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Promoting Resilience in Youth through Mindfulness mEditation (PRYME): Study protocol for a randomized controlled trial investigating the effects of mindfulness training as add-on to care-as-usual on internalizing problems, mental illness development, and associated brain and cognitive processes in help-seeking youth

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Abstract

Background Internalizing problems, such as worrying, anxiety and low mood, are increasingly common in youth and may constitute an early stage of mental illness development. There is thus an urgent need for effective measures to address mental health complaints as they develop and to prevent progression into more serious mental illness. Enhanced understanding of early-stage mental illness development, associated cognitive and brain processes, and their amenability to early intervention is crucial to this effort. Mindfulness-based interventions offer an accessible intervention option with demonstrated positive effects on internalizing disorders such as depression. Furthermore, mindfulness-based interventions may modulate cognitive processes and brain activity patterns associated with internalizing disorders. This study aims to determine how early-stage mindfulness-based intervention impacts internalizing symptom development, associated cognitive and brain processes, and mental illness progression in help-seeking youth.

Methods This longitudinal two-arm randomized controlled trial will be conducted in 155 help-seeking youth between 16 and 25 years of age. The investigational treatment, the Learning to Offset Stress program, is an adaptation of existing mindfulness-based programs. Developed for youth with internalizing problems, the training combines mindfulness exercises with mindful physical activity and yoga in 8 weekly 2-hour sessions. Participants are

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randomized to either Learning to Offset Stress program as an add on to care-as-usual, or care-as-usual-only. Assessments take place at baseline, end of treatment, and 2 months and 6 months after completion of treatment. The primary outcome is the level of internalizing problems measured with the internalizing subscale of the Adult Self Report questionnaire at end of treatment. Secondary outcomes include measures of self-compassion, rumination, experiential avoidance, and well-being. In addition, (functional) magnetic resonance imaging and computerized cognitive tasks are conducted at baseline and at end of treatment.

Discussion The current randomized controlled trial aims to enhance our understanding of the trajectory of emerging mental illness, associated cognitive and brain processes, and their modulation by early-stage mindfulness-based intervention.

Trial registration ClinicalTrials.gov NCT05916651. Registered on 23 June 2023.

Keywords Internalizing problems, Transdiagnostic mental illness, Self-compassion, Rumination, Well-being, Mindfulness-based intervention, Youth, Help-seeking, Randomized controlled trial

Background

Recent years have witnessed a steep drop in youth mental health. Increasing rates of mental health problems are observed since the early 2010s, particularly in people up to 25 years [1]. This deteriorating trend in youth mental health has been attributed to various factors, including performance pressure [2], (over)use of internet-connected devices and social media, associated social comparison and self-esteem issues [3], lack of (digital) downtime, as well as socio-environmental crises [4]. Common mental health complaints in youth include so-called internalizing problems, which are characterized by a tendency to direct emotional distress inward, and are particularly prevalent in women and girls [2, 5–8]. Internalizing problems include sadness, self-criticism, anxiety, rumination (i.e., repetitive thinking or dwelling on negative feelings and their causes and consequences), and social withdrawal. As opposed to externalizing problems (e.g., problems with self- and emotion regulation, aggression, and acting-out behaviors), internalizing problems may go unnoticed by others. However, they are associated with various adverse outcomes, including increased risk for suicidal behavior [9] and adverse school, work, and health outcomes [10–12]. Moreover, internalizing problems, particularly when they manifest in youth, may constitute an early stage of emerging mental illness [13, 14].

Mental illness development

Adolescence and early adulthood are the period of highest risk for the onset of serious mental illness [15–17]. This period of life involves major neurobiological and socio-emotional developments that may contribute to the elevated risk for mental illness [18]. Starting in the early-psychosis field, efforts to capture trajectories of mental illness development have yielded a set of disorder-specific at-risk mental states (e.g., for psychosis, mania, depression, and borderline personality disorder). Recent efforts have been directed towards transdiagnostic clinical staging models [19]. These efforts are inspired by epidemiological data showing that the emergence of psychopathology tends to follow complex patterns, with considerable diagnostic instability and comorbidity [20, 21]. These data underscore the need to adopt a broad transdiagnostic approach to elucidate patterns of mental illness development and underlying mechanisms.

According to transdiagnostic clinical staging models, youth who seek help for non-specific mental health complaints, such as internalizing problems, comprise the earliest stage of mental illness development. Individuals showing moderate but still sub-threshold symptoms represent a subsequent clinical stage. These at-risk stages are distinguished from those with more discrete and persisting symptoms (e.g., perceptual disturbances, manic or severe depressive symptoms) or recurrent or unremitting disorders [18]. These clinical staging models have been developed specifically for individuals entering mental health services (i.e., as opposed to non-clinical, community or population-based samples) and build on the premise that transitions across clinical stages are probabilistic (not inevitable), with interventions at each stage aimed at relieving current symptoms and reducing risk for progression to later, more severe, stages [19]. According to these models, progression in clinical stage, however, is unidirectional, meaning that an individual can progress, for example, from an at-risk to full-syndrome stage, but not in the reverse direction [19]. Clinical *stage* is thus different from clinical *state*, which can undergo partial or full remission. Clinical remission, however, does not mean that the underlying (cognitive and/or neural) vulnerability is no longer present. Rather, prior episodes of mental illness tend to increase risk for subsequent episodes [22]. Elucidating the mechanisms of this enduring risk may help develop targeted early interventions aimed at limiting or halting the downhill progression of mental illness development.

Mindfulness-based intervention

A promising early intervention option for internalizing problems in youth is Mindfulness-Based Intervention (MBI) [23]. Mindfulness-Based Cognitive Therapy (MBCT) has been shown to be effective in a range of internalizing disorders including Major Depressive Disorder (MDD) and anxiety disorders, as well as attention deficit hyperactivity disorder (ADHD) and the prevention of depressive relapse [24–29]. Part of the rationale for MBCT is that individuals who are vulnerable to (internalizing) mental illness tend to engage in habitual patterns of cognitive and emotional processing that can induce or worsen symptom development [30]. In MBCT, individuals learn to become aware of these automatic processes and observe them in a non-judgmental manner. This process of "decentering" or developing a more distanced stance from internal experiences may increase an individual's awareness of rigid or negative narratives about themselves and the world, promote a shift from narrative to embodied self-awareness, and increase self-compassion and flexibility [31–33].

The clinical efficacy of MBIs has been established mainly in adult samples with established mental illness, including depression and anxiety disorders, but research suggests that mindfulness training is also a promising intervention option in youth [23, 34]. These meta-analyses, as well as large clinical trials [35, 36] suggest that mindfulness intervention in youth may be particularly effective in clinical settings, to treat symptoms of psychopathology [34], rather than universal preventive intervention efforts, for example in schools [36]. Indeed, effect sizes in clinical samples are nearly three times greater than those in non-clinical samples [34], suggesting that MBIs may be most beneficial to young individuals with mental health needs.

Neural and cognitive processes implicated in mental illness development

Several neural and cognitive processes that have been implicated in (internalizing) mental illness development may be amenable to mindfulness-based (early) intervention. One potential process implicated in the development of internalizing symptoms involves *self-referential processing*. Negativity biases in self-referential processing have been linked to sadness, self-dislike, and indecision in adults with various levels of depression [35] and in youth with (subclinical) depression [37, 38]. Moreover, such biases have been shown to impact reactivity to negative emotions [39]. Together, preferential attention to negative (self-related) information and cognitive reactivity to negative emotions may be relevant subcomponent processes implicated in the downward spiral in thoughts, mood, and behavior that characterizes the onset and relapse of internalizing disorders.

