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Document: Statistical Analysis Plan (SAP)

Official study title: Cognition in mindfulness; negativity and depression

Acronym: CogMiND

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Statistical analysis plan

Section 1: Administrative information

Title

Statistical analysis plan for the CogMiND study: Cognition in mindfulness; negativity and depression

Trial registration

NL68398.091.18

SAP version

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Roles and responsibilities

Non-signatory names

Jan Spijker – supervision

Anne Speckens – supervision

Mira Cladder-Micus – supervision

Philip Spinhoven – advising on growth curve modeling and cross-lagged structural equation modeling

Signatures of:

Jelle Lubbers (writing the SAP)

Dirk Geurts (co-writer of SAP and principal investigator)

Section 2: Introduction

Background and Rationale *(copy pasted from "Detailed description of Study description" of ClinicalTrials.gov record supplemented with references)*

Depression is highly prevalent and is ranked by the WHO as the number one contributor to disability worldwide (Organization, 2017). The highly recurrent nature of the disorder contributes greatly to the burden of Major Depressive Disorder (MDD) and with every new depressive episode, outcome prospective worsen (Hardeveld et al., 2013). Mindfulness Based Cognitive Therapy (MBCT) is an effective treatment to reduce relapse rates (Kuyken et al., 2016) and (residual) symptoms (Goldberg et al., 2019; Piet & Hougaard, 2011) that contribute to recurrence in MDD. However, the mechanisms underlying this MBCT-induced effect are far from clear (van der Velden et al., 2015).

Elucidating these mechanisms will provide insight in the existing individual differences in effectiveness of MBCT. Consequently, this insight will help to improve effectiveness of treatment and even personalize treatment regimes. One likely candidate that could play a major role in the positive effects of MBCT on depressive symptoms, is repetitive negative thinking (RNT) (van der Velden et al., 2015). Depressive rumination is the most well-studied form in the context of depression and has been described as the process of thinking perseveratively about one's feelings and problems (such as symptoms of depression) and their possible causes and consequences (Nolen-Hoeksema et al., 2008). It is believed that during MBCT participants develop the ability to become aware of automatic maladaptive cognitive processes such as depressive rumination, and learn to decenter and disengage from them (Segal et al., 2013). Because of this core skill to be learned during MBCT patients may be prevented to enter a vicious cycle of ruminative thinking that could otherwise aggravate symptoms of depression or have resulted in a new depressive episode.

Objectives

Our main objectives are (i) to replicate the beneficial effects of MBCT on depressive symptoms and RNT in patients with chronic or recurrent depression (crMDD), and (ii) to investigate whether individual levels of RNT (iia) mediate and/or (iib) moderate the MBCT-induced reduction in depressive symptoms.

To this end self-report questionnaires of depressive symptoms, content-independent RNT and depressive rumination will be administered before, half-way and after MBCT (intervention group) or before, half-way and after a waiting-period (waitlist group).

Secondary objectives

To triangulate research findings we will administer an experimental task (breathing focus task) that measures intrusive thoughts during task performance.

Moreover, we will focus on cognitive control and affective biases therein, because this process is related to RNT. We will measure two major constituents of cognitive control, i.e. working memory processing and motivational biases of cognitive control (with respectively a working-memory update/ignore emotion task and Pavlovian-to-instrumental transfer task) before and after MBCT/waitlist. We will use this behavioural data to assess whether working memory and motivational biases are indeed (i) related to RNT and MDD, (ii) are changed by MBCT and (iii) whether these changes are related to clinical effects of MBCT.

Additionally, we aim to investigate the timing of change by administering weekly self-report questionnaires.

Section 3: Study Methods

Design

Patients will be assigned to intervention (MBCT + TAU) or waitlist (TAU) based on regular clinical assessment procedure and start of treatment groups. The intervention group performs measurements once before (T0), halfway (T1), and once after MBCT (T2), whereas the waitlist performs measurements once before (T0), once during (T1), and once after a waiting period (T2) of at least 7 weeks, but preferably 8-10 weeks. The wait-list group receives MBCT after this waiting period and subsequently performs measurements halfway (T3) and after MBCT (T4).

Sample size – power calculation

Before start of the study, a sample size calculation for the primary analysis (mediation analysis) was conducted using the Monte Carlo Power Analysis Application provided by Schoemann, Boulton, & Short (2017) (https://schoemanna.shinyapps.io/mc_power_med/). This tool enables the researcher to calculate a required sample size for (simple) mediation models by using correlations between the independent variable (IV), dependent variable (DV), and mediator (M). We based the required sample size for the mediation analysis on previously published data on the effectiveness of MBCT for chronic, treatment-resistant depressed patients (Cladder-Micus et al., 2018). We based the calculation on 1000 replications, 20000 Monte Carlo Draws per replication, and a Confidence Level of 95%. The correlation between IV (condition; MBCT + TAU versus TAU) and DV (residual change in depressive symptom; r = .18), IV and mediator (residual change in RRS brooding score; r = .27), and mediator and DV (r = .26) were entered in the application. Based on this calculation, 174 participants would be required. Based on previous studies reporting a drop-out between 10% (Van Aalderen et al., 2012) and 24.5% (Cladder-Micus et al., 2018), we therefore expected a drop-out of 15% and aimed to include 200 participants.

