plasticity [58]. Together, this hinders the effectiveness of NF-based interventions and limits their applicability as transdiagnostic treatment. This study introduces a pharmacological approach in the field of NF by integrating the potential neuroplastic agent psilocybin into the NF paradigm, which is the first in this field. It demonstrates the feasibility and practicality. After three sessions of psilocybin-assisted NF, participants showed a promising trend in improving self-regulation of fm-theta. When comparing the experimental and passive control groups, no notable improvements were observed in objective EF tasks following the shorter version of psilocybin-assisted NF. Nonetheless, significant differences with medium and high effect sizes between the two groups emerged when evaluating self-rated EFs in daily life. The experimental group that underwent psilocybin-assisted NF exhibited significant improvements in all four EF domains, accompanied by substantial effect sizes when compared to the passive control group. Additionally, participants in the experimental group indicated individual training goals across five domains: cognition, presence, mood, connection and other. Importantly, the majority of these training goals showed significant functionality improvements following psilocybin-assisted NF.

In the subsequent discussion, we will elaborate on five key aspects: feasibility outcome of optimizing NF by improving neuroplasticity, limited-efficacy outcomes regarding NF learning and transfer to EFs, secondary outcome measures regarding individual training goals, special features of the microdosing protocol, study limitations, conclusions and outlook drawn from the psilocybin-assisted NF study. As feasibility studies play a crucial role in improving the conduct and quality of subsequent pilot studies or full-scale randomized controlled trials, we suggest possible improvements to the intervention at the end of each section.

(a) Optimizing NF by improving the overall brain state and readiness for learning shows good feasibility

NF shows potential for clinical applications, with ongoing advancements in methodology for precise brain activity identification and extraction [31]. Additionally, human-computer/human-factor approaches consider task-specific factors, cognitive/motivational traits and technology acceptance for NF optimization [101]. Complementary to these efforts, our study focuses moreover on enhancing the overall brain state and its readiness for learning, aiming to boost neuroplasticity to amplify NF's impact: the current approach therefore combines fm-theta NF with psilocybin.

While previous research on psychedelics has largely focused on high-dose studies, including those that highlight acute neuroplasticity (as reviewed by Calder & Hasler [68]), as well as sustained neuroplastic effects specifically of psilocybin [102,103], recent preclinical evidence is also revealing neuroplasticity changes resulting from repeated microdoses of psilocybin [104] and LSD in humans [70]. As we delve deeper into understanding the complex mechanisms of neuroplasticity and the varied effects of psychedelics, the next logical step emerges: skillfully using these insights to improve therapeutic interventions.

Our study is the first to integrate repeated microdosing with NF, a dosage regime that enhances clinical feasibility by minimizing psychoactive effects, functional impairment and the demand for extensive healthcare support, which is optimal for NF. The evaluation of the feasibility of integrating microdosing with NF, especially at the maximum effect of the substance, yielded good results: There was no dropout and there was no need for psychological support, emphasizing the safety and tolerability of the approach. Participant logbooks revealed a high level of connectedness to the study, with NF sessions conducted diligently (commitment measured after NF). Participants felt they used strategies to upregulate fm-theta during the NF sessions. Although participants acknowledged the increased difficulty of the NF task, their commitment to participation remained high, suggesting that the combined intervention was both manageable and positively received. Together, these results, supported by direct feedback from participants and the absence of adverse effects, confirm the potential of microdosing and NF as a complementary training strategy that warrants further exploration in methodologically rigorous studies. For future studies, we suggest explicitly recording side effects with suitable scales, as has been also suggested for studies with high doses [105].

(b) Main findings regarding NF learning indices

The fm-theta self-regulation results revealed variations in the two learning indicators, providing insights into this specific psilocybin-assisted NF protocol.

In our analysis of the first learning index, the learning progress over the three sessions aligned with patterns documented in prior literature (see mega-analysis by Smit *et al.*, in preparation: [46,48,49,57,106]). Specifically, there is an initial increase of theta from the first to the second NF session, followed by a plateau, and a further increase of fm-theta amplitude in later sessions. The improvement in this first learning index was characterized by a large effect size, almost reaching significance.

