BMC Psychiatry

STUDY PROTOCOL

Open Access

# Smartphone-based Monitoring and cognition Modification Against Recurrence of Depression (SMARD): An RCT of Memory Bias Modification Training vs. Cognitive Control Training vs. Attention Bias Modification Training in remitted recurrently depressed patients with 1.5 year follow-up

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## Abstract

**Background** Major Depressive Disorder (MDD) has a 50–80% recurrence rate highlighting the urgent need for more efficient recurrence prevention programs. Currently, recurrences are often identified too late, while existing preventive strategies may not sufficiently address ethio-patho-physiological mechanisms for recurrence. Negative memory bias (the tendency to better remember negative than positive events), negative attention bias (selective attention favoring mood-congruent information), and cognitive control deficits are important factors involved in the onset, maintenance, and recurrence of depressive episodes.

**Methods** Here we describe the protocol for the Smartphone-based Monitoring and cognition Modification Against Recurrence of Depression (SMARD) study, aiming to investigate different forms of cognitive training programs administered via smartphones, in order to develop a second-generation recurrence prevention program. In addition, we will gather Experience Sampling Method (ESM) assessments during a 6-day period, and during the follow-up period we will obtain behavioral data on (social) activities with BEHAPP, a smartphone-based Mobile Passive Monitoring application for remote behavioral monitoring to identify behavioral changes indicative of an imminent depressive episode. In a randomized controlled trial, SMARD will compare the effects of a smartphone-based Memory Bias Modification Training (MBT), Cognitive Control Training (CCT), and Attention Bias Modification Training (ABT) versus cognitive domain-specific (active-) sham trainings in 120 remitted MDD-patients with recurrent-MDD. Over the course of three

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weeks, participants receive multiple daily training sessions. Thereafter, participants will be followed up for 1.5 years with 3-monthly interviews to assess recurrences.

**Discussion** The SMARD study aims to 1. assess the effects of the cognitive training programs versus their training-specific (active-) sham conditions on changes in memory, cognitive control dysfunction and attention; 2. relate training effects to neural networks previously identified in (recurrence of) MDD (therefore we obtain functional Magnetic Resonance Imaging ((f)MRI) scans before and after the training in a subset of participants); 3. link baseline and change in memory, cognitive control, attention and neural functioning, and ESM data to prospective recurrences; 4. examine whether passive smartphone-use monitoring can be used for prediction of recurrences.

**Trial registration** NL-OMON26184 and NL-OMON27513. Registered 12 August 2021—Retrospectively registered, https://onderzoekmetmensen.nl/en/trial/26184 en https://onderzoekmetmensen.nl/en/trial/27513.

**Keywords** Major depressive disorder, Recurrence, Cognitive training, Cognitive bias, Smartphone-based mobile passive monitoring and modification, Neural networks

## Background

Major Depressive Disorder (MDD) is a highly prevalent (global population prevalence: 4.4% [1]) and severe disorder, with a range of negative outcomes such as persistent negative mood (sadness or irritability), loss of interest, impaired cognitive and occupational functioning and psychophysiological disturbances (e.g., in sleep and appetite). Individuals suffering from MDD have a high risk of developing future episodes (estimated recurrence rate: 50–80% [2]), a risk which appears to increase with each recurrent episode [2, 3].

The debilitating impact of MDD on the individual's life and general health sector stresses the importance of prevention programs that aim to reduce the risk, duration and/or severity of recurrence. In order to improve the effectiveness of existing programs and to inform the development of new prevention programs, considerable effort is made in identifying and modifying potential vulnerability factors for depression and particularly the recurrence thereof (e.g. [4–7]).

Up until now, recurrent episodes are often identified too late and ethio-patho-physiological mechanisms underlying recurrence have been addressed insufficiently [8–10]. Recognition of imminent recurrence often comes too late as people tend to experience difficulties in recognizing early (recurrent/subclinical) symptoms. Thus, symptoms might go unnoticed until they develop into the definite onset of a recurrent episode. As a result of this delayed recognition, a critical window of opportunity to stop further symptom development and return to recovery, is often missed. This highlights the need for prevention programs aimed at early identification of recurrence (risk).

Cognitive models of depression [11–14] consider alterations in emotional processing of information as an important vulnerability factor in the pattern of onset, development and remission/recurrence of depression. Negative memory bias – the tendency to encode and recall (autobiographical) negative events or feelings better than positive or neutral information – has consistently been established as a robust cognitive marker of depression [15, 16].While healthy individuals display a slightly positive memory bias [17], dysphoric individuals and those with symptomatic MDD tend to demonstrate a bias for negative, self-relevant information [18–20]. This negative bias seems to persist in individuals remitted from MDD, who are assumed to exhibit a partial negative bias and a less positive bias [15, 21] and has been implicated in the recurrence of MDD [22].

Attention bias is another type of information processing bias that has been addressed in the context of depression. Individuals with an acute or recurrent MDD tend to exhibit selective attention for negative information, in contrast to the bias towards positive information found in never-depressed individuals [4, 23–25]. Indeed, various studies have found that the difficulty to disengage from negative information is particularly related to depressive symptoms [26, 27] and persists when individuals are in remission [28, 29].

In addition to bottom-up cognitive distortions such as memory and attentional biases, depressive symptoms are associated with impaired top-down cognitive control over emotional information [30, 31]. Cognitive control represents a capacity-limited cognitive resource needed for goal-directed behavior and flexible adaptation [32]. It encompasses the ability to inhibit processing of irrelevant information, to shift attention when distracted by irrelevant information and to update/monitor relevant information [33, 34]. Impairments in cognitive control are suggested to predict new and future depressive episodes in at-risk individuals by hindering effective down regulation of negative information and hence negative mood repair [4, 35–37]. This in turn, fosters repetitive negative thinking (e.g., rumination) – a general vulnerability factor for depressive symptom development [38–40]. Findings thus far, however, are mostly based on cross-sectional

work underscoring the need for further research on the longitudinal relationship between persisting cognitive dysfunction and recurrence of MDD [36, 41].

On the neural level, MDD can be characterized as a network-based disorder and has been linked to disrupted large-scale functional connectivity in several resting-state networks, including the default mode network (DMN), salience network (SN), and cognitive-control and attention regulating frontal networks [42–44]. Recent findings in the DELTA-neuroimaging cohort also support the view of disrupted network dynamics, where a decreased probability and duration of a functional connectivity state—consisting of an extensive network connecting frontal areas with default mode network, striatum, and salience areas – was found in patients compared to controls [45]. Recent meta-analysis, however, suggest no or limited convergence in findings across task fMRI [46, 47] and resting-state measures [48]. It may therefore be particularly important to approach the neurobiology of MDD and its recurrence via dynamics [49] of macroscopic neurocognitive brain networks [50–53].

A large-scale brain network model, relevant for examining aberrant neural functioning in MDD, has been proposed to describe the dynamic and adaptive neural responses to acute stress—based on spatial selectivity and temporal effects of stress-evoked catecholamines and glucocorticoids [54]. These neuromodulators lead in effect to short term up-regulation of the 'salience network' (SN), which is later down-regulated by slower effects of glucocorticoids. The salience network is thought to be related to externally directed attention processes [55, 56]. Another large-scale brain network that has also been found in functional connectivity analyses is the executive control network (ECN [56, 57]). In the large-scale brain network model of acute stress, the ECN is deactivated under acute stress (likely triggered by stress neuromodulators). These networks show an anti-correlated association to the task-negative DMN [58, 59]. These large-scale brain network dynamics have also been generalized to self-regulation failure [60]. In this updated model, the DMN has a modulatory role with respect to the salience and executive control network, in preparation for and in response to environmental stimuli [61–63].