Statistical analysis

Clinical effects of MBCT: replication and assessment of moderation

To compare the intervention (MBCT + TAU) with the waitlist-control (TAU only) group on sociodemographic, outcome, and hypothesized mediating and moderating variables, independent-samples t-test or chi-square test will be used. The effect of treatment (MBCT + TAU versus TAU) will be tested in the intention-to-treat sample using latent growth curve models (LGCM; (Duncan & Duncan, 1995)). The intercept (baseline score of dependent variable) and slope (representing change over time) will be modeled as latent variables from data at pre-treatment (T0), mid-treatment (T1) and post-treatment (T2) (see Figure 1). First, unconditional models will be estimated separately in each group (MBCT + TAU versus TAU) to test whether a linear (0, 4 and 8 weeks) or non-linear trend of change over time would fit the data best. Second, group (MBCT + TAU = 1 ; TAU = 2) will be added to the model as predictor of the latent growth factors. The path from Group to Slope reflects differences in the trajectories of change on the outcome measure(s) between groups whereas the path from Group to Intercept reflect baseline differences on outcome measures. To assess the rate of change within each group, within-subject cohens d effect sizes will be calculated by dividing the mean-difference (T2-T0) by the standard deviation (SD) of the difference, with 0.2, 0.5, 0.8 representing small, medium and large effects respectively. To compare the rate of change between groups, a between group effect size for growth modeling analysis (GMA) will be calculated using the following equation: $= \frac{\beta 11 * \text{time}}{Pooled\ SD\ raw\ scores}$ (Feingold, 2009), in which $\beta 11$ is the difference between the means of the unstandardized slopes of the MBCT + TAU versus TAU group. $\beta 11$ must by multiplied by time (in our case 8) to obtain the difference between the model-estimated means of both groups at the end of the study (adjusted for baseline differences). Third, potential moderators of treatment effect, such as baseline levels of different measures of RNT, will be added as predictor of the latent growth factors. A significant interaction effect between moderator, group and slope would mean a moderated treatment effect. As a sensitivity analysis and as a basis for the analyses regarding mechanisms of change (for which a minimal effective MBCT-dose is a requisite), the LGCM analyses will be repeated in the per protocol sample (minimal effective dose of ≥ 4 sessions (Teasdale et al., 2000)).

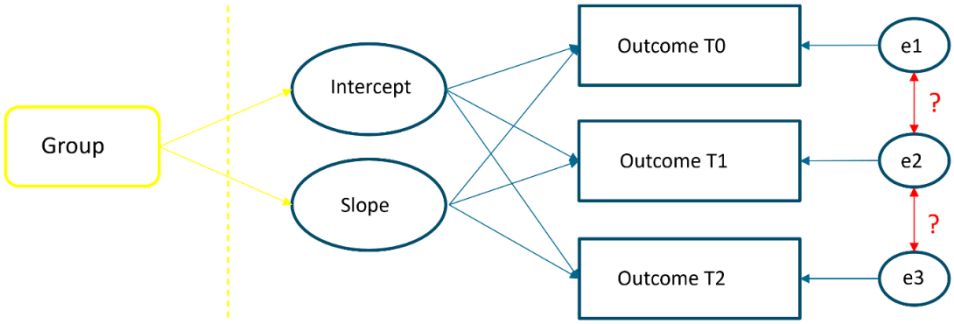

Figure 1. Structure of the Latent Growth Curve Models (LGCM) for the different outcome measures that were assessed before (T0), mid-way (T1) and after (T2) treatment. First unconditional models will be run (blue part). Subsequently a conditional model will be run, with group (MBCT + TAU versus TAU) as predictor of the latent growth factors (yellow).

Mediation analyses

To test for mediation of the effect of MBCT + TAU versus TAU on depressive symptoms (primary outcome; IDS-SR) and overall functioning (secondary outcome; OQ-45) by primary (the different RNT measures (RRS brooding subscale, PTQ, negative intrusive thoughts on BFT) and secondary mediators of interest (FFMQ, SCS)), cross-lagged structural equation models (CLSEM) will be run (Figure 2) in the per protocol sample. For the primary analysis we deliberately choose for a CLSEM approach instead of using the frequently used Process Macro by Hayes (Hayes et al., 2017) (on which power calculation was based) because of practical and content-related reasons. We choose for CLSEM because (i) the nature of the data. We anticipate to have relatively more missing data at specific time points (i.e. the first, second or third measurement moment) because of the COVID-19 pandemic. CLSEM can handle missing data whereas with PROESS all participants with at least one score missing at one of the time points will be deleted from analyses. (ii) CLSEM provides more information on how variables change (each other) over time, i.e. we model (iia) autoregressive and (iib) cross-lagged effects. And (iii) CLSEM enables modeling of individual participants, and because of that, within-person processes can be separated from stable between-person differences by means of inclusion of random intercepts.

Thus, separate three-wave CLSEM will be run to test mediation of the effect of group by potential mediators on outcome measures (IDS-SR and OQ-45). We will include the following paths within those models: autoregression effects (stability effects) for mediators and outcome variables,

within time correlations between mediator and outcome variables, longitudinal cross-lagged effects of mediator and outcome variables, effect of outcome at T0 on outcome at T2 and mediator at T0 on mediator at T2. In addition, we will test whether group (MBCT + TAU versus TAU) will have a significant differential effect on outcome at T2 (path a), on mediator at T1 (path b), and whether mediating variables at mid-treatment (T1) predict outcome post-treatment (T2). Finally, as a formal test of mediation, the indirect effect of group (MBCT + TAU versus TAU) on outcome at post-treatment (T2) via mediating variables at mid-treatment (T1) will be estimated using bootstrapping procedures (Selig & Preacher, 2009) consisting of 5000 bootstrap samples. We will calculate 95% confidence intervals (CI) of indirect effects (Preacher and Hayes, 2008). To separate within-person processes from stable between-person differences we will repeat the CLSEM models with the inclusion of random intercepts (Hamaker et al., 2015; Mulder & Hamaker, 2021), and compare results.