Neural correlates of self-referential processing are found in cortical midline structures comprising the default mode network (DMN) [40, 41]. The DMN is an intrinsic brain network that exhibits consistent activation patterns during rest. Core regions include the posterior cingulate cortex (PCC) and medial prefrontal cortex (mPFC) [42]. Increased DMN activity and connectivity during self-referential processing have been observed in neuroimaging studies of persons with depression and their (at-risk) relatives [43, 44]. Moreover, DMN hyperactivity during self-referential processing has been found to correlate with elevated levels of internalizing problems in (at-risk) children and youth [45]. MBIs may alleviate internalizing problems by reducing excessive self-focus and modulating activity and connectivity of self-referential brain circuits, including DMN. Through the process of decentering, mindfulness training is thought to promote a shift from (excessive) narrative self-focus to more present-centered experiential awareness. This voluntary and effortful process may increase top-down prefrontal control over brain regions involved in self-referential processing [46]. In line with this hypothesis, Brewer et al. [47] observed reduced activation of key DMN nodes (medial prefrontal and posterior cingulate cortex) in experienced meditators, compared to meditation-naïve controls during resting-state functional magnetic resonance imaging (fMRI), along with stronger functional connectivity between posterior cingulate, dorsal anterior cingulate, and dorsolateral prefrontal cortices. Using a Self-Referent Encoding Task (SRET [48]) conducted during fMRI scanning, the current study will assess self-referential processing and its neural correlates, as a function of internalizing problems and mindfulness training, in help-seeking youth. Specific hypotheses for the SRET and associated fMRI data have been preregistered (https://aspredicted.org/v4qt2.pdf).

Another process implicated in emerging (internalizing) psychopathology is *experiential avoidance* [49–51]. Experiential avoidance refers to an unwillingness to stay in contact with unpleasant internal experiences (e.g. thoughts, emotions, bodily sensations) and attempts to alter or suppress them [52]. Although the avoidance of unwanted inner experiences may alleviate distress in the short-term, it tends to exacerbate problems in the long run [53, 54]. Current evidence on experiential avoidance relies predominantly on self-report measures, which are limited by subjective biases. To gain more comprehensive insights into this process, combining self-report with more objective measures is important. The current study complements self-report measures with an experimental paradigm designed to

assess behavioral action biases in the context of aversive stimuli [55]. Assessing the presence and direction of such biases in help-seeking youth may help clarify how aversive action biases, as part of the putative underlying process of experiential avoidance, contribute internalizing mental illness development. The corresponding hypotheses are described in the preregistration of this task (https://aspredicted.org/ui9uf.pdf).

Excessive (or otherwise aberrant) aversive avoidance biases and internalizing problems may stem from abnormalities in the Pavlovian system (cf. [56–58]). The interaction between Pavlovian and instrumental control systems is key for adaptive motivated behavior and contributes to various neuropsychiatric disorders [59]. Pavlovian-to-Instrumental Transfer (PIT) occurs when classically conditioned Pavlovian stimuli, predicting rewarding or punishing outcomes, motivate or inhibit instrumental, goal-oriented behaviors [60, 61]. In recent years, there has been a growing interest in PIT paradigms for understanding healthy behavior [60] as well as psychopathology [59, 62]. However, relatively few studies have been conducted in internalizing disorders [59]. First studies suggest that the inhibitory motivational effect of aversive cues on approach behaviors is either similar [63] or increased [64] in depressed individuals compared to healthy controls. Moreover, the differential motivating impact of the same Pavlovian cues on withdrawal compared to approach actions may be predictive of symptomatic recovery in depression [63]. In the current study, a PIT paradigm will be used to examine how PIT effects are related to internalizing problems and how they are influenced by mindfulness training. The preregistration of this task can be consulted for an overview of the hypotheses (https://aspredicted.org/j7r7-82w5.pdf).

Finally, internalizing symptom development may involve a reduced ability to estimate the *controllability* of the environment. Evidence from work with experimental animals indicates that exposure to uncontrollable stressors induces passivity and a failure to escape subsequent stressors, which does not occur when stressors are controllable [65]. A perceived lack of control over stressors is thought to lead to a failure to learn, a phenomenon called "learned helplessness," which has been widely studied. Learned helplessness has been associated with psychopathology and is known to be enhanced in depression and anxiety disorders [66, 67]. Furthermore, it has been observed that task controllability estimates are lower in highly anxious individuals, especially after exposure to inescapable stress [68]. In the current study, an established paradigm is used to measure controllability estimation [68]. An overview of the hypotheses is provided in the corresponding preregistration (https://aspredicted.org/js5bx.pdf).

Mindfulness-based early intervention in help-seeking youth

Early intervention is crucial to improve outcomes in mental illness. This goal requires improved understanding of the differential stages of emerging mental illness and associated neural and cognitive processes. The current randomized controlled trial (RCT) aims to determine (1) how early-stage MBI impacts internalizing problems, and their potential development into more serious mental illness, in help-seeking youth. In addition, (2) by investigating associated clinical measures and cognitive processes implicated in (internalizing) mental illness, including self-referential processing, this study aims to determine how these processes contribute to mental illness development and whether they can be modulated by MBI. Furthermore, neuroimaging data is acquired to (3) examine neural correlates of self-referential processing and assess structural and functional brain network connectivity.

Methods

Design

This study constitutes a single-blind, two-arm RCT that has been approved by the regional medical research ethics committee (MREC Oost-Nederland), see Fig. 1 for an overview of the recruitment and study procedure. Participants are randomized to either the intervention group, which receives an 8-week MBI program as add-on to care-as-usual (CAU), or the CAU-only control group. Upon completion of the informed consent procedure, participants undergo a general screening and a structured diagnostic interview Mini International Neuropsychiatric Interview Simplified for DSM5 – NL (MINI-S-DSM-5-NL) administered in Dutch by a (resident) psychiatrist to assess DSM-5 criteria and determine eligibility for participation in the study according to the inclusion and exclusion criteria. Included participants then complete the baseline assessment (T0) including self-report questionnaires, (f)MRI scanning, and a set of computerized cognitive behavioral tasks. After data collection at T0, participants are randomly assigned to MBI + CAU or CAU-only. Following the MBI, or approximately three months after T0 for the CAU-only group, participants complete an end of treatment assessment (T1). At T1, the self-report questionnaires, (f)MRI scanning, and cognitive behavioral tasks are repeated. Approximately eight weeks after the end of the MBI, participants assigned to the MBI + CAU group are offered a booster session to refresh skills acquired during training and to troubleshoot any potential issues that may have risen during self-practice in the weeks since completing the training program. Follow-up measurements for both groups are conducted at approximately two months and

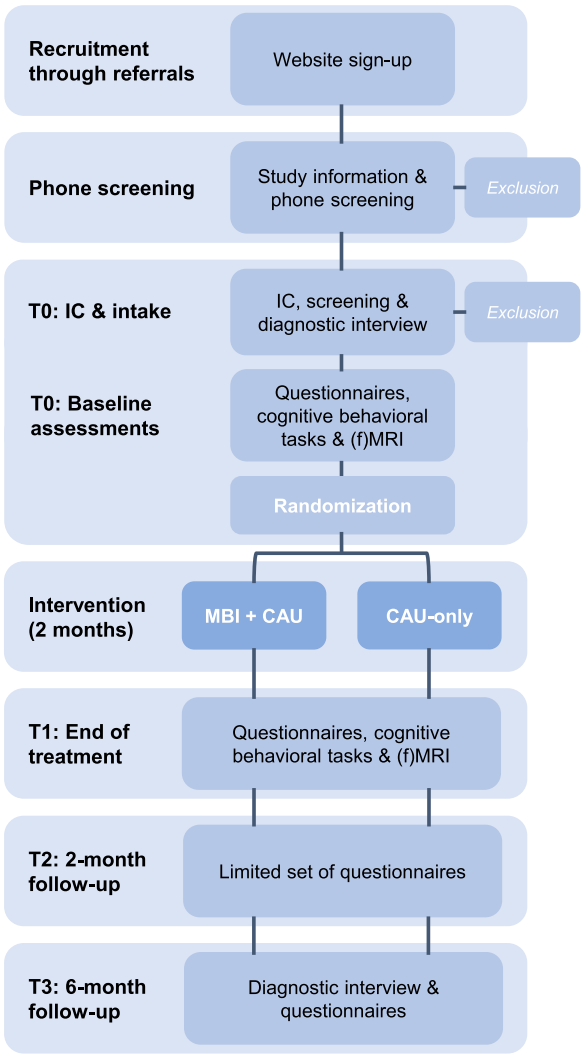

Fig. 1 Recruitment and assessment procedure. A basic screening for inclusion and exclusion criteria is performed over telephone prior to study participation. During the baseline visit (T0), participants undergo a general screening and a structured diagnostic interview to test for eligibility and assess classifications according to DSM-5. Assessments take place at baseline (T0), end of treatment (T1; ± 3 months after baseline), 2-months follow-up (T2; ± 5 months after baseline) and 6-months follow-up (T3; ± 9 months after baseline). Participants assigned to the CAU-only group who participate in the MBI after T3 are invited to complete a small subset of questionnaires upon finishing the training (T4; not shown in this figure). IC = Informed Consent; MBI = Mindfulness Based Intervention; CAU = Care-As-Usual; (f)MRI = (functional) Magnetic Resonance Imaging

six months after completion of the MBI. The 2-months follow-up assessment (T2) involves a subset of self-report questionnaires to be completed at home, assessing internalizing problems, rumination, self-compassion, and well-being. At 6-months follow-up (T3), the structured diagnostic interview (MINI-S-DSM-5-NL) is repeated to assess mental illness development as per DSM-5 criteria over the course of the study and a final set of self-report questionnaires is administered. When completing the study, participants assigned to the CAU-only group have the option to participate in the MBI. Upon finishing the training, these participants are invited to complete a set of questionnaires (T4), comprising the same set of self-report questionnaires as those administered at T2.