The key role of the DMN in modulating large-scale network dynamics further fits with previous studies suggesting that dominance of activity in this network is associated with MDD recurrence and related to rumination [7, 64]. This is particularly relevant for recurrence of MDD, where self-regulation failure underlies cognitive performance disruption, abnormal affective reactivity and behavioral abnormalities. In fact, depressive symptoms have been defined as a prolonged and severe state of self-regulation failure [65, 66]. Therefore, a common neuronal pattern of shifting large-scale brain networks is likely implicated in both stress and self-regulation [60]. Hence, network disruptions may serve as prospective biomarkers for the onset as well as recurrence of MDD.

In an attempt to ameliorate aberrant information processing biases or cognitive control impairment, various studies investigated the effects of computerized cognitive trainings. Interestingly, when it comes to bias modification trainings, attention bias has received considerably more attention in the literature than memory bias, likely due to its origin in anxiety research. Attention bias modification training (ABT) aims to systemically direct attention toward more benign/positive stimuli and has been found to reduce residual symptoms and recurrence risk in remitted MDD patients [67–69]. Recently, Memory Bias Modification Training (MBT) has been postulated as an alternative to ABT for depression. Results so far indicate that repeated emotional memory training could result in mood changes, increased positive autobiographical recall and lower depressive symptoms [70–72] and results of a smartphone-based MBT were promising [73]. Nevertheless, the field is waiting for a critical test in patients. In line with these developments, cognitive control training (CCT) has been introduced to improve cognitive control impairments in (remitted) MDD individuals, and indeed demonstrated beneficial effects in reducing (residual) depressive symptoms and cognitive vulnerability [74]. Taken together, these cognitive training programs aim to strengthen top-down control and/or reduce bottom-up influences, which in turn, should increase resilience and lower risk of recurrence.

The cognitive trainings described above have often been administered in a laboratory-controlled environment and in single-session settings [75]. The embedded use of smartphones in our daily lives fosters the delivery of trainings in a naturalistic setting and over a longer period of time [76]. Indeed, an increasing number of studies aimed at modification of cognitive biases and cognitive control disseminated trainings through smartphones to increase ecological validity (offering training in the context of daily events and at different locations) and the generalization of potential training effects [77–79]. Therefore, smartphone-based cognitive trainings could serve as promising second-generation recurrence prevention program tools.

### Aims

The general aim of the Smartphone-based Monitoring and cognition Modification Against Recurrence of Depression (SMARD) study is twofold. First, it aims to investigate the effects of different smartphone-based cognitive training programs (i.e., MBT, CCT and ABT)

delivered over the course of three weeks, on cognitive functioning, relevant neural networks and MDD recurrence in a sample of remitted MDD patients with recurrent MDD. The development of recurrence might be identified based on early changes in emotional and behavioral patterns before actual symptoms become apparent. Therefore, the second aim of SMARD is to measure early changes in behavior, indicative of an imminent depressive episode by using continuous and passive monitoring[1] of behavioral data (e.g., GPS, social media use, etc.) with the BEHAPP (https://behapp.org/) smartphone application [81, 82] and to associate Experience Sampling Method (ESM) data with prospective recurrences.

## Methods

### Design

The current study is a double-blind randomized controlled trial (RCT) with six conditions (MBT, CCT, and ABT vs. sham MBT, active-sham Peripheral Vision Task (PVT) and sham ABT) with an observational one-year follow-up, conducted at Radboud university medical centre, Nijmegen, the Netherlands. After obtaining approval for the study from the Medical Ethics Committee Arnhem-Nijmegen (NL60033.091.16/2016–3009), recruitment started in January 2019. The study is registered at the Overview of Medical Research in the Netherlands (NL-OMON26184 and NL-OMON27513). See Supplementary Material for summary of trial registration data.

In brief, remitted MDD-patients with recurrent-MDD will complete baseline cognitive tasks on their smartphone, pre- and post-training. Then, they will receive one or multiple training sessions per day (depending on condition, described below) on their smartphone, over the course of three weeks. MRI-eligible participants will be invited to the research site to acquire a pre- and post-training MRI-scan. Four weeks after the end of the training period, participants again complete cognitive tasks on their smartphone. During a subsequent one-year follow-up, participants will be called every three months to assess recurrence-status of depression (using the Structured Clinical Interview for Axis I Disorders; SCID-I [83]. See Fig. 1 for an overview of the recruitment and design. Substantial amendments to the research protocol will be addressed to all relevant parties (i.e., medical ethics committee, trial register, journals). The reporting of this manuscript is in compliance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.

### Recruitment of participants

Participants will be recruited via advertisements in newspapers, common website and forums for depression. Interested participants can easily contact the researchers. Moreover, individuals with known MDD in remission can be referred by health care professionals in primary care (e.g., general practitioners) and/or mental healthcare organizations. In addition, we will send information letters to potentially eligible patients with recurrent MDD identified from previous studies, electronic medical records in our outpatient departments, and general practitioners. Interested individuals will be informed with written information about the study and contacted by telephone to elucidate this information within a week.

### In- and exclusion criteria for participants

#### *Inclusion criteria*

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Recurrent MDD diagnoses and at least three previous MDD-episodes assessed by a SCID-I;
- Not fulfilling criteria for a current active MDD episode (based on the SCID-I);
- Score $\leq 10$ on the Hamilton Depression Rating Scale (HDRS [84]);
- Being in stable remission ($\geq$ 8 weeks)
- Age 18–65 years;
- In possession of a smartphone[2] and experienced in the use thereof.

#### *Exclusion criteria*

Individuals who meet any of the following criteria will be excluded from participation in this study:

- Diagnosis of bipolar, primary psychotic or borderline/antisocial personality disorder or strong suspicion of this type of disorder;
- Primary diagnosis of substance use or anxiety disorder with secondary MDD (comorbid secondary anxiety disorders are allowed for participation);
- Electroconvulsive therapy (ECT) within two months before inclusion;
- Average alcohol intake of > 3 units/day;
- Daily use of benzodiazepines ($\geq$ 5 mg diazepam or equivalent).

[1] Smartphone-based data collection is one method comprised in the concept 'Digital Phenotyping', defined. [80] as 'moment-by-moment quantification of the individual-level human phenotype in-situ using data from smartphones and other personal digital devices' (p.73).

[2] Participants do the cognitive training on their own smartphone.