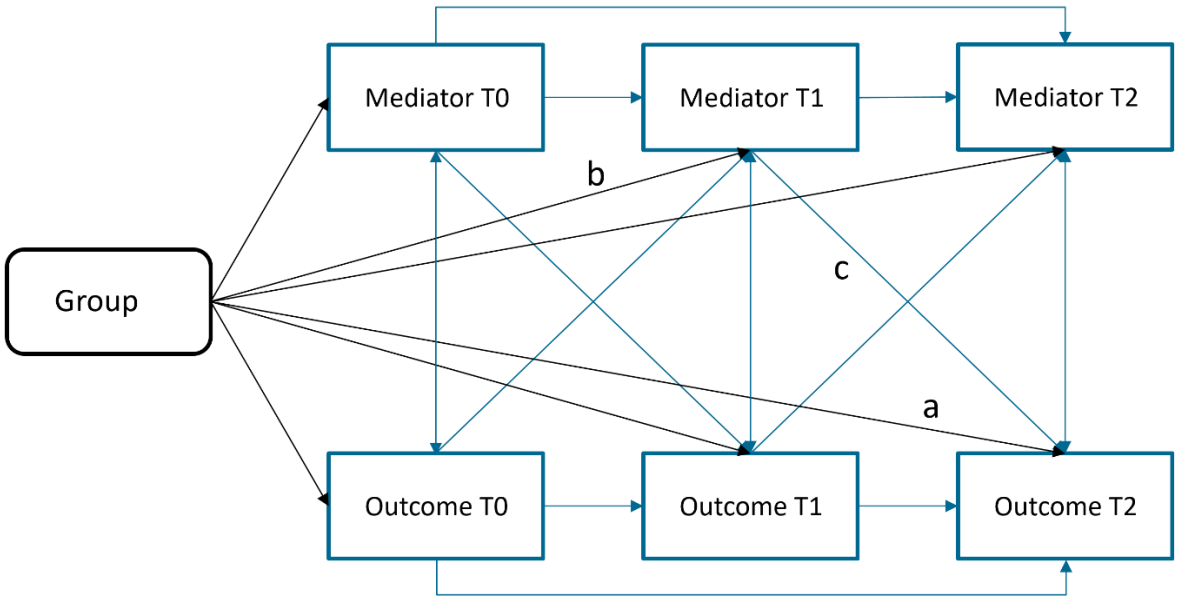

Figure 2. Structure of Cross-Lagged Structural Equation Models (CLSEM) of mediation for outcome at post-treatment (T2) by mediator at mid-treatment (T1). a represents the direct path of group on outcome, b the effect of group on mediator at mid-treatment, c the effect mediator of mid-treatment on outcome at post-treatment, while b*c represents the indirect path from group on outcome at post-treatment via mediator at mid-treatment. Note. Group = Mindfulness-based Cognitive Therapy (MBCT) + Treatment as usual (TAU) versus TAU, T0 = pre-treatment, T1 = mid-treatment, T2 = post-treatment.

As a sensitivity analysis we will perform a simple mediation analysis by using the PROCESS macro provided by Hayes et al. (2013). Group (MBCT + TAU versus TAU) will be entered as IV, pre- to post-treatment residualized change in depressive symptoms (IDS-SR) as DV, while pre- to mid-treatment residualized change in RNT/rumination (PTQ/RRS brooding subscale) will be entered as mediator. Other potential mediators of interest will be tested in an analogues manner.

Secondary outcomes: experimental tasks

1. Pavlovian to Instrumental Transfer Task

The Pavlovian-to-Instrumental Transfer (PIT) paradigm is a behavioral task used to investigate how Pavlovian conditioned stimuli (CS) (de)motivate instrumental behavior. In the PIT paradigm, participants undergo three phases: Pavlovian conditioning, instrumental training and a transfer phase (Figure 3). In the Pavlovian phase, a stimulus (CS) is paired with an outcome (unconditioned stimulus, US) to create an association. In the instrumental phase, participants learn to perform an action to obtain a reward and/or prevent a punishment (e.g., pressing a button upon seeing a stimulus to obtain points). During the transfer phase, participants are presented with the CS from the Pavlovian phase, while instructed to continue their learned instrumental response to earn points, but now are not given any rewards. The question is whether the presence of the CS will influence the instrumental behavior, i.e., whether the CS will serve as a signal to guide (i.e. bias) the choice of the action that leads to the reward. Indeed, a large literature shows that these contextual CSs (de)motivate instrumental behavior (Rescorla and Solomon, 1967; Holmes et al., 2010; Garbusow et al., 2022). Previously, amongst others, we have shown, that CSs can invigorate or inhibit behavior dependent on the valence of the CS (appetitive vs. negative) and nature of the instrumental action (approach vs. avoidance): for example, the appetitive CS promotes and the negative CS inhibits approach actions, whereas the aversive CS promotes and the appetitive CS inhibits withdrawal actions (Huys et al., 2011a; Geurts et al., 2013a, 2022b, 2022c). Thus, on the cognitive level the PIT paradigm can measure the motivational impact of contextual reward and punishment information on approach and avoidance behaviors.

On the neural level, PIT is associated with amygdala, (ventral) striatal and ventromedial prefrontal cortex processing subserved by catecholaminergic and serotonergic transmission (Talmi et

al., 2008; Holmes et al., 2010; Wassum et al., 2011; Geurts et al., 2013a; Hebart and Gläscher, 2015; Salamone et al., 2015; Cartoni et al., 2016; Garbusow et al., 2022).