The second learning index showed greater variability than typically reported in the literature, with no significant increases and with a medium effect size. This observation gives rise to the question of how the immediate effects of the substance may

influence the ability to self-regulate brain activity. Research by Cavanna *et al*. [107] demonstrates that microdosing psilocybin can acutely reduce global theta power, a finding that has also been shown in studies of LSD microdosing [108,109]. This reduction in theta power may interfere with the objective of fm- theta NF, which aims to enhance theta activity. Consequently, this interaction could explain the observed attenuation of learning curves within our study. Given the potential of psilocybin to open an activity-dependent neuroplasticity window, it is critical to consider the timing of NF sessions in relation to substance.

Future research should explore the most favourable timing that will mitigate the potentially counterproductive effects of the substance on brain activity while taking advantage of the neuroplasticity window that psilocybin may offer.

(c) Main findings regarding objective and self-assessed EFs

The current study took a comprehensive approach, encompassing both experimental EF tasks and participants' self-assessments of their daily life EFs. This dual approach enhances our understanding of cognitive performance in more ideal conditions and its practical application in everyday life. For instance, van Aken *et al.* [110] found that self-assessment of EFs is predictive of daily life outcomes within a psychotic clinical group, whereas performance-based measures did not. Vlagsma *et al*. [111] demonstrated that both objective and self-assessment of EFs could predict the level of patient participation in daily life. Interestingly, the subjective assessment alone was indicative of the quality of life in individuals with Parkinson's disease. These findings argue in favour of a more integrated approach to the assessment of EFs that considers both objective performance and subjective experience in order to fully understand the different measured underlying constructs of EFs.

Regarding the transfer of psilocybin-assisted NF to EFs, we found notable effects on self-reported daily life EFs with a high effect size. However, there were no discernible effects observed in experimental objective tasks. Basically, this may mean that there are no improvements in EFs and that the improvements in self-assessed measures are simple non-specific effects. This explanation is possible because an active control group is missing, which is necessary to elucidate specific effects on cognition. However, it does not explain the different effects seen in the significant results of self-assessed EFs and non-significant results in experimental tasks. In addition, the reduced number of fm-theta NF sessions to three sessions in this feasibility study makes it challenging to specify the improvement compared to the standard training duration of seven [106] or eight sessions [96].

On the other hand, the configuration of the different results on the experimental and the self-assessments may also mean that the three sessions of psilocybin-assisted NF affects the underlying aspects of EFs as measured by the two different ways differently. For example, performance-based measures are thought to measure the efficiency and peak performance of EFs by assessing them in a controlled, optimal performance environment. In contrast, self-assessments primarily reflect an individual's ability to apply EFs in everyday life by capturing the effective integration and application of these functions in real-life scenarios [112,113]. This might suggest that just three sessions may enhance existing daily life EF capacities without immediate improvements in objective task performance, which may manifest later with the typical duration of fm-theta NF. This interpretation is also supported by the fact that there were no differences between the experimental and passive control group in terms of the placebo proxies (suggestibility and dispositional optimism and microdosing expectancies) reflecting explicit aspects of placebo in contrast to implicit. Explicit placebo effects are particularly important to investigate since they are triggered by direct methods such as verbal suggestions (e.g. giving positive information about the training) [114].

Nevertheless, a methodologically sound double-blind study with an active control group and the usual eight sessions is essential for future follow-up studies, and the decision for an active control intervention with microdosing is less problematic compared to high doses, which leads to strong acute subjective experiences and are often recognized as a control condition.

(d) Participant's individual training goals show the external relevance of psilocybin-assisted NF

Furthermore, the incorporation of participant's training goals is deemed essential in the development of effective treatments [115,116]. Participant's training goals identified in our study encompassed various domains, including cognition, and the results indicate significant effects in this regard. This means that participants perceive favourable effects in their priority areas when undergoing psilocybin-assisted NF, underscoring the importance of considering these outcomes for the future acceptance and feasibility of the training in real-world applications emphasizing the external relevance of this training approach. Additionally, this approach supports ecological validity and facilitates the assessment of benefits in real-life scenarios.