Throughout the study, participants are regularly contacted to schedule sessions and receive email reminders to ensure completion of assessments and maintain retention. To further support retention, all participants receive a newsletter twice during the study period (between T0 and T1, and between T2 and T3) with trial updates and knowledge insights related to the study topic. For participants in the MBI + CAU group, the newsletter also includes information on mindfulness and its potential benefits to encourage adherence to the mindfulness practice.

Study population

The target population for this RCT is youth between 16 and 25 years of age who consult primary (mental) health services because of mental health complaints, and who have no lifetime diagnosis of serious mental illness (for definition, see inclusion and exclusion criteria below). Primary (mental) health care providers may include general practitioners, practice nurses, student psychologists, and student support services in the Nijmegen area in the Netherlands. Participants are required to have an adequate mastery of the Dutch language and should be able to provide written informed consent. Participants are excluded if they (1) have a lifetime diagnosis of a schizophrenia spectrum or other psychotic disorder, bipolar disorder, severe MDD, post-traumatic stress disorder (PTSD), or any personality disorder, (2) have a history of a major medical or neurological illness, (3) participated in a formal mindfulness training program in the past year, (4) currently participate in another intervention study, (5) have current moderate to severe substance abuse disorder, (6) experience current active suicidality, or (7) have diagnosed or suspected (mild) intellectual impairment (estimated IQ < 75). Individuals with contraindications for or objections against magnetic resonance imaging (MRI; e.g., ferrous objects in or around the body or claustrophobia) can participate in the study; these individuals complete only the clinical and cognitive-behavioral assessments.

Sample size calculation

The sample size was calculated to ensure sufficient power to detect significant group-differences from T0 to T1 in the primary outcome measure: i.e., internalizing

problems measured with broadband internalizing subscale of the Adult Self Report (ASR) [69]. The estimated effect size for the power analysis was $d=0.4$, based on a meta-analysis of MBIs in youth, reporting an average effect of MBIs on internalizing problems of $g=0.392$ across 29 controlled studies including almost 3000 participants [23]. Given that most of these studies involved non-clinical, school-based samples (with lower variance in internalizing problems), this effect size is expected to be a conservative estimate for the target population of help-seeking youth, as transdiagnostic clinical samples tend to report effect sizes in the 0.40 s and 0.50 s range (e.g., [70]). The required sample size for the current trial was calculated with correction for correlations between internalizing problems at baseline and end of treatment [71], as test–retest reliability of the ASR is in the 0.80 s and 0.90 s range [69] and repeated measurements of internalizing problems in adolescents at one-year intervals have been reported in the 0.50 s and 0.60 s range [72]. Given that the assessment interval in the current study is much shorter at 2 months, 0.65 was taken as a reasonable estimate of the correlation in internalizing problems between baseline and end of treatment. Clustering of data in the intervention arm is accounted for, as mindfulness training is given in groups. Based on prior research in the Radboudumc Expertise Center for Mindfulness (cf. [73]) demonstrating low intraclass coefficients (ICC) in large multicenter trials, the clustering effect in the current single-center trial is anticipated to be small at $\rho=0.01$. The design effect (DE), also known as the variance inflation ratio, is calculated to account for clustering in the data and its impact on the variance of the estimate [74]. With group sizes of around 9 participants on average and no expected change in standard deviation of the outcome due to the intervention, the design effect for this design is .62, given by:

$$DE_{equal} = \frac{1}{2}\left\{[1+(n_1-1)\rho_1]\cdot\left(\frac{\sigma_1^2}{\sigma_{base}^2}\right)+\left(\frac{\sigma_0^2}{\sigma_{base}^2}\right)-2r^2\right\}$$

$$= \frac{1}{2}\left\{[1+(9-1)0.01]\cdot 1+1-2(0.65)^2\right\} = 0.62$$

where σ is the standard deviation (SD) in the intervention group (subscript 1), control group (subscript 0) and of both groups at baseline (base) [75]. The sample size for a post-test design (only follow-up measurement) with 80% power and two-sided significance testing at $p<0.05$ is 200 subjects. Multiplying with the above design effect yields 124 subjects. With a conservative drop-out rate of around 20% (based on clinical trial experience at the Radboud Expertise Center for Mindfulness), a total of $N=124/0.8=155$ youth (i.e., approximately $N=78$ per group, effective sample size of $N=124$ participants) will be recruited. Based on consultations with regional mental health care providers, a sufficiently large source population for the recruitment of study participants is anticipated.

Intervention

The investigational treatment is an 8-week mindfulness program that combines the core elements of Mindfulness-Based Stress Reduction (MBSR) [76, 77] and MBCT [78] with mindful physical activity and yoga in every session, as implemented in the Mindful2Work program [79, 80]. The combined program called the "Learning to Offset Stress" (in Dutch: Leren Omgaan met Stress) (LOS) training, was first developed in 2019 as a clinical program for adolescents with internalizing problems by de Bruin and colleagues at UvA minds, a youth and family treatment center affiliated with the University of Amsterdam (UvA), in liaison with the municipality of Amsterdam. In 2022, the program was piloted and adapted to accommodate the needs of help-seeking youth up to 25 years of age at the Radboudumc Center of Expertise for Mindfulness (Nijmegen, the Netherlands). The LOS program consists of 8 weekly 2-h training sessions that each include approximately 15 min of mindful active movement (i.e., jogging, bootcamp exercises), 15 min of yoga, and 90 min of mindfulness exercises, inquiry, psychoeducation, and cognitive therapy elements. The program also includes compassion elements such as a kindness meditation, modelled after practices from "Mindfulness: A practical guide to finding peace in a frantic world" [81]. Participants are encouraged to engage in a range of at-home exercises including daily mindfulness practices for approximately 20 min per day, with audio support. They receive a workbook tailored in language and style to youth, with week titles kept purposefully short, accessible language, and frequent use of figures. The LOS program does not include an all-day silent retreat. See Table 1 for an overview of the training protocol (a more detailed overview of the training program and at-home exercises can be found in Supplementary Table 1). The LOS training is administered by qualified mindfulness trainers who meet criteria of the Dutch professional association of mindfulness-based trainers (Vereniging Mindfulness Based trainers Nederland; VMBN, https://www.vmbn.nl). Training sessions are videotaped for treatment integrity purposes. For each mindfulness trainer, a random selection of video recordings will be used to assess competency using the Mindfulness-Based Interventions: Teaching Assessment Criteria (MBI:TAC [82]).