PIT and depression

Problems in motivation, reward and punishment processing and approach and avoidance behaviors have been central to cognitive-behavioral theories on depression (MDD) (see for reviews: Trew, 2011; Chen et al., 2015; Huys et al., 2015). The PIT paradigm therefore seems exceptionally suited to deliver rich behavioral information on the (individual variation of) affective-cognitive aspects relevant to depression in addition to for example questionnaire data. Indeed, two studies investigated PIT within MDD samples (Huys et al., 2016; Nord et al., 2018). Both studies find that MDD patients do not differ from healthy controls in the acquisition of instrumental contingencies (based on reward and punishment reinforcement learning) or Pavlovian contingencies (based on passive classical conditioning). However, in both studies the action specific PIT effect differs from HC, but in opposite directions: Nord et al. (2018) show that MDD patients show enhanced action-specific aversive PIT (i.e. the difference between the effect of an aversive CS on approach vs withdrawal actions), whereas Huys et al. (2016) show that MDD patients do show PIT in approach context, but that action-specificity is disturbed. Moreover, Nord et al. found a positive relation across (but not within) groups between depression symptom severity and action-specific aversive PIT, whereas Huys et al. found a negative relation between depression scores and action specific PIT within the patient sample. Moreover, Huys et al. found that action-specificity was related to improvement of depressive symptoms across 4-6 months.

Notably, explanation of these equivocal findings might contribute substantially to understanding the (cognitive-behavioral) variation within the heterogeneous MDD population. This might extend to the observed differences in populations recruited in these studies: Where Huys et al. included also MDD patients using psychtropic medication, Nord et al. did not. Here we set out to contribute to understanding these differences and extend our knowledge on PIT in MDD by addressing the following research questions:

(1) First, we ask how, especially aversive, PIT differs between healthy controls, MDD patients with a current depressive episode or in remission.

(2) Second, within the MDD sample, we ask how depressive symptoms are related to PIT. We will explore the role of medication status on PIT in the MDD sample.
(3) Third, we ask whether, especially action-specific aversive PIT is predictive of recovery of MDD in the currently depressed sample.

In addition, ample evidence shows that mindfulness-based cognitive therapy has beneficial effects for patients with MDD (Kuyken et al., 2016; Goldberg et al., 2019; Geurts et al., 2020). There are only some preliminary studies addressing the effect of mindfulness on PIT (Geurts et al., 2022a; Rosenthal et al., 2023). Geurts et al. (2022a) show that an 8 week MBCT course enhances aversive inhibition in patients with ADHD. Given the beneficial effect of MBCT on depression and a putative modulating role of MBCT on aversive Pavlovian inhibition we will assess whether MBCT indeed changes depressive symptoms in MDD patients compared to a waitlist control and how these changes are related to changes in PIT.

(4) Fourth, we will assess (a) what effect MBCT has on PIT in an MDD patient sample and (b) whether this relates to the change in depressive symptoms from pre-to-post MBCT.

Next to the main research questions, related to MDD and (the recovery of) depressive symptoms, we will assess on an exploratory basis the relation of PIT with rumination, based on the hypothesis that rumination is a consequence of lowered aversive PIT (cf. Huys et al., 2015) or increased active avoidance (Nord et al., 2018) and one of the proposed foci in the mode of action of MBCT.

Statistical analyses PIT

We will first perform an analysis to assess whether the data is better captured by a model that coded 3 valence levels (positive, neutral, negative, i.e. averaging across the high and low conditions within each Valence Context), or by a model that each of the 5 levels of Valence Context separately (cf. Huys et al., 2011b; Geurts et al., 2013b).

To assess the influence of motivational cues on instrumental behaviour, we will analyze invigoration (Go vs. NoGo responding) during Pavlovian to Instrumental transfer. To account for both

between- and within-subject variability these data will be analysed with logistic mixed-level models using the lme4 package in R (Bates et al., 2014). Reflecting our objectives, the mixed models will include where appropriate the within-subject factors treatment (MBCT, waitlist), Action Context (approach vs. withdrawal) and Valence Context (appetitive/neutral/aversive), and the between-subject factors Group (HC, MDDremitted, MDDcurrent), medication status (serotonergic/catecholaminergic medication, no medication) and depressive symptom severity (in terms of IDS-SR score) or rumination (inter terms of RRS brooding score). Models include all main effects and interactions. All models will contain a full random effects structure (Barr et al., 2013). When the full random effects structure prevents the models to converge, we will make amends.

Planned contrasts involve those contrasts focusing on action-specific aversive PIT, i.e. those interaction including an interaction between Valence Context (neu, aversive) x Action Context (approach, withdrawal). Next to the planned contrasts we will explore the full model. Thus, models relating to the different research questions will be:

(1) Valence Context * Action Context * Group + full random effects structure

MDD sample:

(2) Valence Context * Action Context * IDS-SR + random effects structure

(3) Valence Context * Action Context * IDS-SRchange + random effects structure

(4a) Time * Valence Context * Action Context * Treatment + random effects structure

(4b) Time * Valence Context * Action Context * Treatment * IDS-SRchange + random effects structure.

We will report effects significant at an alpha-level of <.05. Any significant higher order interactions will be analysed using post-hoc simple interactions for ease of interpretation.

Control analyses PIT

As sensitivity analyses we will conduct a number of control analyses that confirm the robustness of the results: we will assess the i) lack of effect of covariates of no interest, including age, gender, intelligence; ii) robustness of the results to exclusion of participants with deterministic PIT

responding; iii) successful instrumental conditioning, where we will also assess the influence of the degree of instrumental conditioning, and iv) Pavlovian conditioning on the main results.