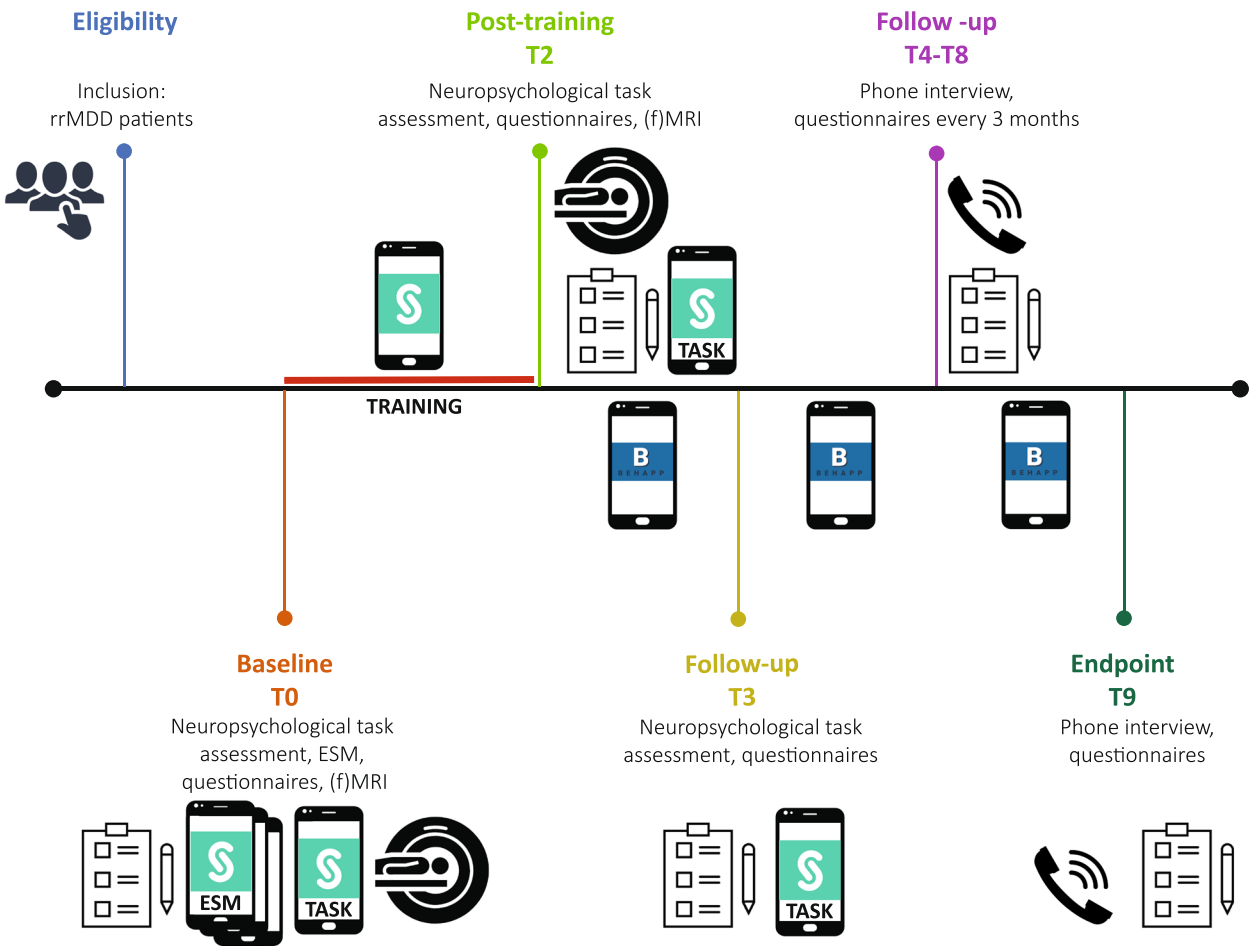


**Fig.1** Design of the Smartphone-based Monitoring and cognition Modification Against Recurrence of Depression (SMARD) study. Assessment time-points of the study are shown in chronological order from left to right. For a description of the questionnaires please see Supplementary Material

***Additional general exclusion criteria***

- Ongoing psychotherapy during the cognitive training;
- Previous CCT, MBT or ABT training.

***Additional MRI exclusion criteria***

For the MRI-part of this study, standard MRI exclusion criteria will apply:

- Metal objects in the body;
- Claustrophobia;
- A history of head trauma or neurological disease, severe general physical illness.

If a participant uses more than one smartphone, they will be requested to complete the assessments and cognitive training on the smartphone used for private matters. Participants with ongoing use of antidepressants are allowed to participate. For neuroimaging no exclusions will be based on handedness.

**Randomization and blinding**

Before the start of the cognitive training, participants are randomized by one of the investigators (HGR or AT; not involved in diagnostic follow-ups) to receive either true MBT, sham MBT, true CCT (Paced Auditory Serial Addition Task; PASAT [85]), active-sham CCT (PVT), true (positively skewed) ABT or sham (equally distributed) ABT. Randomization will be stratified for use of antidepressants (i.e., yes or no) and residual depressive

complaints (i.e., HDRS >5 vs. HDRS ≤5). Concealment of randomization is secured by using the randomization program of Castor EDC, a cloud-based Electronic Data Capture platform, to safely collect, integrate and manage data. True vs. (active-) sham condition will be fully blinded for the MBT, CCT, and ABT, for both participants and clinical assessors. Randomization is managed by a researcher not involved in the assessments.

In order to compensate for withdrawal from the study all participants with insufficient cognitive training (< 80% of completed sessions) will be replaced. In order to obtain adequate groups for neuroimaging, ≥20 participants per true or (active-) sham condition will be recruited with useable pre and post-training MRI data; therefore quality of MRI data will be checked shortly after acquisition.

## Randomized training

### *Memory Bias Modification Training (MBT) versus sham MBT*

In the true MBT and sham MBT, eight prompts will be given per day for a period of 21 days. All prompts will be delivered in semi-random intervals between 06.30 and 23.30 h, tailored to the individual's normal routine of waking up and going to bed. Completion of a prompt takes approximately 3 min.

Every day, participants will receive a prompt at the start of the day with a sleep-related question ("I slept well) with answer options on a 7-point scale ranging from 'not at all' to 'very well'. At each prompt the participant will be asked to assess his/her current mood using statements regarding positive mood, negative mood, relaxation and stress ("I feel happy", "I feel sad", "I feel relaxed" and "I feel stressed") that should be answered on a 7-point scale ranging from 'not at all' to 'very much'.

Next, participant in the true MBT condition will be asked to recall a recent positive event ("Think about the best and most enjoyable event since the previous set of questions. Try to imagine the event as if are experiencing it right now, as vividly as possible"). On a 7-point scale, they have to evaluate this positive event ('very unpleasant' – 'very pleasant'), indicate how much they have thought about it ('not at all' – 'very much'). Moreover, they have to indicate how long ago the event happened