Table 1 Overview of Learning to Offset Stress (LOS) training protocol

Week: *Theme*	Content
Week 1: *Attention*	Introduction | Mindful Active Movement (MAM) | Yoga | Raisin exercise | Bodyscan
Week 2: *The body*	MAM | Bodyscan | Yoga | Exercise: 'Walking down the street' | Sitting with the breath
Week 3: *The breath*	MAM | Breath & body meditation | Yoga | Exercise: Pleasant events | 3-min breathing space (intro)
Week 4: *Stress*	MAM | Sitting with sounds & thoughts | Walking meditation | Exercise: Unpleasant events | Yoga
Week 5: *Dealing with difficulty*	MAM | Mid-way evaluation | Yoga | Exercise: Reaction vs. response | Exploring difficulty meditation | 3-min breathing space
Week 6: *Kindness*	MAM | Sitting meditation | Yoga | Exercise: Mindful communication | Kindness meditation | 3-min breathing space
Week 7: *Taking care of yourself*	MAM | Sitting in awareness | Yoga | Exercise: Energy givers & takers | Walking meditation
Week 8: *On your own feet*	MAM | Mountain meditation | Yoga | Sitting meditation | Evaluation | Well-wishing meditation

Overview of key exercises by week and theme for the Learning to Offset Stress (LOS) training program. A more detailed overview of the program, including at-home exercises, is available in Supplementary Table 1

Randomization and blinding procedures

Participants are randomly assigned to either MBI + CAU or CAU-only. Randomization is conducted at the end of T0, and participants are informed about group allocation immediately. The randomization procedure is performed by CastorEDC, an Electronic Data Capture program (www.castoredc.com), and includes stratified, variable block randomization. Stratification factors are sex (M/F) and education level: vocational education vs. (applied) academic education. Stratification is performed because of sex-differences in the prevalence and severity of internalizing problems [83, 84] and underrepresentation of men and lower-educated individuals in mindfulness trials, in order to prevent unbalanced groups.

The Castor EDC system allows for blinded (concealed) randomization. Clinical outcome assessors (including PL) will be blinded to intervention allocation to ensure unbiased outcome assessment. For pragmatic reasons, it is not possible to keep other researchers blinded, as they are involved in performing group allocation and in participant communication. Blinded researchers are informed of group allocation after the structured diagnostic interview and self-report questionnaires at T3 are finalized. Unblinding is considered in case of (suspected) occurrence of an adverse event (AE) or serious adverse event (SAE). In this case, clinical assessors consult with the principal investigator (GC) or senior advisor (AS) to determine if unblinding is deemed necessary for safety reasons. If an outcome assessor is unblinded, any subsequent outcome assessments are performed by another (blinded) outcome assessor. Participants are instructed not to disclose their group allocation to clinical outcome assessors until after their final assessment. Participants can direct potential questions regarding their group allocation to researchers not involved in clinical outcome assessments or to one of the mindfulness trainers.

Clinical assessments

Table 2 provides an overview of assessments per timepoint.

Structured diagnostic interview

The presence of psychiatric disorders is assessed using the MINI-S-DSM5-NL, through Castor EDC. This structured diagnostic interview is conducted at T0 and T3 by a (resident) psychiatrist. Participants who meet lifetime DSM-5 criteria for a psychotic disorder, bipolar disorder, or PTSD at baseline are excluded from the study. If a participant meets criteria for MDD or substance use disorder, the (resident) psychiatrist clinically assesses severity. Participants with mild to moderate symptoms are included; those with severe symptoms are excluded and referred to their own mental health care provider. Suicidality is assessed separately; participants with active current suicidality or any prior suicide attempt are excluded and referred to their own mental health care provider.

Questionnaires

All self-report questionnaire data is acquired using Castor EDC.

Primary outcome measure Internalizing problems are measured using the broadband internalizing subscale of the Adult Self Report (ASR [69]). This self-report inventory contains 126 items comprising eight syndrome scales: anxious/depressed, withdrawn, somatic complaints, thought problems, attention problems, aggressive behavior, rule-breaking behavior, and intrusive behavior. The broadband "internalizing problems" scale is computed as the sum of scores on anxious/depressed, withdrawn, and somatic complaints syndrome scales [69]. Items are rated on a 3-point scale: 0-Not True, 1-Somewhat or Sometimes True, 2-Very True or Often True and

Table 2 Assessments per timepoint

Measurements	Timepoints			
Demographic and clinical assessment				
Demographics (incl. climate anxiety)	T0			
Psychopathology (MINI-S-DSM-5-NL)	T0			T3
Care as usual (CAU)	T0	T1		T3
Screen time	T0	T1		T3
Questionnaires				
Primary outcome measure				
Internalizing and externalizing problems (ASR[b])	T0	T1[a]	T2	T3
Secondary outcome measures				
Self-compassion (SCS)	T0	T1	T2	T3
Rumination (RRQ, brooding subscale)	T0	T1	T2	T3
Experiential Avoidance (AAQ-II)	T0	T1		T3
Emotional and social well-being (MHC-SF)	T0	T1	T2	T3
Other outcome measures				
Trait mindfulness (FFMQ-SF)	T0	T1		T3
Perceived Stress (PSS-10)	T0	T1		T3
Self-esteem (RSES)	T0	T1		T3
Adaptive self-concepts (ASCQ)	T0	T1		T3
Resilience (CD-RISC-10[b])	T0	T1		T3
At-home mindfulness practice				
Adherence (MAQ)		T1	T2	T3
Cognitive behavioral assessments				
Self-Referent Encoding Task (SRET)	T0	T1		
Escape/Avoid Go/No-Go task	T0	T1		
Pavlovian to Instrumental Transfer (PIT) task (optional)	T0	T1		
Control Belief Updating (CBU) task (optional)	T0	T1		
Neuroimaging ((f)MRI)				
Structural scan (T1 MPRAGE)	T0	T1		
Resting-state fMRI (rs-fMRI)	T0	T1		
Task-fMRI (SRET task)	T0	T1		
Diffusion-weighted imaging (DWI)	T0			

T0 = baseline; T1 = end of treatment (± 3 months after baseline); T2 = 2-month follow-up (± 5 months after baseline); T3 = 6-months follow-up (± 9 months after baseline). The PIT and CBU tasks are optional and can be completed online at home within one week after the respective visit. At-home mindfulness practice is only assessed in the MBI + CAU group

[a] primary outcome

[b] permission has been obtained from the copyright owner

concern the past 6 months. The internalizing scale of the ASR has a high internal consistency (Cronbach's α = 0.91) and test–retest reliability of the ASR is in the .80s and .90s [85, 86].

Secondary outcome measures Self-compassion is measured using the Self-Compassion Scale (SCS). The original SCS developed by Neff [87] comprises 26 items. The Dutch version of the SCS, however, excludes two items due to translation challenges, resulting in 24 items in total [88]. Items are scored on a 7-point Likert scale with total scores ranging from 24 to 168. The SCS has a good test–retest reliability and high internal consistency (Cronbach's α = 0.86) [89].

Rumination is measured using the Rumination-Reflection Questionnaire (RRQ) brooding subscale, which contains 12 items scored on a 5-point Likert scale with total scores ranging from 12 to 60 [90]. The brooding subscale of the RRQ has a high internal consistency (Cronbach's α = 0.91) [91, 92].

The Acceptance and Action Questionnaire – II (AAQ-II [93]) is used to measure experiential avoidance. The AAQ-II consists of 10 items, scored on a 7-point Likert scale with total scores ranging from 10 to 70, with higher scores indicating greater levels of experiential avoidance. The mean alpha coefficient for the AAQ-II is 0.84 (0.78 – 0.88). The 3-month test–retest reliability is 0.81 and the test–retest reliability at 12 months is 0.79 [93].

Emotional and social well-being is measured using the Mental Health Continuum – Short Form (MHC-SF [94]). This 14-item questionnaire uses a 6-point Likert scale and total scores range from 0 to 70. The internal consistency for the MHC-SF is high (Cronbach's α = 0.91) [95, 96].

Other outcome measures Mindfulness skills are measured using the Five Facets of Mindfulness Questionnaire - Short Form (FFMQ – SF [97]). This 24-item questionnaire uses a 5-point Likert scale and total scores range from 24 to 120. Internal consistency is high with Cronbach's α ranging from 0.73 to 0.91 for the different subscales. Test–retest reliability is good for subscales describing and acting with awareness ($r = 0.74$ and $r = 0.61$, respectively) and fair for subscales observing, non-judging, and non-reactivity ($r = 0.54$, $r = 0.55$, $r = 0.59$, respectively) [98].

Perceived stress is measured using the Perceived Stress Scale – 10 items (PSS-10 [99]). The PSS uses a 5-point Likert scale, with total scores ranging from 0 to 40. The scale has a high internal consistency (Cronbach's α. = 0.74 – 0.91) and good test–retest reliability ($r = 0.71$ – 0.88) [100].