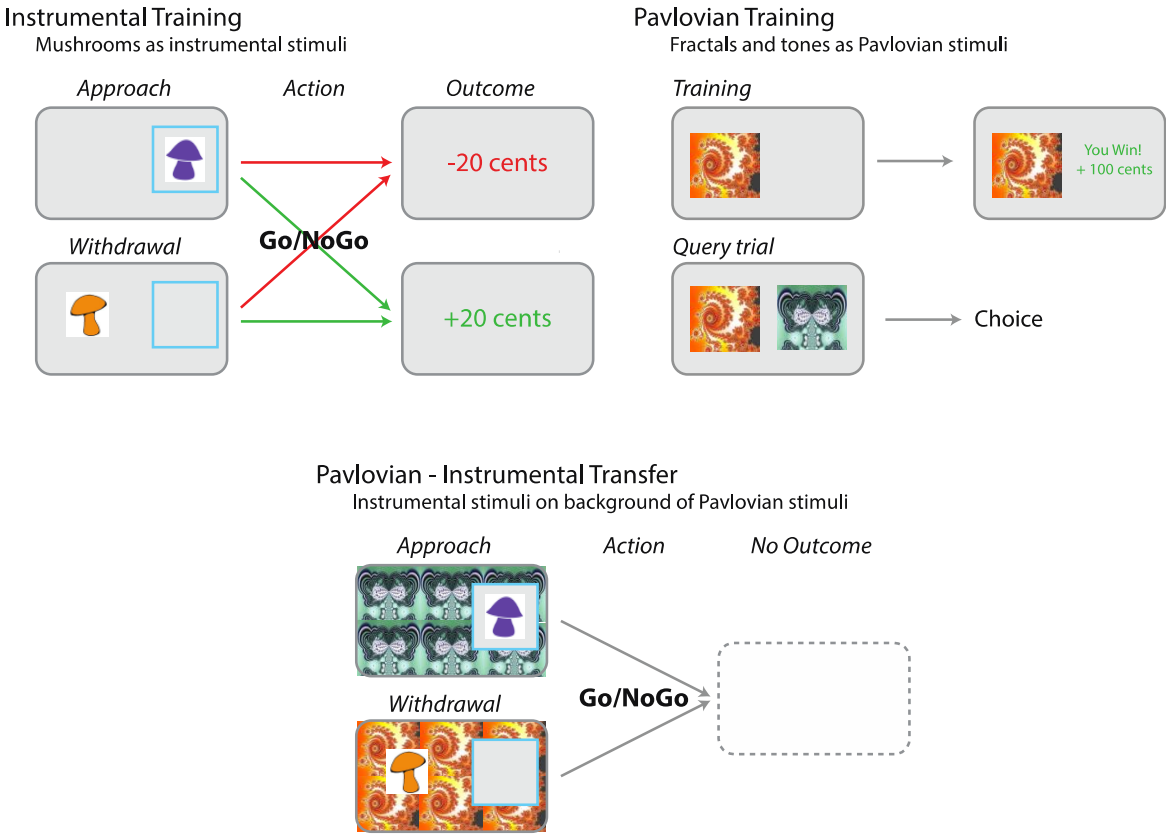

Figure 3. **Instrumental training.** To centre the cursor, participants click in a central square. The experiment consists of a block with exclusively instrumental approach trials (n=120) and a block with exclusively withdrawal trials (n=120). In approach trials (top), participants chose whether to move the cursor towards the mushroom and click inside the blue frame onto the mushroom (go), or do nothing (nogo). In withdrawal trials, they instead moved the cursor away from the mushroom and clicked in the empty blue frame (go) or did nothing (nogo). Outcomes are presented immediately after go actions, or after 1.5 seconds. Per block there are 3 "good" and 3 "bad" instrumental stimuli. Participants play each block ones per testing day. Instrumental stimuli are different for both blocks and both days. **Pavlovian training.** Participants passively view stimuli and hear auditory tones, followed by wins and losses. There are five fractal/tone combinations. Each combination is displayed 12 times in the first block and another 6 times in the second block. **Pavlovian-instrumental transfer.** Participants respond to the instrumental stimuli trained during the instrumental training stage, with Pavlovian stimuli tiling the background. No outcomes are presented, but participants are instructed that their choices count towards the final total. No explicit instructions about the contribution of Pavlovian stimuli towards the final total are given.

2. The working memory update ignore emotion task (WMUIET)

The WMUIET (see Figure 4) contains black and white pictures of sad and neutral emotional faces. The task assesses the influence of emotional information on distractor resistance (ignore) and update capacity of working memory with (emotional) faces as target stimuli. Each trial contains three distinct phases separated by three delay periods.

First set of faces

Participants will be instructed to remember both the place of presentation and the face of two simultaneously presented black and white photographs when, and only when, the letter "T" (= target) appeared in the middle of the screen. Each presented set of photographs always contains two faces with the same emotion (neutral or sad).

Second set of faces

In the second set, again two black and white pictures of faces will be presented. In total, there are four positions (top left/right, bottom left/right) and the first set always contains opposite positions compared to the second set, so that all four positions have shown a face once in every trial. In the second set, either a "T" or a "+" is presented in the middle of the screen. A "T" (= new Target) again indicates that this set of faces needs to be remembered (= update trial). A "+" (= distractor) indicates that the second set can be ignored (ignore trial). The participants are instructed that only the last target ("T") set has to be remembered. Thus, the second set determines whether a trial consists of an ignore or update trial.

Probe phase

In the third phase, the probe phase, one face of the last target set is presented, and subjects will be asked to indicate at which position this face was presented in the last target-set with the D, K, C or M key on the laptop keyboard (see Figure 4).

No-interference (NI) trials - controls

In addition to normal ignore and update trials, the task also includes control, or so called no-interference, trials. In these trials, one of the representations does not consist of faces but of blank

rectangles. Therefore, only one set of faces is presented and should be remembered and there will be no influence of update or ignore functions of the working memory. In the update trials, the first set is blank, in the ignore trials the second set because these sets were not the final target sets in normal trials.