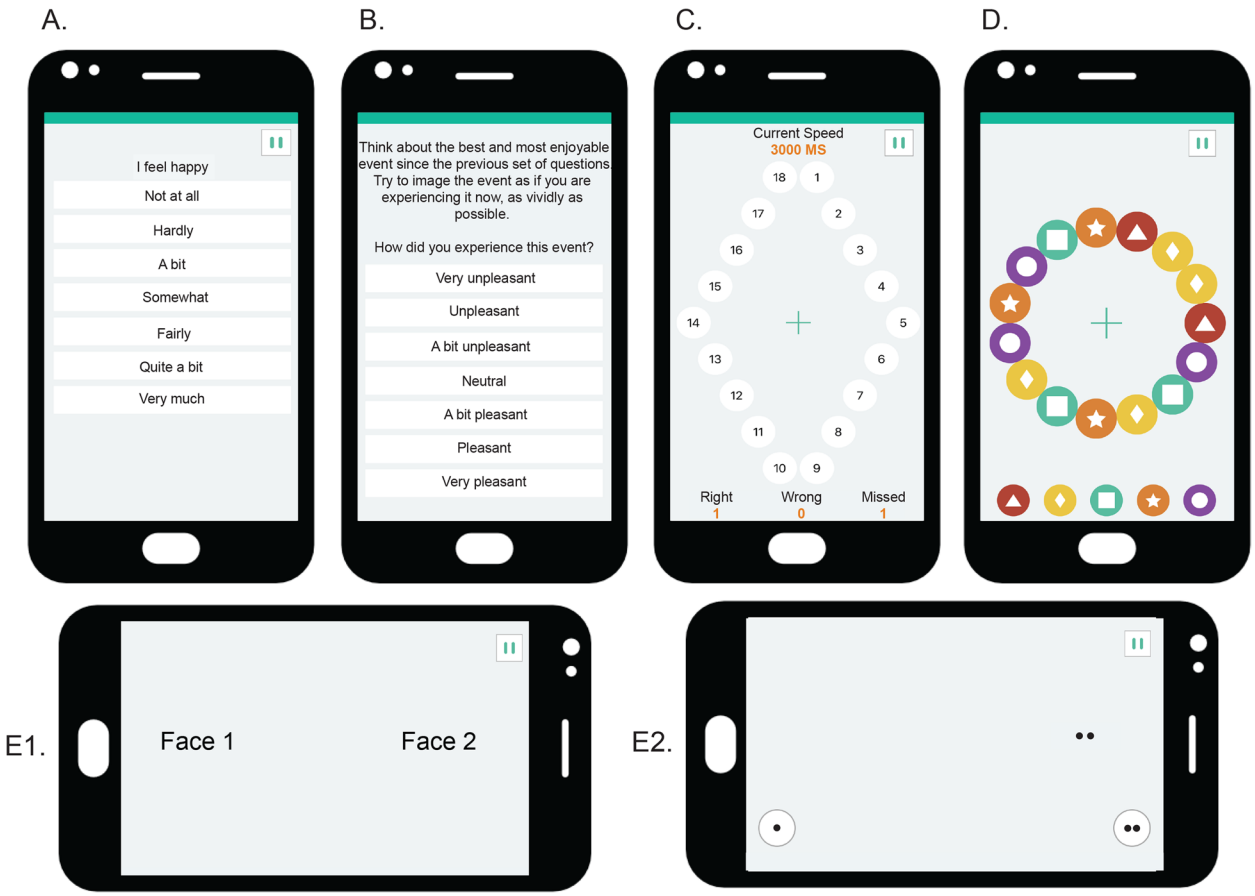


**Fig. 2** Example images of the content displayed on a smartphone during ESM (**A**) and the designated training MBT (**B**), CCT (**C**), PVT (**D**), and ABT – faces (E1; face 1 = AF01 AFS and face 2 = AF26HAS) and dot-probe (E2)

(past 30 min, 30–60 min ago, more than an hour ago) and to briefly describe the event with a minimum of 5 words using the keyboard of their smartphone (Fig. 2). We are primarily interested in the evaluation of the recalled positive event, the description is included for training specificity purposes and to ensure that participants are thinking of an actual positive event. Because we want to avoid participants actively remembering events to answer the memory question during the next prompt (true condition only), the recall of a positive event will be asked at five out of eight prompts only. In the sham MBT, participants will be asked to evaluate and describe their current location ("Think about where you right now. Look around you.") using similar questions as in the true MBT condition at the given prompt with maximally 5 words. Again, these questions are only addressed at five out of eight prompts.

To measure training-specific change in memory, memory will be assessed at two different prompts at the beginning of the first training day and at the end of the last day, by asking participants to think of a recent autobiographical event ("Think about the most important event since the previous set of questions.") evaluate it (i.e., Recall/Evaluation Task) and to provide a brief 5-word description of this event. The last prompt of the day will include questions about the past day ("I have had fun today.", "I am satisfied with what I have achieved today." and "How much did you move today?"), which should be answered on a 7-point scale ranging from 'not at all' to 'very much'.

#### *Cognitive Control Training (CCT) versus active-sham CCT*

For the true CCT, the PASAT will be used to exercise the maintenance of cognitive control/working memory in the face of mild frustration/negative affect and differs from episodic affective memory biases [85]. During a session, a series of single digits 1–9 is presented auditorily. Participants are instructed to continuously add each presented digit with the one that preceded it (i.e., the sum of the two last digits), and to click on the corresponding outcome (ranging from 1–18), which are presented in a diamond-shaped array (Fig. 2). The initial inter-stimulus interval (ISI) is 3000 ms, however, the PASAT is adaptive and the ISI decreases/increases by 100 ms after four accurate/inaccurate consecutive responses. As a result, the task is slightly frustrating, which is necessary to train cognitive control with increasing emotional load, while the task is adjusted to a person's level of cognitive functioning. As such, the PASAT provides the possibility for both assessment and training of capacities [85, 86]. At each new training session, the PASAT resumes with the median ISI of the previous training.

As an active-sham CCT condition, the Peripheral Visual Training (PVT [87]) will be used to exclude potential effects of performing a computerized training. The PVT has similar characteristics to the CCT (e.g., adaptive). Participants view a circular array of colored discs (green, purple, yellow, orange or red) including an internal shape (square, circle, diamond, star, triangle, respectively) to accommodate color-blind participants, but have to keep their eyes focused on a central fixation point. Using peripheral vision (not eyes), participants have to move one disc at a time in a counter-clockwise direction in response to repeated auditory cues that signal 'go'. When an auditory 'stop' cue is presented participants have to indicate the color/internal shape of this 'stop' cue using a button press on the smartphone. In line with the adaptive property of the PASAT, the PVT starts with a circular array of 15 discs after which one disc is added/removed after four accurate/inaccurate consecutive responses. At each new training the PVT resumes with the median number of discs of the previous session. Participants will be asked to complete either a PASAT or PVT training session of 20 min once a day for a period of 21 days.

#### *Attentional Bias modification Training (ABT) versus sham ABT*

In the ABT, two pictures (3 cm × 3 cm) of emotional faces (i.e., positive, neutral or negative) are concurrently presented on the most left and most right side of the screen (landscape orientation of smartphone with a screen width of approximately 14 cm (horizontal) × 7 cm (vertical), or scaled accordingly [67, 88, 89]. In each trial, one face is replaced by a visual probe (1 or 2 dots), to which participant are instructed to respond as soon and accurate as possible by pressing the corresponding button (1 or 2 dots) on lower left and right corner of the screen (Fig. 2). In the true (positively skewed) ABT, probes will replace 87.5% of the most positive faces of a pair, which is positive-neutral, positive–negative, or neutral-negative. Thus, participants implicitly learn to deploy attention toward positive stimuli. In the sham ABT condition, an identical procedure will be followed, except that the probe will equally often replace positive and neutral/negative faces. In line with previous work [67], participants in both conditions will be asked to complete two training sessions a day (20 min per session), for a period of 21 days. Faces for the ABT were taken from the Karolinska Directed Emotional Faces (KDEF) dataset [90].

### Outcome measures

Table 1 presents an overview of the measurements across all time-points in the SMARD study.

#### *Primary outcome measures*

Participants complete one of six training conditions (MBT, CCT, and ABT vs. sham MBT, active-sham PVT and sham ABT), and all four pre- and post-training

**Table 1** Overview of the measurements across all time-points in the SMARD study

| Measure | Eligibility | Baseline | MRI Baseline | MRI Post-training | Follow-up | | | | | Endpoint |
|---|---|---|---|---|---|---|---|---|---|---|
| | T0 | T1 | T1[a] | T2[a] | T3 | T4 | T5 | T7 | T8 | T9 |
| SCID-I | X | | | | | X[b] | | | | X[b] |
| $HDRS_{17}$ | X | X[c] | | | X | X | | | | X |
| MRI eligibility | X | | | | | | | | | |
| ESM | | X | | | | | | | | |
| Recall/Evaluation Task | | X | | | X | | | | | |
| PASAT | | X | | | X | | | | | |
| PVT | | X | | | X | | | | | |
| Visual dot-probe task | | X | | | X | | | | | |
| IDS-SR | | X | | | X | X | | | | X |
| SHAPS | | X | | | X | X | | | | X |
| RRS-NL | | X | | | X | X | | | | X |
| LEIDS-SR | | X | | | | | | | | |
| DAS | | X | | | | | | | | |
| APL | | X | | | X | X | | | | X |
| UCL | | X | | | | | | | | |
| JTV-SR | | X | | | | | | | | |
| IRS | | X | | | X | X | | | | X |
| DART | | X | | | | | | | | |
| WHOQOL | | X | | | | X | | | | X |
| NEO-FFI | | X | X | | X | X | | | | X |
| BEHAPP | | | | X | X | X | X | X | X | X |
| STAI-I | | X | | | | | | | | |
| STAI-II | | X | | | | | | | | |