Global self-esteem is measured using the Rosenberg Self-Esteem Scale (RSES [101]). The RSES is a 10-item questionnaire that uses a 4-point Likert scale with total scores ranging from 10 to 40. The questionnaire has a good internal consistency (Cronbach's α = 0.72 – 0.87) and test–retest reliability ($r = 0.85$) [102, 103].

The Adaptive Self-Concept Questionnaire (ASCQ [104]) assesses properties of the self-concept associated with adaptability. It consists of 25 items that are scored on a 6-point Likert scale. The internal consistency is high for 4 out of 5 subscales, including clarity of the

self-concept (Cronbach's α = 0.75), non-ruminative self-awareness (Cronbach's α = 0.88), openness to self-relevant information (Cronbach's α = 0.79), and modifiability of the self-concept (Cronbach's α = 0.78), and moderate for the self-distance subscale (Cronbach's α = 0.65) [104].

Resilience is measured using the Connor-Davidson Resilience Scale – 10 items (CD-RISC-10 [105]). This questionnaire uses a 5-point Likert scale, and total scores range from 0 to 40. The CD-RISC-10 has a high internal consistency (Cronbach's α = 0.94) and high test–retest reliability (r = 0.88) [106].

At home mindfulness practice for the MBI + CAU participants is assessed using the Mindfulness Adherence Questionnaire (MAQ [107]). The MAQ is a 12-item questionnaire that assesses quality and quantity of formal and quality of informal mindfulness practice in the past week. Items are scored on a 7-point Likert scale ranging from 0 (never) to 6 (always). The MAQ has adequate internal consistency (Cronbach's α = 0.79) [108]. For the current study, questions were adapted to capture average practice per week since the previous study assessment.

Climate anxiety is screened for at T0 using two questions from a recent global survey on climate anxiety in youth [4].

Digital screen time is estimated by asking participants to retrieve their mobile phone and look up their average daily screen time directly from the screen time settings on their phones. Average screentime is based on the days of the last full week registered by their phones. Using screen time settings, participants are asked to provide the percentage of their total screen time that is dedicated to social media usage.

Lastly, all participants provide information regarding the care they received both prior to and during the study as part of their care-as-usual (CAU). At T0, a broad history of the participant's (mental) health care is obtained, along with a detailed assessment of CAU received in the three months prior to the study. At T1 and T3, mental health care use is assessed for the period from T0 to T1 and from T1 to T3, respectively. At each of these time point (T0, T1 and T3), recorded information includes the type of caregiver (e.g., psychologist, nurse practitioner), the form of treatment (e.g., cognitive behavioral therapy), the frequency and duration of sessions, as well as the start date and, if applicable, the end date of treatment.

Cognitive behavioral assessments

Cognitive behavioral tasks are administered at T0 and T1 at the Donders Centre for Cognitive Neuroimaging (DCCN). A schematic overview with experimental task designs of the cognitive behavioral tasks implemented in the current study can be found in Fig. 2. First, a Self-Referent Encoding Task (SRET) is performed partly in the MRI scanner (endorsement phase) and partly in a behavioral lab (free recall and recognition phase). The second task is an Escape/Avoid Go/No-Go task, conducted in a behavioral lab. Two additional tasks, a Pavlovian-to-instrumental transfer (PIT) task and Control Belief Updating (CBU) task, are optional and offered online to be completed at home within one week after the respective visit (T0 or T1). Each task is pre-registered separately on AsPredicted.com, outlining hypotheses and analysis plans per task.

Self-Referent Encoding Task (SRET)

Biases in self-referential processing are measured using a SRET (cf. [48]) (https://aspredicted.org/v4qt2.pdf), see Fig. 2a. Expyriment, a Python library for cognitive and neuroscientific experiments [109], is used to present task stimuli and assess behavioral responses (e.g. reaction times). In the MRI-scanner (or behavioral lab for participants who are not MRI-eligible), participants view a series of positive and negative trait adjectives (e.g., kind, friendly, lazy, boring). For each word, participants are asked to indicate whether or not (yes/no) the adjective describes them (self-condition), their best friend (other-condition) or whether the adjective is a positive trait or not (semantic condition). Directly following completion of the endorsement phase, participants are taken out of the scanner and transferred to a behavioral lab to perform the free recall phase in which they are asked to recall as many words from the SRET endorsement phase as they can remember. Finally, during the recognition phase, participants are presented with trait adjectives on a computer screen (both familiar words and new "distractor" words) and are asked to indicate (yes/no) whether they recall seeing the adjective before. Negativity biases in the context of the SRET are defined as greater endorsement of, and memory for, negative trait adjectives as compared to positive trait adjectives.

Escape/Avoid Go/No-Go Task

Escape and avoidance biases are explored using an established Escape/Avoid Go/No-Go task [55, 110] (https://aspredicted.org/ui9uf.pdf), see Fig. 2b. This task quantifies the bias to invigorate responding when attempting to escape from aversive stimuli, and the bias to inhibit responding when trying to avoid aversive stimuli. Participants learn to either make or withhold a response to escape from or avoid an aversive auditory stimulus. Each trial begins with a cue/response phase, in which a visual cue (fractal image) is presented. On Escape trials, an aversive sound is played (80–85 dB through headphones) together with the visual cue. On avoid trials, cue presentation is accompanied by silence. During cue presentation, participants can either make a response (Go) or

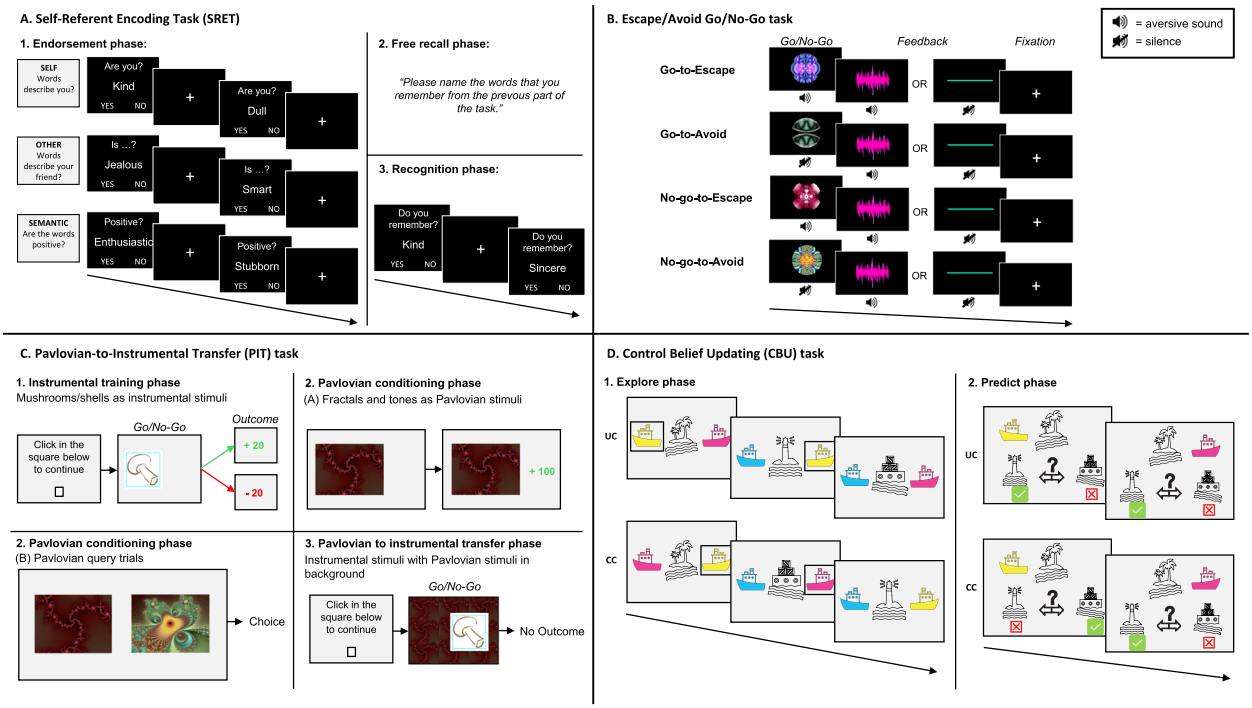

Fig. 2 Overview of experimental designs for the cognitive behavioral tasks in the PRYME study. Panel **A** illustrates the Self-Referent Encoding Task (SRET), panel **B** the Escape/avoid Go/No-Go task, panel **C** the Pavlovian-to-instrumental Transfer (PIT) task, and panel **D** the Control Belief Updating (CBU) task (UC = Uncontrollable Condition, CC = Controllable Condition). The SRET and Escape/Avoid Go/No-Go task are administered at T0 and T1. The SRET involves three phases: an endorsement phase, completed in the MRI scanner, and a free recall and recognition phase, performed outside the scanner in a behavioral lab. During the 'other' condition of the endorsement phase, the name of the participant's best friend is displayed on the screen. The Escape/Avoid Go/No-Go task is fully performed in a behavioral lab. The PIT and CBU tasks are an optional and are offered online to be completed at home within one week after the respective visit (T0 or T1). Detailed descriptions for each cognitive behavioral task can be found in the Methods section