Possible combinations

Consequently, the task consists of 12 different types of trials. Four types of trails in both the ignore and update trials (sad→ update: sad; sad → update: neutral; neutral→ update: sad; neutral→update: neutral and sad→ ignore: sad; sad→ ignore: neutral; neutral→ignore: sad; neutral→ignore: neutral), two types of no interference ignore trials (neutral→ blank; sad→ blank) and two types of no interference update trials (blank→ neutral; blank→ sad). Each of these types consist of 20 trials, so there are 240 trials per participant.

Task variables

Accuracy will be measured as a correct or a false answer, so a dichotomous variable will be created, and reaction time is measured as a numeric variable. Thus, this task enables us to measure accuracy and reaction time as a function of emotion of the first presentation (3 levels: sad/neutral/NI-update), emotion of the second presentation (3 levels: sad/neutral/NI-ignore), and trial type (2 levels: update/ignore). Note, that this is not a full factorial model with respect to the no interference trials, because these trials only contain one emotion presentation.

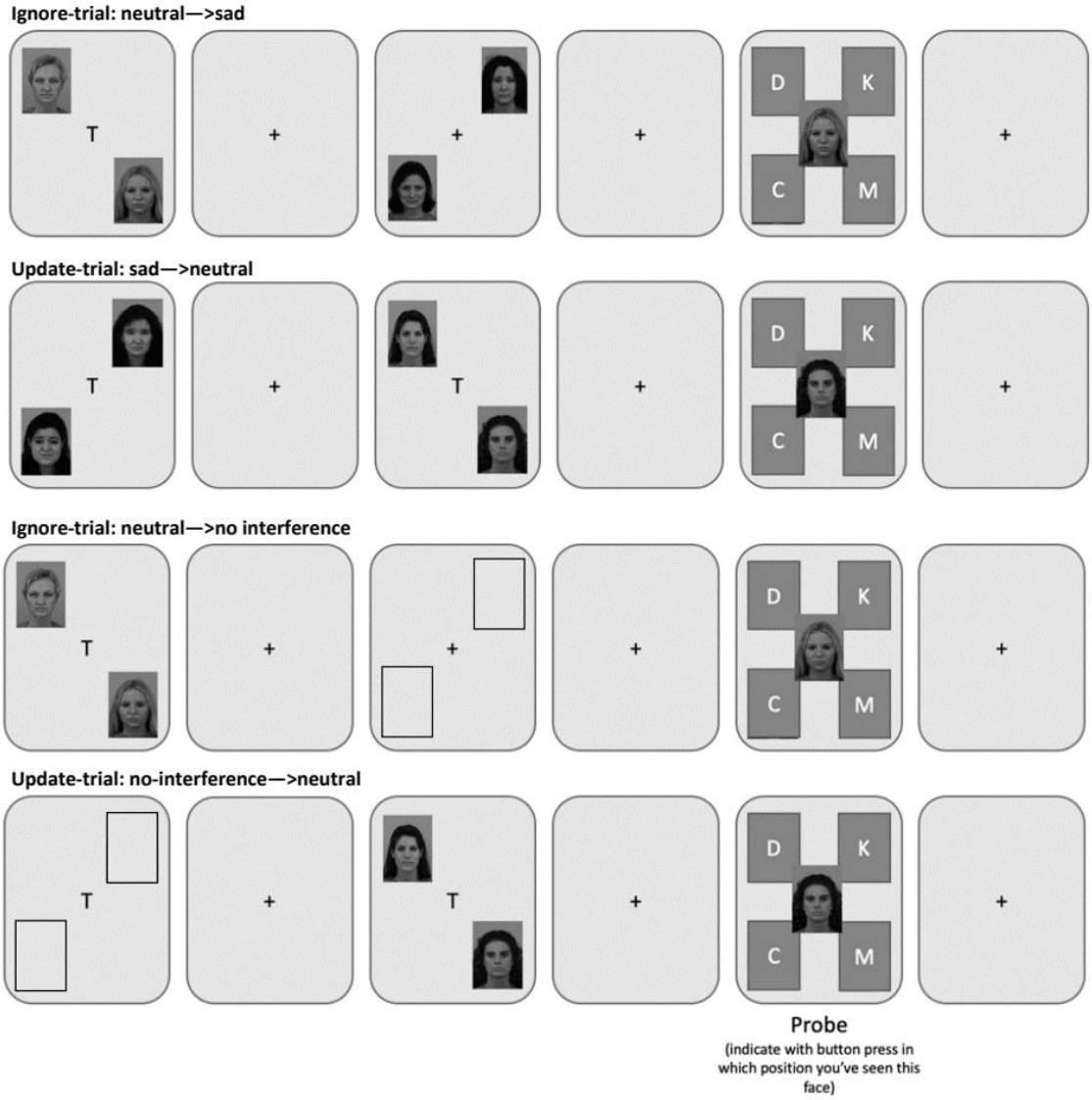

Figure 4. **Working Memory Update/Ignore Emotion Task.** Subjects are instructed to remember the *last* set of faces with a T presented in between and forget about all the earlier presented faces and to-be presented faces without a T in between. In the ignore (distractor resistance) trials, top row, subjects are supposed to remember the target set while interfering information is displayed in the ignore phase. In the depicted case, neutral faces have to be kept in working memory while resisting the sad distractor faces. Whether inhibiting the sad information from working memory was successful is tested in the probe phase, where subjects have to indicate the position where the presented probe face (always from the target set) was presented. In the update trials (2nd row), subjects are supposed to update the first target set with a new target set. In the probe phase, it is tested whether this updating was successful. In the depicted trial subjects are supposed to update a set of sad faces with neutral faces. As a control condition, no interference trials are used with either a blank screen before or after presentation of one set of faces to act as a control condition for ignore and update trials respectively (3rd and 4th row).