*Note.* SCID-I Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) diagnoses, *$HDRS_{17}$* Hamilton Depression Rating Scale, *MRI* Magnetic Resonance Imaging, *ESM* Experience Sampling Methodology, *PASAT* Paced Auditory Serial Addition Task, *PVT* Peripheral Vision Task, *IDS-SR* Inventory of Depressive Symptomatology – Self Rated, *SHAPS* Snaith-Hamilton Pleasure Scale, *RRS-NL* Ruminative Response Scale (Dutch version), *LEIDS-SR* Leiden Index of Depression Sensitivity – Revised, *DAS* Dysfunctional Attitudes Scale, *APL* Daily Hassles/Stress (Dutch: Alledaagse Problemen Lijst), *UCL* Utrecht Coping List, *JTV-SR* Childhood Trauma Questionnaire (Dutch: Jeugd Trauma Vragenlijst – Self Rated), *IRS* Insomnia Rating Scale, *DART* Dutch Adult Reading Test, *WHOQOL* World Health Organization Quality of Life, *NEO-FFI* NEO-Five Factor Inventory, *STAI-I* Spielberger State Anxiety Inventory, *STAI-II* Spielberger Trait Anxiety Inventory

[a] For MRI eligible participants only

[b] Only assessment of Major Depressive episode module

[c] If > 1wk after eligibility

assessment measures (memory, attention, cognitive control, peripheral vision). Therefore, main outcome measures are change in memory, change in attention, change in cognitive control and change in peripheral vision. SCID-positive recurrence of depression is an additional main outcome measure during follow-up.

*Memory* The Recall/Evaluation task [73] is used to assess change in memory from pre- to post-training. In this task three prompts are given where participants are asked to think of a recent autobiographical event, describe this event, and to evaluate it briefly on a Likert scale ranging from very unpleasant (score − 3) to very pleasant (score +3). The participant's evaluation of each autobiographical event at pre- and post-training is used to assess training related changes in memory.

*Cognitive control* For each participant, the ISI of each PASAT trial at pre-training and each trial at post-training will be used to assess training related changes in cognitive control. In this respect, a decrease in ISI indicates improvement of cognitive control, whereas an increase indicates a deterioration of cognitive control.

*Peripheral vision* The PVT, which is unrelated to cognitive control/working memory, will be used as an active control assessment [91]. Training related changes in peripheral vision from pre- to post-training will be assessed using the number of colored discs in each trial.

*Attention* Change in attention from pre- to post-training is assessed using the visual dot-probe task [67] where the visual probe replaces the most positive face

(congruent) in 50% of the trials and the most negative face (incongruent) in 50% of the trials. The reaction time to each probe at pre-training and at post-training is used to assess changes in attention.

*Recurrence of depression and depression severity* During the follow-up period, positive recurrences of depression will be assessed by telephone interviews every three months where the SCID-I [83] will be administered regarding the period since the last (SCID-I) assessment. Additionally, the 17-item Hamilton Depression Rating Scale (HDRS [84]) will be administered to assess severity of recurrence or residual symptoms during follow-up. The HDRS is an observer rated MDD symptom scale with 17 items, assessing depressive symptoms over the past seven days, administered as a semi-structured interview [92]. Items are scored on either a 3- (0 = absent; 1 = doubtful or mild; 2 = clearly present) or 5-point (0 = absent; 1 = doubtful or mild; 2 = mild to moderate; 3 = moderate to severe; 4 = very severe) scale, the sum score varies between 0–52.

#### *Secondary outcome measures*

A more detailed description of all questionnaires and neuropsychological tests is given in the Supplementary Material.

*Rumination* Change in rumination will be assessed with the Dutch version of the Ruminative Response Scale (RRS [93, 94]). The 26-item RSS assesses the tendency to engage in ruminative thinking that is focused on the self, symptoms or consequences of depressive mood. It consists of two subscales: reflective pondering and maladaptive brooding.

*Neural networks* A range of MRI scans will be obtained to assess training-related changes in neural networks. All scans will be made on a 3 T MRI-scanner with a 32 channel head-coil: (1) a structural scan (7 min) – a high resolution 3D T1-scan for detailed anatomic information; (2) resting-state scan (10 min); (3) Diffusion Tensor Imaging (DTI; 7 min) measures whole brain fractional anisotropy (FA) which can quantify white matter abnormalities by voxel-based analyses [95], (4) emotional reactivity will be assessed with the Hariri paradigm [96] consisting of 12 blocks (3 trials each) in which participant have to indicate which of two facial expressions (angry or fearful) presented on the bottom of the screen match the target expression of the face at the top of the screen. In 5 control blocks participants have to indicate which of two shapes (horizontal or vertical oval) presented at the bottom of the screen match the target shape at the top of the screen; (5) cognitive emotion regulation will be measured using an adapted version of the emotion regulation (ER) task used before [97, 98] during which participants view pictures of different emotion categories (negative or neutral) and are instructed to either passively view the image or actively regulate the elicited emotion by reappraising the pictures in a more positive perspective. After each picture presentation, participants have to rate their feelings and arousal level using a 5-point Self-Assessment Mannekin (SAM) scale; (6) inhibitory control will be assessed with the classic (non-emotional) Stroop Task [99, 100], in which each trial starts with a target stimulus – a color name, written in either matching (congruent) or non-matching (incongruent) ink – to which participant have to respond as quickly and accurate as possible by indicating the ink color of the word with a button press.

*Training drop-out/non-compliance* Drop-out (impossibility to obtain a post-training measurement and loss to follow-up) and non-compliance (number of performed training sessions relative to the total number of training sessions) rates on the MBT, CCT, ABT and respective (active-) sham conditions will be assessed.

*BEHAPP* BEHAPP is a smartphone application enabling longitudinal, 24/7 measures of an individual's behavior (https://behapp.org/). The hallmark feature of BEHAPP is that it passively monitors behavior 'in the background'; as such it can be considered a Mobile Passive Monitoring application. Passive monitoring implies that after initial informed consent and installation of the app on the smartphone, no further active input from the participant is required. A diversity of social communication and exploratory behavioral endpoint features are extracted from continuously collected smartphone sensor information such as GPS, text-messages, phone, social media (e.g., Facebook, Twitter, WhatsApp), WiFi, access (social density) signals. This data is collected at low battery-consumption. Every time the smartphone connects to WiFi, data is transferred in encrypted form to highly secured servers and wiped from the smartphone. Thus, BEHAPP enables objective behavioral observations of subjects in their natural environment. Importantly, BEHAPP never records or collects content of any spoken or written messages. Also, any identifying information related to communication partners, that is any person the participants interact with, is irretrievably obfuscated before being sent to the secured data servers. BEHAPP has been implemented in a variety of European Union (EU) projects and multi centre studies (e.g. [101, 102]) and is compliant to the General Data Protection Regulation (GDPR [82]).

*Experience sampling method (ESM)* Prior to the baseline assessment we will obtain 6 days with 10 semi-random measurements/day, applied via the smartphone of participants (see [103]). ESM is a structured diary method developed to study participants in their daily surroundings. We will obtain ESM-ratings regarding positive and negative affect – which are hypothesized to be separate but correlated latent factors [104] – and possible influencing factors (e.g., social activities).