withhold a response (No-Go). The task has a 2×2 design with two stimuli for each condition (Escape/Avoid), and two stimuli for each required response (Go/NoGo). For a go-to-avoid cue, the participant should make a response to avoid the sound from coming on, while for a no-go-to-avoid cue, the participant should refrain from responding to avoid the sound from coming on. For a go-to-escape cue, the participant should make a response to silence the aversive sound, whereas for a no-go-to-escape cue, the participant should withhold responding to silence the aversive sound. Cue presentation is followed by feedback: if the response was correct, this is followed by silence. However, feedback is probabilistic; for each cue, on approximately 20% of the trials, the unpleasant sound is played even if the correct response was made, and vice versa for incorrect responses, with silence for 20% of trials. PsychoPy, an open source software package for creating behavioral experiments [111] (version 2022.2.5), is used to present task stimuli and assess behavioral responses (e.g. reaction times, response accuracy).

Pavlovian to Instrumental Transfer (PIT) task

A Pavlovian to Instrumental Transfer (PIT) task is administered to assess the influence of Pavlovian stimuli on goal-directed instrumental behavior (https://aspredicted.org/j7r7-82w5.pdf), see Fig. 2c. The paradigm consists of (1) an instrumental learning phase; (2) a Pavlovian conditioning phase; and (3) a PIT phase. In the instrumental learning phase, participants are presented with instrumental stimuli (i.e., mushrooms or shells) and learn stimulus-specific associations between Go/No-Go actions and outcomes. The task consists of two action conditions: an approach and a withdrawal condition. In the approach condition, participants must make a 'Go' response to collect 'Good' mushrooms/shells; in the withdrawal condition, participants have to make a 'Go' response to discard 'Bad' mushrooms/shells. Next, in the Pavlovian conditioning phase, a neutral stimulus (i.e., a background fractal) is paired with a reward or punishment (i.e., winning or losing points, combined with "happy" high tones or "sad" low tones respectively) or kept neutral (i.e., no

winning or losing of points and a neutral tone), thereby creating appetitive, aversive, and neutral stimuli. Lastly, in the PIT phase, previously learned instrumental trials are combined with the now paired aversive, appetitive, and neutral stimuli shown in the background. The PIT effect is defined as the difference between instrumental responding, which is operationalized as the proportion of 'Go' actions in the presence of neutral cues compared to instrumental responding in the presence of either appetitive or aversive cues in approach and withdrawal conditions. This task is offered in an online format using the web-based Gorilla Experiment Builder (www.gorilla.sc) [112] as an optional part of the study and can be completed by participants at home at their own time within one week after the respective visit.

Control Belief Updating (CBU) task

Participants are also invited to engage in an online task designed to measure the ability to flexibly update beliefs about task controllability (https://aspredicted.org/js5bx.pdf), see Fig. 2d. This task is based on an explore-and-predict paradigm developed by Ligneul et al. [68], in which participants are presented with a sequence of destinations (i.e., a lighthouse, an island or a harbor; presented one at a time), and each destination is accompanied by two differently colored boats (pink, blue or yellow). Participants are instructed to figure out whether the transition to the next destination depends on which boat they chose. The key experimental manipulation is task controllability, which corresponds to the degree to which their actions (that is, their choice between the boats) determines the transitions between destinations. Task controllability alternates between two types of transition blocks. In the uncontrollable blocks (uncontrollable condition; UC), state-state transitions do not depend on the actions of the participant; it does not matter which boat the participant choses, the next destination is determined by the current destination (i.e. lighthouse follows after island). Conversely, in the controllable blocks (controllable condition, CC), the next destination does depend on which boat was chosen by the participant (state-action-state, i.e. yellow boat goes to the harbor). UC and CC rules switch during the task, so that UC and CC phases alternate, and the goal for the participant is to figure out which rule they think is currently active by exploring the environment. To increase the difficulty of the task, 10% transition noise is introduced. After 4 to 6 trials of exploration, participants are asked to predict the next destination given a specific current destination and a boat during so called prediction trials. In the prediction trial example in Fig. 2d, participants are asked (1) if you are at the island and take the yellow boat, will you go to the lighthouse or the harbor? (2) If you are at the island and take the pink boat, will you go to the lighthouse or the harbor? Note that in the UC rule, the correct answer is lighthouse on both trials, while in the CC rule the correct answers are (1) harbor and (2) lighthouse. These prediction trials are used to infer if participants think the environment is controllable or not. If participants think it is controllable, they should answer differently on the two trials. If participants instead think it is uncontrollable, they should answer with the same response on both trials. The current paradigm allows us to index both the average tendency to perceive the task environment as controllable or uncontrollable, as well as the ability to flexibly update this belief about control when the task environment changes from controllable to uncontrollable or vice versa. The task is implemented using jsPsych [113] (version 7.3.0).

Neuroimaging

MRI images are acquired using a Siemens Skyra 3T MR system (Siemens, Erlangen, Germany), with a 32-channel receiver head coil.

High resolution *T1-weighted magnetization-prepared rapid gradient echo (MPRAGE)* anatomical images are acquired to assess morphometry and for co-registration and normalization purposes (TR: 2300 ms, TE: 3.03 ms, FA: 8°, voxel size: 1.0×1.0×1.0 mm, FOV: 256×256 x 192 mm, GRAPPA acceleration factor: 2; acquisition time: 5m21s).

Functional EPI images are acquired using the same MRI sequence (multi-band 3, multi-echo 3, TR: 1500 ms, TE: 12.40 ms / 34.30 ms / 56.20 ms, FA: 75°, voxel size: 2.5×2.5×2.5 mm, FOV: 210 mm, number of volumes: 325, GRAPPA acceleration factor: 2). Resting state images will be acquired to assess resting-state functional connectivity (rs-FC). Participants are instructed to look at a fixation cross on a screen and let their mind wander, without thinking of anything specific (acquisition time: 8m21s). In addition, task-fMRI will be obtained during the endorsement phase of the SRET to assess changes in brain activation and connectivity during self-referential processing, relative to other-referential and/or semantic processing, as a function of levels of internalizing problems and changes following mindfulness training (acquisition time: 19m28s).

Diffusion weighted images (DWI) scans are acquired to assess structural connectivity and investigate inter-individual differences in structural connectivity in relation to rs-FC and symptom development. DWI data are acquired once, at T0 (or T1 if the scan was not successfully obtained at baseline), as no significant alterations in structural connectivity are anticipated between T0 and T1. Data are acquired while participants view part of a nature documentary (TR: 3320 ms, TE: 93 ms, FA: 90°,

voxel size: 1.9×1.9×1.9, diffusion directions: 131, B-values: 0 and 2000s/mm^2, FOV: 212 mm, GRAPPA acceleration factor: 2; acquisition time: 8m55s).

During all (f)MRI measurements, respiration and heart rate signals are recorded using BrainVision Recorder (Brain Products; Gliching, Germany) to correct MR images for physiological noise.

Statistical analyses

All analyses will be performed on an intention-to-treat basis, with sensitivity analyses conducted according to a per-protocol approach. Analysis plans for the cognitive behavioral assessments are described in more detail in separate preregistrations, which will be referenced throughout.