(e) Special feature of the microdosing protocol in this study

In this study, we aimed to create a practical environment that combines elements of both controlled laboratory conditions and the complex realities of everyday life. To ensure a subjective effect-based approach, we use a unique dosing strategy where participants are encouraged to find their own optimal dose during an adjustment week based on their experiences, following standardized instructions. We observed a stable dose range between 0.3 and 2.0 g of fresh truffles after the adjustment week. This deviates from the 'one size fits all' approach seen in other studies on psilocybin microdosing [107,117,118]. Given the high variability of subjective effects given a fixed dose (e.g. [119]), which appears to stem from variable genetic factors influencing the metabolism of psychedelics (e.g. functionality of liver enzymes [120,121]) and 5HT2a receptor functionality [122], this subjective dose-finding method provides an advantage. It helps create a consistent experience for participants by circumventing these differences in drug sensitivity and metabolism rates, potentially reducing the variability of the drug effect. Additionally, this methodology closely reflects real-world practices outside of trials where individuals often adjust their doses to maximize benefits while minimizing potential negative effects [123,124].

(f) Feasibility study limitations

Although inherent to the nature of a feasibility study, the reduced number of sessions and only a passive control group can be seen as a limitation, from the perspective of assessing the full potential of the intervention with typical seven or eight sessions. The lack of an active control group poses a challenge regarding discerning whether the observed benefits in self-assessed EFs are specific to the training or due to non-specific factors. Although we analysed both explicit placebo proxies, implicit placebo effects could also play a role [125]. The potential effects of implicit placebos in this study are difficult to assess and are best controlled by an active control group, as they develop through associative learning and positive experiences with the relevant interventions. It is also possible that implicit placebo is even less significant in the context of psilocybin-assisted NF, as this particular combination is new and lacks prior experience.

A limitation of this feasibility study is the lack of laboratory testing to accurately determine the psilocybin dosage in the truffles. Natural substances like truffles can exhibit fluctuations in psilocybin concentration, which can lead to inconsistencies in dosing. This means that although we know how many psilocybin-containing truffles, measured in grams, were ingested, we do not know the actual dose of the pure active ingredient psilocybin ingested by the participants.

(g) Conclusions and outlook

Our study introduces a novel neuroplasticity intervention and shows the feasibility and practicality of psilocybin-assisted NF. This approach offers a unique perspective on psychiatric disorders by focusing on crucial transdiagnostic impairments in EFs, combining neuropharmacology, cognitive neurosciences and psychology in an interdisciplinary way. The essence of psilocybin-assisted NF lies in the potential to induce an increased state of neuroplasticity for a critical period of time, during which NF can be introduced. If confirmed by future replications, pilot studies and full-scale randomized controlled trials, this approach could significantly enhance and sustain therapeutic outcomes. Potential candidates for psilocybin-assisted NF are individuals who face deficits in EFs and experience diminished neuroplasticity, such as those with psychiatric conditions (particularly depression) and the elderly, as such populations could particularly benefit from interventions that include a neuroplasticity enhancer.

Ethics. The study was approved by the Ethics Committee of the Faculty of Behavioural and Social Sciences at the University of Groningen and was conducted in accordance with the Declaration of Helsinki.

Data accessibility. The preprint along with the data can be found on OSF [126].

Supplementary material is available online [127].

Declaration of AI use. We have not used AI-assisted technologies in creating this article.

Authors' contributions. S.E.-G.: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing—original draft, writing—review and editing; J.K.: formal analysis, software, methodology, visualization, writing—original draft, writing—review and editing; F.J.O.: formal analysis, methodology, software, visualization, writing—original draft, writing—review and editing. M.L.: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, visualization, writing—original draft, writing—review and editing, writing—proof reading.

All authors gave final approval for publication and agreed to be held accountable for the work performed therein.

Conflict of interests. We declare we have no competing interests.

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