## Procedure

### *Eligibility assessment, pre-training measures, randomization and post-training measure*

After expressing their interest in the SMARD study, potential participants will be contacted by telephone within a week to receive more information about the study. Those interested in further participation will receive written information about the SMARD study and an informed consent form. According to Dutch law, only after informed consent is obtained, a second appointment by telephone is made to assess eligibility (T0), including possible MRI eligibility, based on the inclusion and exclusion criteria, using the depression, psychosis, mania, anxiety, and addiction modules of theSCID-I [83]. In addition, residual depressive complaints (HDRS), the number and duration of past recurrent major depressive episodes, the type and duration of pharmacological and psychological treatment (if applicable) during past episodes, and current pharmacological and psychological treatment (if applicable) will be asked. Participants eligible for participation are invited for the baseline assessment. If participants do not want to participate in MRI-scanning or fail to meet criteria for the MRI scan, they will only be excluded for the MRI session.

At the start of the study (T1) participants receive baseline questionnaires (see Supplementary Material) by email, after which the SMARD software application (SMARD app) for the ESM assessment is installed and initialized. When the ESM assessment is obtained, participants receive instructions (written, by phone, and instruction videos) to complete four cognitive tasks (Recall/Evaluation task, PASAT, PVT, and the visual dot-probe task) on their smartphones using the SMARD app. This provides a baseline measurement of cognitive performance prior to training. For eligible participants, the first MRI-scan will be done thereafter.

After the baseline assessments, participants are randomly assigned to either MBT, MBT-sham, PASAT, active-sham PVT, ABT or ABT-sham conditions. The HDRS is re-assessed if the period between randomization and start of the cognitive training or control condition exceeds a period of three weeks. Participants will be instructed (also via written information) to complete the cognitive training either five times (MBT/MBT-sham), once (PASAT/active-sham PVT) or twice (ABT/ABT-sham) a day, for 21 consecutive days and to abstain from any psychotropic medication for $\geq 2$ h before the cognitive training is started. The timing of the training during the day will be scheduled according to the individual preference of the participant. Participants will be informed that the SMARD app records (the number of) training sessions. Two to three days after the start of training, a researcher will inquire via telephone whether the SMARD app works and whether instructions are clear.

At the end of the training period (T2), participants will perform similar post-measurements as before training. They are instructed to complete the questionnaires and all four cognitive tasks (Recall/Evaluation task, PASAT, PVT, and the visual dot-probe task) delivered by the SMARD app, to acquire a post-training measurement of cognitive performance. We record potential changes in pharmacological and/psychological treatment since the start of the study. Participants who underwent pre-training MRI-scanning will again be invited for a post-training MRI scan. If participants do not complete the planned ESM assessment, cognitive tasks, or questionnaires, they receive a reminder email and/or phone call from the clinical assessor who asks them to complete the given assessment.

### *Follow-up assessments*

Four weeks after completing the three-week cognitive training (first follow-up assessment; T3) the HDRS is administered by phone and four smartphone-based (SMARD app) cognitive tasks are repeated in line with previous research [67]. Again, we record changes in pharmacological or psychological treatment (since T2; post-training assessment). Hereafter, a one-year follow-up period starts with 3-monthly assessments (T4-T6, T9 [endpoint]) by phone. Before each follow-up assessment, participants receive questionnaires (see Supplementary Material) by email. During each assessment we identify recurrent depressive episodes by administering the SCID-I [83] record changes in pharmacological and/or psychological treatment, and measure severity of (residual) depressive symptoms (HDRS). When a recurrence is expected/identified, participants will be advised to seek professional help. Any adverse events that occur after enrollment in the study and before the end of the follow-up period, will be recorded. An adverse event that meets the criteria for a serious adverse event (SAE) will be reported to the ethical medical committee.

### Data handling

All study-related information is electronically stored on secured servers (Google Cloud or within the Radboud university medical centre) with access by involved researchers only. Questionnaire data, demographic data, data on previous MDD episodes and treatment is collected, stored and managed via Castor EDC. For Castor EDC, full audit trail is available to log change(s) to the data as well as which user (researcher) made the change. To ensure anonymity and confidentiality, all data is anonymized with a unique participant ID code. The key file linking this participant ID to personal information is stored in a separate, password-protected file at the Radboud university medical centre. Only researchers, an independent monitor from the Radboud university medical centre and the Inspection for Healthcare and Youth have access to these key files. Smartphone data of cognitive trainings, ESM and BEHAPP will be uploaded anonymously to the Google Cloud Platform, which employs a security model built on 15 years of experience in protecting customer data. This platform is compliant with HIPAA, ISO 27001 and the EU Data Protection Directive. No directly identifiable participant information is stored. Participants are represented by unique IDs, which can only be associated with identifiable information via the key to these IDs, stored at Radboud university medical centre. BEHAPP monitoring data is encrypted before being locally stored on the smartphone and after each successful upload to the BEHAPP servers, all of the local monitoring data is wiped from the smartphone. Likewise, data of cognitive trainings and ESM are uploaded after each task and then cleared from the smartphone. These measures seek to maximally reduce the risk of revealing privacy-sensitive information to third parties in case of loss or theft of the smartphone. Information gathered about identities of third persons, for example participants' contacts, are obfuscated on the phone before being uploaded to BEHAPP servers. Obfuscation is performed using so called one-way-hashing/encryption techniques. This allows the researchers to determine whether the same instance (person or device) has been recorded more than once, while preventing them from directly identifying the recorded instance.

Data will be stored for 15 years after participant inclusion has ended. Only researchers who are part of the research team are able to access the data. The study has low to negligibly risks therefore the monitoring plan will be performed in line with the Radboud university medical centre regulations and the procedures as described in the brochure "Kwaliteitsborging mensgebonden onderzoek 2.0" by the Dutch Federation of Universities (NFU). Results of the SMARD study will be published in (inter-)national, peer-reviewed scientific journals, and presented at (inter-)national conferences. Moreover, participants will receive a summary of the study results.

### Statistical analyses

Following the Consolidated Standards of Reporting Trials (CONSORT [105]) all primary and secondary outcome analyses will first be conducted in accordance with the intention-to-treat (ITT) principle. Second, we will perform an analysis to explore dose–response relationships of trainings (with percentage of completed training sessions as covariates) followed by a per-protocol analysis where we will analyze effects only in participants who completed $\geq 80\%$ of trainings. Missing values (except for incomplete training sessions or loss to follow-up) will be imputed (e.g., by using multiple imputation (MI) or expectation maximization (EM)). In addition, sensitivity analyses will be carried out to gauge the robustness of findings as a result of including/excluding participants with missing data in the analysis. In case cognitive training groups differ regarding potential confounders, despite randomization, these variables will be added as covariates in the analyses described below.

#### *Primary outcome analyses*

The effects of cognitive training (MBT vs. sham MBT, CCT vs. active-sham CCT, ABT vs. sham ABT) on the primary outcome measures will be analyzed using linear mixed-effects models (LMEM). LMEM are 'mixed-effects' models as they consider both fixed and random effects. Fixed effects are parameters that do not vary across units of interest (e.g., participants or stimuli). Random effects, however, are parameters that do vary across units of interest. Random effects include random intercepts (i.e., variation of intercepts) and random slopes (i.e., variation in the relation between the independent variable(s) and dependent variables), Disregarding these random effects may lead to inflated Type-I error rates [106], which is why LMEM is preferred over traditional analysis of variance (ANOVA) techniques that only consider fixed effects [107, 108]. Moreover, LMEM analyze data on the trial level instead of aggregating data (e.g., mean/median reaction time of all trials of a visual dot-probe task).