Statistical analysis of primary outcome measure

The primary outcome measure is the level of internalizing problems as measured with the ASR broadband internalizing problems scale at timepoint T1. Effects of mindfulness training (MBI + CAU vs. CAU-only) on internalizing problems will be assessed using a linear-mixed effects (LME) model. The LME will contain the ASR internalizing score as the dependent variable. The fixed effects in the model are treatment (MBI + CAU vs. CAU-only) and timepoint (categorical variable with three categories: T1, T2, T3), and their interactions. In addition, baseline ASR internalizing score will be included in the model to control for possible differences in baseline scores. Random effects are included for training group (in intervention arm only) and participant (nested in training group if the participant is in the intervention arm). The effect of training group will be evaluated by testing whether the variance of the random effect is significantly different from zero, and will be excluded from the model if the null hypothesis of zero variance cannot be rejected. The interaction between timepoint and treatment is included in the model to be able to study treatment effects that change over time. Timepoint T1 is chosen as the reference category. That means that the estimate of treatment main effect corresponds to the primary outcome of interest: whether internalizing scores differ between treatment groups at end of treatment (T1). As a sensitivity analysis, possible confounds are assessed and accounted for by including covariates (e.g. age, sex, and level of education at baseline) in the model.

Statistical analysis of secondary outcome measures

Secondary outcome measures

Key secondary clinical outcomes, in order of estimated probability of showing changes in response to mindfulness training, are (1) self-compassion, (2) rumination, (3) experiential avoidance, and (4) well-being. These are computed as (1) the total score on the SCS, (2) brooding subscale score of the RRQ, (3) total score on the AAQ-II, and (4) total score on the MHC-SF respectively. The same models used for the primary outcome will be applied to assess the effects of the intervention condition on these secondary outcomes. Following recommended strategies for secondary outcomes, the predefined set of key secondary outcome measures will be tested for statistical significance using sequential order with fixed sequence testing to mitigate multiple comparisons [114]. The testing chain will be broken once there is no significant difference between groups (MBI + CAU vs. CAU-only) for the contrast at T1.

Other outcome measures

Other clinical outcome measures will be reported as exploratory results. These include mindfulness skills (FFMQ), perceived stress (PSS-10), self-esteem (RSES), adaptive self-concept (ASCQ), resilience (CD-RISC-10), and adherence (MAQ). The same models used for the primary and secondary outcome measures will be applied.

Statistical analysis of cognitive task and (f)MRI data

Self-Referent Encoding task (SRET)

Endorsement, recall and recognition of negative and positive trait adjectives in the three experimental conditions (self, other and semantic) will be used for behavioral analysis. Repeated measurements of these data will be compared between experimental groups (MBI + CAU vs. CAU-only) using LME. Details on the analysis are outlined in the preregistration for this task (https://aspredicted.org/v4qt2.pdf).

Escape/Avoid Go/No-Go task

A combination of logistic mixed regressions and computational modelling, in a convergent approach, will be used to address hypotheses for the Escape/Avoid Go/No-Go task. The same approach as in Scholz et al. [115] will be followed. Further details on the analysis can be found in the corresponding preregistration (https://aspredicted.org/ui9uf.pdf).

Pavlovian to Instrumental Transfer (PIT) task

General Linear Mixed-effects Models (GLMMs) will be used to analyze the PIT task data. Depending on the research question, the within-subject factors Pavlovian Valence (either 5 levels: $S^P_{++}/S^P_{+}/S^P_{n}/S^P_{-}/S^P_{--}$, or 3 levels; appetitive, neutral, aversive), Action Context (2 levels: Approach/Withdrawal), Timepoint (2 levels: T0/T1), and between-subject ASR internalizing subscale and ASR internalizing subscale score change from T0 to T1 will be used as fixed effects. The preregistration for this task can

be consulted for further analysis details, such as model specification per research question and sensitivity analyses (https://aspredicted.org/j7r7-82w5.pdf).

Control Belief Updating (CBU) task

A combination of logistic mixed regression and computational modeling, in a convergent approach, will be used to address hypotheses on the CBU task. For this purpose, the same approach as in Ligneul et al. [68] will be followed. Further details on the analyses are described in the corresponding preregistration (https://aspredicted.org/js5bx.pdf).

fMRI analyses

Resting-state fMRI data will be preprocessed using fMRIPrep, a robust preprocessing pipeline for fMRI data [116]. Preprocessing includes brain extraction, spatial normalization, and alignment to the T1 reference. In addition, spatial smoothing will be performed. Preprocessed data will be corrected for physiological noise and motion. A combination of seed-based and network-based approaches will be used to analyze the corrected resting-state data and assess group differences (MBI + CAU vs. CAU-only) in functional connectivity.

Diffusion weighted data will be preprocessed and analyzed using dedicated neuroimaging software packages (e.g. FMRIB Software Library (FSL); https://fsl.fmrib.ox.ac.uk/fsl/, MRTRIX; https://www.mrtrix.org). Data will be denoised, corrected for Eddy currents and B1 field inhomogeneities. Estimated response functions will be used for tractography. Individual tractograms will be used to reconstruct structural connectomes, which will be analyzed using graph theoretical analysis.

fMRI task data (SRET) will be analyzed using neuroimaging software packages, including FSL and Statistical Parametric Mapping (SPM; https://www.fil.ion.ucl.ac.uk/spm/), as well as custom analysis scripts. Data will be preprocessed using fMRIPrep. At first level, a General Linear Model (GLM) will be applied with regressors representing task activity. An additional set of regressors, including motion regressors and physiological noise components will be added as nuisance parameters to remove artifacts. Parameter estimates will then be entered into second level and group-level (MBI + CAU vs. CAU-only) models. Main contrasts of interest include *self-reference > other-reference and/or self-reference > semantic processing*. Both whole-brain and region of interest (ROI) analyses will be performed, focusing mainly on DMN/cortical midline activation (https://aspredicted.org/v4qt2.pdf).

Associations with clinical outcomes measures and diagnostic syndromes

Behavioral outcomes on cognitive tasks and (f)MRI findings will be tested for associations with levels of internalizing problems according to ASR, secondary clinical outcome measures and changes in these measures from pre- to post-intervention (MBI + CAU vs. CAU-only).

Furthermore, exploratory analyses will be performed to assess whether the presence of diagnostic syndromes, as identified through DSM-oriented scales on the ASR and/or MINI-S-DSM-5 classifications, is associated with differences in clinical, cognitive behavioral and neural outcomes. Comparisons will be made between participants with diagnosed syndromes (e.g., depression) and those without, to explore potential variations in intervention effects across these subgroups.

Data management and monitoring

Data is collected at the Radboud university medical center (Radboudumc, Nijmegen, the Netherlands) and DCCN (Radboud University, Nijmegen, the Netherlands). Collaboration between these institutes is based on legal agreements and a Clinical Trial Agreement (CTA) and Joint Controller Data Exchange Agreement are in place between the two entities. Handling of personal data is in compliance with the European General Data Protection Regulation (GDPR). In all study documents, participants are identified by an identification code (pseudonym) only. Access to personal data is granted only to core members of the research team and to the study monitor if requested. Data is preserved for at least 15 years, according to Netherlands Federation of University Medical Centres (NFU) data preservation norms for clinical studies. In correspondence with NFU guidelines, the study will be monitored by an independent, certified monitor who will evaluate (1) the protection of the rights and well-being of the participants, (2) whether the reported research data is accurate and completely verifiable in source documents, and (3) whether the implementation of the research is consistent with the approved protocol/amendment(s) at that time, with GCP and the applicable legal requirements. The frequency and extent of study monitoring is defined in a monitor plan, which has been approved by the Radboudumc Board of Directors as part of the local feasibility application.

Risks and discomforts associated with participation in this study are low/negligible. A detailed data management plan (DMP) has been set up for the current trial and has been approved by data stewards at the Radboudumc and DCCN as part of the local feasibility application process. Adverse events (AEs) are defined as any undesirable experience occurring to a participant during the study including deterioration in mental health (as reported by participants) and development of, or increase in, suicidal ideation (actively screened for using ASR items on suicidality), whether or not related to the mindfulness intervention. All AEs reported spontaneously by the

subject or observed by the investigators during lab visits will be recorded in CastorEDC. Serious adverse events (SAEs), resulting in death (e.g., suicide), life threatening conditions (e.g., attempted suicide), or hospitalization (e.g., admission to a psychiatric hospital), persistent or significant disability or incapacity or other important medical events will be recorded in CastorEDC, and will be reported to the medical research ethics committee following national regulations. SAEs will be reported within 15 days after first knowledge of the SAE or within 7 days if they result in death or are life threatening.