Update and distractor resistance capacity of working memory in MDD

Depressed individuals have difficulty in (i) inhibiting negative information from entering working memory (ignoring) (De Lissnyder et al., 2010; Goeleven et al., 2006; Joormann, 2004; Joormann & Gotlib, 2010), and (ii) removing negative information from working memory (updating) (Joormann &

Gotlib, 2008). This difficulty in inhibiting of (De Lissnyder et al., 2012; Joormann & Gotlib, 2010) and updating from (Joormann & Tran, 2009) negative information in depressed individuals has been found to be related to depressive rumination. Depressive rumination is a form of repetitive negative thinking (RNT) which is characterized by repetitive, (partly) intrusive thoughts about the causes and consequences of symptoms of depression, that are hard to disengage from (Nolen-Hoeksema et al., 2008). Deficits in cognitive control over mood-congruent material, such as the impaired ability to disengage from or inhibit negative information in working memory, may contribute to the use of maladaptive emotion regulation strategies such as depressive rumination that might perpetuate current depressive symptoms and might predispose for recurrent depressive episodes (Huys et al., 2015; LeMoult & Gotlib, 2019).

Despite the demonstrated relationship between deficits in cognitive control over mood-congruent material and depressive rumination, the interplay with depressive symptoms is not well understood and no evidence is found for a direct relation with the influence of negative information in cognitive control (Everaert et al., 2017; LeMoult & Gotlib, 2019). Furthermore, most studies that investigate the effect of emotional valence on ignoring and updating of WM do not concomitantly measure and analyze the effects of both ignore and update processes within one task. A task measuring both processes will enable a more comprehensive analysis of the interacting relationship between updating and ignoring of the WM. More specifically, the influence of emotional valence on updating and ignoring processes in the WM, the interaction between those processes and the relation with clinical constructs such as rumination and depressive symptoms could be elucidated. It could be, for example, that ignoring and updating are reflections of the same disturbed mechanism with no additional value over each other in relation to clinical constructs. Alternatively, these processes might reflect different mechanisms that have additive explanatory value with respect to rumination and/or depressive symptoms. Recently, a new task has been developed to measure updating and ignoring of WM (Fallon & Cools, 2014; Fallon et al., 2017). For the current study, this task was extended with emotion manipulation to assess the emotion dependence of updating and ignoring, resulting in the Working Memory Update/Ignore Emotion Task (WMUIET). Our aim is to use this task to investigate whether

(i) negative information influences task accuracy,

(ii) depressive symptom severity (in terms of IDS-SR score) and/or rumination (brooding subscale of RRS) are correlated with updating and/or ignoring negative information in WM, and

(iii) influence of negative information on ignoring and updating of WM is related to each other and have an interacting relation with other variables in patients with (remitted) persistent or recurrent MDD.

We hypothesize that negative information in WM in MDD patients will attenuate updating based on the disengagement hypothesis (Koster et al., 2011; Southworth et al., 2017) and that MDD patients have more difficulty in ignoring negative information (less distractor resistance). Moreover, we hypothesize that MDD patients will show improved performance when asked to remember negative information. We expect these difficulties to be accompanied by increased rumination and we expect MBCT to normalize these findings.

Statistical Analysis WMUIET To answer our research question, we will employ generalized mixed effects models with correct choice as dependent variable. We will build the following models: (a) A model for the update trials; (b) a model for the Ignore trials; and (c) an omnibus model encompassing update and ignore trials to compare the relation between update and ignore processes. All models include the subjects as a random effect and will be constructed using a maximal fitting approach with random slopes and intercepts for all the non-correcting independent variables with more than one level (Barr, 2013; Barr et al., 2013).

Model (a) on update trials will include the within subject factors ‘Emotion of first set’ (2 levels: neutral/sad) and ‘Emotion of second set’ (2 levels: neutral/sad). Note that in this model the first set must be updated by the second set (thus the second set must be remembered) to come to a correct answer.

Model (b) on ignore trials will include the within subject factors ‘Emotion of first set’ (2 levels: neutral/sad) and ‘Emotion of second set’ (2 levels: neutral/sad). Note that in this model the second set must be ignored (thus the first set must be remembered) to come to a correct answer.

Moreover, when significant main effects of emotion for the second set for update trials and of the first set for ignore trials were found, we will assess whether these were indeed due to specifically the update or ignore process respectively by incorporating the no-interference trial and Type of Trial (no-interference/interference) as additional factor in the model.

Furthermore, to investigate the the within-subject relation between the update and ignore trials, an omnibus model will be constructed combining both update and ignore trials with the additional factor Type of Trial (Update/Ignore).

We will assess whether there are differences between healthy controls (HC) and remitted and currently depressed MDD patients by incorporating a factor Group with three levels.

To further answer whether the update and ignore processes are related to rumination and/or depressive symptoms we will add these scores separately to the models described above with only the MDD patients. Any significant interaction with one of these covariates would indicate a relation between emotion dependent WM processing and rumination or depressive symptom severity.

We will report effects significant at an alpha-level of <.05. Any significant higher order interactions will be analysed using post-hoc simple interactions for ease of interpretation.

Control analyses WMUIET

As sensitivity analyses we will conduct a number of control analyses that confirm the robustness of the results: we will assess the lack of effect of covariates of no interest, including age and gender.

3. Weekly self-report questionnaires

The weekly self-report questionnaires will be administered after each MBCT session (8 times) and on a weekly basis in the wait-list control group. We will use these measurements for exploration of the (variation in the) timing of individual change processes.