Here, four separate LMEM will be conducted (Table 2) on trial level data[3] using R statistical computing language [109]. Each model will include one of the outcome measures as the dependent variable (model 1: Memory (Recall/Evaluation Task); model 2: Cognitive control

[3] Trial level data refers to the evaluation of each prompt of the Recall/Evaluation Task for Memory, the ISI of each trial on the PASAT for Cognitive control, the number of colored discs visible at each trial of the PVT for Peripheral vision, and the reaction time to the probe of the visual dot-probe task for Attention.

**Table 2** R Syntax of planned analyses

| | **Fixed effects DV ~ IVs** | **Random effects (1 + random slope(s) \| random intercept)** |
|---|---|---|
| Primary outcomes | | |
| Model 1 | Memory bias ~ Time * Training condition | + (1 + Time \| Participant) |
| Model 2 | Cognitive control ~ Time * Training condition | + (1 + Time \| Participant) |
| Model 3 | Peripheral vision ~ Time * Training condition | + (1 + Time \| Participant) + (1 + Time \| Color) |
| Model 4 | Attention bias ~ Time * Stimulus valance * Congruency * Training condition | + (1 + Time * Stimulus valance * Congruency \| Participant) + (1 + Time * Stimulus valance * Congruency \| Actor ID) |
| Secondary outcomes | | |
| Model 5 | Rumination ~ Time * Training condition | + (1 + Time \| Participant) |
| Model 6 | Depressive complaints ~ Time * Training condition | + (1 + Time \| Participant) |

R statistical computing language syntax (R Development Core Team, 2017) is used to denote effects. All Fixed effects are noted as 'dependent variable ~ independent variables'; Random effects are noted as (1 + random slope(s) | random intercept); * refers to an interaction effect and includes all lower order effects

(PASAT); model 3: Peripheral vision (PVT); model 4: Attention (visual dot-probe task)). All models will have the independent variables Time (pre-training, post-training) and Training condition (MBT, sham MBT, CCT, active-sham CCT, ABT, sham ABT) as fixed effects. In addition, a random intercept for Participant and a random slope for Time will be included as random effects.

Furthermore, for the dependent variable in the PVT (model 3) color/shape[4] will be included as an additional random intercept with a random slope of Time. Likewise, the dependent variable Attention (model 4) will include the independent variables Stimulus valance (happy, neutral, angry, sad) and Congruency (congruent, incongruent) as fixed effects. This model will also include a random intercept for Participant and a random intercept for Actor ID, with random slopes for Time, Stimulus valance and Congruency, as well as the interaction between Time, Stimulus valance and Congruency varying over Participant and over Actor ID.[5] For all of the models outlined above, the interaction effect(s) and all lower order effects will be analyzed.

#### *Investigation of the association between passive behavioral data (BEHAPP) and recurrences*

In order to predict positive recurrences of depression during follow-up, the multidimensional data obtained by BEHAPP will be associated with SCID-I positive recurrences of depression as determined during follow-up. To this end, multivariate pattern recognition machine learning will be used to develop an algorithm that can distinguish behavioral aspects associated with a depressed versus non-depressed state. This algorithm will be developed to identify an individual's behavioral changes characterizing an evolution from a non-depressed state towards recurrence. Algorithms to detect changes in activity [110] and/or indications for directions of signals [111] exist. We will especially investigate whether early changes in behavior can be detected in the weeks before the recurrence becomes evident. Finally, the algorithm will be improved such to obtain highest sensitivity (at reasonable specificity). With ongoing/additional data collection of the SMARD study, we aim to replicate and improve the algorithm. For example, with knowledge of medication use of participants and an increasing dataset, we can investigate whether medication use modifies our predictions by performing stratified analyses to obtain predictive algorithms, and to compare these with the overall prediction. Finally, we will investigate possibilities to develop improvement of the algorithm into a self-learning system.

#### *Secondary outcome analyses*

Effects on the secondary outcomes change in rumination (RRS) and depressive severity (HDRS) will also be analyzed by means of LMEM. Two models (see Table 2) will be conducted including the outcome measure as dependent variable (model 5: Rumination (RRS); model 6: Depressive symptoms (HDRS)). Both models include the independent variables Time (pre-training, post-training) and Training condition (MBT, sham MBT, CCT, active-sham CCT, ABT, sham ABT) as fixed effects, and a random intercept for Participant and a random slope for Time as random effects. For these two models, the interaction effect and all lower order effects will be analyzed.

*Power and sample size* The power analyses described here are based on repeated-measures ANOVA as for LMEM no power calculations have been specified, except

[4] The PVT includes a circular array of discs that are green, purple, yellow, orange or red with an internal shape (square, circle, diamond, star, or triangle, respectively).

[5] The ABT task makes use of different actors all showing a happy, neutral, angry and sad expression.

for data simulations. For our primary outcome, change in outcomes of memory (Recall/Evaluation), cognitive control (PASAT), peripheral vision (PVT) and attention (visual dot-probe task) with three training programs (MBT, CCT or ABT) with comparisons of two groups (training vs. (active-) sham) of 20 persons we will have power to show medium-large effect-sizes for each comparison ($\alpha = 0.05$; $\beta = 0.2$; effect-sizes for F-test of ANOVA with two groups (training vs. (active-) sham), 3 measures (time, group and interaction = 0.56 [G*Power v3.1.5 [112]). These numbers will also allow comparison of the effects of (true) MBT vs. CCT vs. ABT. In a previous study the CCT was successful in reducing the median interstimulus interval with a difference in pre-post changes between CCT vs. active-sham CCT of 734.78 (± 571.1) milliseconds, representing an effect-size of 1.29 [85]. Moreover, regarding the outcome rumination, although not our primary outcome but associated with the intentional purpose of the CCT (i.e., reduction of ruminative thought processes), effect sizes of − 1.42 in the CCT condition versus − 0.04 in the Treatment As Usual (TAU) group were reported [85], both representing large effect sizes. For MBT and ABT available data is not useable to perform power calculations, but the effect size is expected to be > 0.5 (Browning, personal communication; Vrijsen, personal communication).

*Neuroimaging* In general, changes in relevant neural networks are assessed with different types of (f) MRI scans and tasks for which analyses will be briefly described. For each analysis of imaging data we will a priori register an analysis plan. First, we will analyze the resting state and task data with time-averaged functional connectivity (Independent Component Analysis and seed-based connectivity [113]). For resting-state measures, we will extract connectivity strength estimates of the ECN, DMN and SN (by applying independent template masks [56, 57]). The same procedure will be applied to the three task measures (Stroop, Hariri, Emotion Regulation), tapping into cognitive control, salience (arousal), and regulation networks. For these time-averaged connectivity measures, we will investigate the change over time (pre- to post-training) in association with MBT vs. sham, CCT vs. active-sham and ABT vs. sham.

Growing evidence shows that brain activity at rest is not stable, but slowly changes in a series of time-varying, but reoccurring, states of coupling among brain regions [114]. We will therefore also analyze, resting state dynamic functional connectivity from a whole brain perspective, following Figueroa and colleagues [45] and Deco and colleagues [115]. DTI will be used to inform and complement this analysis (as described in [115]). In brief, for dynamic connectivity measures, brain regions are labeled by spatial overlap with independent template masks. Between these regions we will determine dynamic functional connectivity patterns, summarized by measures like overall lifetime of dynamic brain states and switching frequency (probabilities) between these brain states as described before [45, 116, 117]. We will investigate the change of these dynamic functional connectivity patterns (i.e., durations and probabilities of different states) over time in association with MBT vs. sham, CCT vs. active-sham and ABT vs. sham.