Discussion

Summary

Internalizing problems such as worrying, anxiety, stress. and low mood are increasingly common in youth and may constitute an early clinical stage of mental illness development [117–119]. Current care for youth with these types of problems lacks preventive measures and thus tends to focus on supportive counselling and watchful waiting, while taking advantage of the opportunity for early intervention may prevent progression to more serious mental illness. The current study aims to investigate the effect of an early-stage MBI on internalizing problems and their longitudinal development in help-seeking youth. A broad range of measures is obtained; in addition to careful clinical evaluation, cognitive tasks and (f)MRI scans are collected, to elucidate putative underlying cognitive processes and neural substrates of early mental illness development and whether, and if so how, these are modulated through mindfulness-based early intervention.

Strengths

The mindfulness training program implemented in this RCT is a tailored program developed specifically for youth, but grounded in the exhaustively researched MBSR and MBCT programs. Each training group is guided by two certified mindfulness trainers, including a licensed clinician, who receive supervision from an experienced mindfulness and meditation teacher (AC) and are evaluated for competence based on video recordings assessed using the MBI-TAC. Trainings are administered at the Radboudumc Expertise Center for Mindfulness. A heterogeneous population of youth experiencing internalizing problems is targeted by applying a limited set of inclusion and exclusion criteria, making the study results generalizable to clinical practice. CAU received prior to and during study participation are carefully registered in both groups to detect potential differences in CAU in the CAU-only group compared to the MBI + CAU group, as the mindfulness intervention may influence the need for other treatment modalities or referrals. Clinician-researchers conducting the structured diagnostic interview at 6-month follow-up are blind to group allocation to prevent bias in clinical assessments. In addition to self-report instruments, this study deploys a variety of techniques to acquire more objectively valid data such as a structured diagnostic interview, cognitive behavioral tasks and (f)MRI scanning, whereby creating a rich, extensively phenotyped clinical dataset. Neural substrates and cognitive processes will be assessed through neuroimaging and cognitive behavioral tasks to elucidate underlying factors involved in the potential development of mental illness and how they are modulated by mindfulness-based intervention. Lastly, implementing follow-up assessments at 2 months and 6 months after completion of treatment will give insight in the retainment of possible effects of the MBI after training completion and will allow us to gauge the impact of an (early-stage) MBI on subsequent trajectories of mental illness development.

Limitations

Previous research has shown an overrepresentation of highly-educated and female participants in mindfulness trials [120]. This imbalance is anticipated in the current study as well. Efforts are made to include men and lower-educated participants, by involving mental health care providers in areas of lower socioeconomic status and by explicitly encouraging providers to refer male participants. Another limitation of the current study is the relatively short follow-up period relative to the typical timeline from early-stage symptoms to overt mental illness. Intervention effects on broad outcome measures, such as mental disorders according to DSM-5 criteria as assessed in the structured diagnostic interview, would likely be more informative with a longer follow-up period, but it was considered unfeasible and unethical to withhold the mindfulness intervention from the CAU-only group for longer than the current study duration (approximately 9 months in total). Lastly, neural and cognitive assessments are only collected pre- and post-intervention, and not at 2- and 6-months follow-up due to practical and financial constraints. Therefore, longer lasting effects of the mindfulness intervention on neural and cognitive processes cannot be assessed.

Trial status

The study protocol described here has the following version numbers: Algemeen Beoordelings-en Registratieformulier number NL82568.091.22, and Commissie Mensgebonden Onderzoek Oost-Nederland number CMO2022-16024, version 5.0 (February 12, 2024). The first participant for this study was included on July 7th, 2023. As of November 29th 2024, 87 participants have been included. Of these, 33 participants have finished

all study procedures. Post-intervention measures for the required sample size are expected to be completed by early 2026. Thus far, recruitment is on schedule and sample size estimation is expected to be conservative as drop-out rates to date remain well below the anticipated 20%.

Conclusion

This protocol describes a methodologically robust, two-armed, randomized controlled, single-blinded study design assessing effects of a group-MBI on clinical, cognitive and neural measures acquired in a heterogeneous population of help-seeking youth. The study incorporates a comprehensive range of measurements, including self-report questionnaires, structured diagnostic interviews, cognitive tasks, and (f)MRI assessments at different timepoints. Given a paucity of research into the effects of MBIs in this population, this clinical trial is expected to advance the field of early intervention in mental illness and may contribute to the implementation of MBIs in clinical settings for help-seeking youth at a stage when intervention is potentially more beneficial, less burdensome, and more cost-efficient than treatments required when more serious psychiatric disorders have developed. In addition, the study can contribute to increased understanding of cognitive and neural processes underlying mental illness development and effects of mindfulness-based early intervention on these processes.

Abbreviations

MBI	Mindfulness-Based Intervention
MBCT	Mindfulness-Based Cognitive Therapy
ADHD	Attention Deficit Hyperactivity Disorder
MDD	Major Depressive Disorder
DMN	Default-Mode Network
PCC	Posterior Cingulate Cortex
mPFC	Medial Prefrontal Cortex
(f)MRI	(Functional) Magnetic Resonance Imaging
SRET	Self-Referent Encoding Task
PIT	Pavlovian-to-Instrumental Transfer
RCT	Randomized Controlled Trial
CAU	Care-As-Usual
PTSD	Post-Traumatic Stress Disorder
ASR	Adult Self Report
ICC	Intraclass Coefficient
DE	Design Effect
SD	Standard Deviation
MBSR	Mindfulness-Based Stress Reduction
UvA	University of Amsterdam
LOS	Learning to Offset Stress
M2W	Mindful2Work
VMBN	Vereniging Mindfulness Based trainers Nederland
MBI:TAC	Mindfulness-Based Interventions: Teaching Assessment Criteria
MAM	Mindful Active Movement
AE	Adverse Event
SAE	Serious Adverse Event
SCS	Self-Compassion Scale
RRQ	Rumination-Reflection Questionnaire
AAQ-II	Acceptance and Action Questionnaire
MHC-SF	Mental Health Continuum – Short Form
FFMQ – SF	Five Facets of Mindfulness Questionnaire - Short Form
PSS	Perceived Stress Scale
RSES	Rosenberg Self-Esteem Scale
ASCQ	Adaptive Self-Concept Questionnaire
CD-RISC	Connor-Davidson Resilience Scale
MAQ	Mindfulness Adherence Questionnaire
DCCN	Donders Centre for Cognitive Neuroimaging
CBU	Control Belief Updating
UC	Uncontrollable Condition
CC	Controllable Condition
TR	Repetition Time
TE	Echo Time
FA	Flip Angle
FOV	Field of View
GRAPPA	Generalized Autocalibrating Partial Parallel Acquisition
Rs-FC	Resting-State Functional Connectivity
DWI	Diffusion Weighted Imaging
LME	Linear Mixed Effects
GLMM	General Linear Mixed-effects Model
FSL	FMRIB Software Library
SPM	Statistical Parametric Mapping
GLM	General Linear Model
ROI	Region Of Interest
Radboudumc	Radboud University Medical Center
CTA	Clinical Trial Agreement
GDPR	General Data Protection Regulation
NFU	Netherlands Federation of University Medical Centres
DMP	Data Management Plan

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-024-06430-7.

Supplementary Material 1.

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Authors' contributions

MS and PL share first authorship for the manuscript. GC, AS and RC contributed to the conceptualization and design of the study; GC received funding. GC wrote the first version of the study protocol and all authors contributed to the further development of the study protocol. Participant inclusion, data collection and study management are performed by GC, MS, and P.L. GC is the principal investigator. AS is responsible for supervision of the mindfulness teachers. MS, PL and GC have a major contribution in writing the manuscript, MS and PL contributed equally. AS, RC, DG, HO and FK edited the manuscript. All authors have read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study has received ethical approval from the regional medical ethics committee (METC Oost-Nederland) and is registered under number CMO2022-16024. All participants provide written informed consent before participating in the study. Amendments of the study protocol will be communicated to the medical ethical committee. Substantial amendments will not be implemented until approval by the ethical committee has been obtained.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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