*Prediction of recurrence* Association of change in biases or cognitive control with positive recurrences during follow-up will be assessed by including changes in Recall/Evaluation, visual dot-probe, PASAT, PVT, ER, Harriri and Stroop performance in Cox regression models to predict future recurrences of depression during follow-up. These variables will be used as independent predictors in association with known predictors (number of previous episodes, residual symptoms, Leiden Index of Depression Sensitivity (LEIDS) score [118]). Trend wise significant parameters ($p < 0.1$) will be further tested in multivariate Cox-models.

For prediction of recurrences with neuroimaging data, we will extract summative measures of DMN, ECN and SN static connectivity from resting state and task paradigms (ER, Hariri, Stroop). Additionally, measures of dynamic functional connectivity will be obtained from the resting state scans. Matrices containing these brain measures, together with summary measures from affective and cognitive phenotyping and ESM conducted in SMARD will be fed into a hierarchical, logistic regression model that predicts recurrence status at 1-year follow-up. Thereby we will be able to determine the predictive value of the various variables we enter in the analyses. Further steps will aim to elaborate on machine learning that will give an optimal prediction.

## Discussion

The SMARD study aims A) to investigate the effects of three different smartphone-based cognitive training programs on cognitive functioning, relevant neural networks and MDD recurrence in a sample of remitted MDD patients with recurrent MDD; and B) to identify changes in behavior indicative of an imminent depressive episode by continuous, passive monitoring with the BEHAPP smartphone application (https://behapp.org/). We do so by first assessing the effects of the cognitive training programs versus their training-specific (active-) sham conditions on changes in memory, cognitive control

dysfunction and attention. Second, we will relate these (pre- to post-) training effects to neural networks associated with (recurrence of) MDD. Third, baseline and training-related changes of memory, cognitive control, attention and neural functioning will be associated with prospective recurrences. Fourth, passive smartphone-use monitoring via BEHAPP for prediction of recurrences will be examined.

Despite considerable efforts, existing recurrence prevention programs (e.g., antidepressant use [119], mindfulness based cognitive therapy [120] and preventive cognitive therapy [121] insufficiently address ethio-patho-physiological mechanisms involved in the recurrence of MDD and are not always appt for long-term use due to limited availability and/or costs. The high risk of recurrence, which might increase with each recurrent episode, highlights the necessity of understanding the psychological, behavioral and neural factors that render individuals vulnerable for MDD recurrences and the respective levels where interventions can be applied to.

The onset of a recurrence is also retrospectively marked by changes in symptom and behavioral patterns before actual emotional changes become apparent. Continuous smartphone monitoring of behavioral patterns (in combination with known vulnerability factors) is nowadays within reach and should be validated as a possibility to identify specific markers for an impending recurrence. When this is shown to be possible, the time-period directly preceding a recurrence can serve as a window of opportunity to rapidly implement interventions to prevent full-blown recurrences of depression and regain recovery.

The SMARD study provides a comparison of potential intervention strategies – three smartphone-based cognitive training programs (MBT, CCT and ABT versus training specific (active-) sham trainings), and does so in a highly relevant target group, that is remitted-MDD patients with recurrent MDD. A distinct strength of this study is that it not only tests the effectiveness of delivering these cognitive training programs by smartphones, but also relates changes in memory, attention, and cognitive control to neural networks and recurrence risk. In addition, SMARD integrates passive smartphone-use monitoring over a one-year follow-up period in order to develop a prediction algorithm to detect an imminent depressive episode. The integration of potentially moderating and mediating variables (e.g., cognitive flexibility and rumination) can provide further insights into the mechanisms through which cognitive trainings achieve their effects. This might also provide information about who will benefit most from cognitive training.

In sum, the use of cognitive training and monitoring in a long-term, longitudinal approach in SMARD allows for an improved understanding of the (changes in) symptoms and neural networks implicated in (the prevention of) recurrent MDD-vulnerability. These insights on potential targets and (bio-)markers will feed the development of an algorithm to predict recurrence and tailor interventions. Together, cognitive training interventions and passive monitoring might be combined in a second-generation, even personalized preventive treatment. The results of this study will provide building blocks for this treatment. As a proof of principle, in a next step randomized controlled trial, recurrence rates in established recurrence prevention programs should be compared to programs enriched with additional memory/cognitive/attentional bias modification and passive monitoring and signaling of imminent recurrences.

**Abbreviations**

| | |
|---|---|
| ABT | Attention bias modification training |
| ANOVA | Analysis of variance |
| CCT | Cognitive control training |
| CONSORT | Consolidated Standards of Reporting Trials |
| DELTA | Depression Evaluation Longitudinal Therapy Assessment |
| DMN | Default Mode Network |
| DSM | Diagnostic and Statistical Manual |
| DTI | Diffusion Tensor Imaging |
| ECN | Executive control network |
| ECT | Electroconvulsive therapy |
| EDC | Electronic Data Capture |
| EM | Expectation maximization |
| ER | Emotion regulation |
| ESM | Experience Sampling Method |
| FA | Fractional anisotropy |
| GDPR | General Data Protection Regulation |
| GPS | Global Positioning System |
| HDRS | Hamilton Depression Rating Scale |
| ISI | Inter-stimulus-interval |
| ITT | Intention-to-treat |
| KDEF | Karolinska Directed Emotional Faces |
| LEIDS | Leiden Index of Depression Severity |
| LMEM | Linear mixed-effects models |
| MBT | Memory bias modification training |
| MDD | Major Depressive Disorder |
| MI | Multiple imputation |
| MRI | Magnetic Resonance Imaging |
| PASAT | Paced Auditory Serial Addition Task |
| PVT | Peripheral Vision Task |
| RCT | Randomized Controlled Trial |
| RRS | Ruminative Response Scale |
| SAM | Self-Assessment Mannekin |
| SCID-I | Structured Clinical Interview for DSM-IV Axis I Disorders |
| SMARD | Smartphone-based Monitoring and cognition Modification Against Recurrence of Depression |
| SPIRIT | Standard Protocol Items: Recommendations for Interventional Trials |
| SN | Salience network |
| TAU | Treatment As Usual |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-025-06860-x.

Supplementary Material 1.

**Acknowledgements**
This trial protocol is written in compliance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.

**Protocol version**
This is protocol version 01 (issue date: 26 Mar 2025).

**Authors' contributions**
All authors participated in the design of the study. HGR is the principal investigator of the study and obtained funding from the Dutch Brain Foundation. NI and AT wrote the manuscript, and coordinate and carry out recruitment and data-collection. HGR, JNV, NK, NG, GJS, AHS, JASV, CJH and MJK commented on and revised the manuscript. All authors have approved the final manuscript.

**Funding**
The study is funded by the Dutch Brain Foundation (Hersenstichting) with grant number HA2015.01.07. Prior to granting the funding by the Dutch Brain Foundation extensive peer has been carried out. The Dutch Brain Foundation is not involved in the design of the study and does not participate in the data collection/analysis of the data and writing of forthcoming manuscripts. CJH is supported by the Oxford Health NIHR Biomedical Research Centre.

**Data availability**
No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**
The study was approved by the Medical Ethics Committee of Radboud University Medical Centre (CMO Arnhem-Nijmegen) ((NL60033.091.16/2016–3009)) and is registered at the Overview of Medical Research in the Netherlands (NL-OMON26184 and NL-OMON27513; registered August 12, 2021). All potential participants are provided with printed study information and called for an oral explanation of the study. Before conducting assessments, written informed consent will be obtained from all individual participants.

**Consent for publication**
Not applicable.

**Competing interests**
HGR (Dr. Eric Ruhe) received speaking fees from Lundbeck not related to this work.

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Received: 27 March 2025 Accepted: 15 April 2025
Published online: 01 May 2025

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