References

Barr, D. J. (2013). Random effects structure for testing interactions in linear mixed-effects models. *Front Psychol*, *4*, 328. https://doi.org/10.3389/fpsyg.2013.00328

Barr, D. J., Levy, R., Scheepers, C., & Tily, H. J. (2013). Random effects structure for confirmatory hypothesis testing: Keep it maximal. *J Mem Lang*, *68*(3). https://doi.org/10.1016/j.jml.2012.11.001

Cladder-Micus, M. B., Speckens, A. E., Vrijsen, J. N., T. Donders, A. R., Becker, E. S., & Spijker, J. (2018). Mindfulness-based cognitive therapy for patients with chronic, treatment-resistant depression: A pragmatic randomized controlled trial. *Depression and anxiety*, *35*(10), 914-924.

Dai, Q., & Feng, Z. (2009). Deficient inhibition of return for emotional faces in depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *33*(6), 921-932.

De Lissnyder, E., Koster, E. H., Derakshan, N., & De Raedt, R. (2010). The association between depressive symptoms and executive control impairments in response to emotional and non-emotional information. *Cognition and Emotion*, *24*(2), 264-280.

De Lissnyder, E., Koster, E. H., Goubert, L., Onraedt, T., Vanderhasselt, M.-A., & De Raedt, R. (2012). Cognitive control moderates the association between stress and rumination. *Journal of Behavior Therapy and Experimental Psychiatry*, *43*(1), 519-525.

Duncan, T. E., & Duncan, S. C. (1995). Modeling the processes of development via latent variable growth curve methodology. *Structural equation modeling: A multidisciplinary Journal*, *2*(3), 187-213.

Everaert, J., Podina, I. R., & Koster, E. H. (2017). A comprehensive meta-analysis of interpretation biases in depression. *Clinical psychology review*, *58*, 33-48.

Fallon, S. J., & Cools, R. (2014). Reward acts on the pFC to enhance distractor resistance of working memory representations. *J Cogn Neurosci*, *26*(12), 2812-2826. https://doi.org/10.1162/jocn_a_00676

Fallon, S. J., van der Schaaf, M. E., Ter Huurne, N., & Cools, R. (2017). The Neurocognitive Cost of Enhancing Cognition with Methylphenidate: Improved Distractor Resistance but Impaired Updating. *J Cogn Neurosci*, *29*(4), 652-663. https://doi.org/10.1162/jocn_a_01065

Feingold, A. (2009). Effect sizes for growth-modeling analysis for controlled clinical trials in the same metric as for classical analysis. *Psychological methods*, *14*(1), 43.

Goeleven, E., De Raedt, R., Baert, S., & Koster, E. H. (2006). Deficient inhibition of emotional information in depression. *Journal of affective disorders*, *93*(1-3), 149-157.

Goldberg, S. B., Tucker, R. P., Greene, P. A., Davidson, R. J., Kearney, D. J., & Simpson, T. L. (2019). Mindfulness-based cognitive therapy for the treatment of current depressive symptoms: a meta-analysis. *Cognitive behaviour therapy*, *48*(6), 445-462.

Hamaker, E. L., Kuiper, R. M., & Grasman, R. P. (2015). A critique of the cross-lagged panel model. *Psychological methods*, *20*(1), 102.

Hardeveld, F., Spijker, J., De Graaf, R., Hendriks, S. M., Licht, C. M., Nolen, W. A., Penninx, B. W., & Beekman, A. T. (2013). Recurrence of major depressive disorder across different treatment settings: results from the NESDA study. *Journal of affective disorders*, *147*(1-3), 225-231.

Hayes, A. F., Montoya, A. K., & Rockwood, N. J. (2017). The analysis of mechanisms and their contingencies: PROCESS versus structural equation modeling. *Australasian Marketing Journal*, *25*(1), 76-81.

Huys, Q. J., Daw, N. D., & Dayan, P. (2015). Depression: a decision-theoretic analysis. *Annual review of neuroscience*, *38*, 1-23.

Joormann, J. (2004). Attentional bias in dysphoria: The role of inhibitory processes. *Cognition and Emotion*, *18*(1), 125-147.

Joormann, J., & Gotlib, I. H. (2008). Updating the contents of working memory in depression: interference from irrelevant negative material. *Journal of abnormal psychology*, *117*(1), 182.

Joormann, J., & Gotlib, I. H. (2010). Emotion regulation in depression: Relation to cognitive inhibition. *Cognition and Emotion*, *24*(2), 281-298.

Joormann, J., & Tran, T. B. (2009). Rumination and intentional forgetting of emotional material. *Cognition and Emotion*, *23*(6), 1233-1246.

Koster, E. H., De Lissnyder, E., Derakshan, N., & De Raedt, R. (2011). Understanding depressive rumination from a cognitive science perspective: the impaired disengagement hypothesis. *Clin Psychol Rev*, *31*(1), 138-145. https://doi.org/10.1016/j.cpr.2010.08.005

Kuyken, W., Warren, F. C., Taylor, R. S., Whalley, B., Crane, C., Bondolfi, G., Hayes, R., Huijbers, M., Ma, H., & Schweizer, S. (2016). Efficacy of mindfulness-based cognitive therapy in prevention of depressive relapse: an individual patient data meta-analysis from randomized trials. *JAMA psychiatry*, *73*(6), 565-574.

LeMoult, J., & Gotlib, I. H. (2019). Depression: A cognitive perspective. *Clinical psychology review*, *69*, 51-66.

Mulder, J. D., & Hamaker, E. L. (2021). Three extensions of the random intercept cross-lagged panel model. *Structural equation modeling: A multidisciplinary Journal*, *28*(4), 638-648.

Nolen-Hoeksema, S., Wisco, B. E., & Lyubomirsky, S. (2008). Rethinking rumination. *Perspectives on psychological science*, *3*(5), 400-424.

Organization, W. H. (2017). *Depression and Other Common Mental Disorders: Global Health Estimates*. WHO. https://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf

Piet, J., & Hougaard, E. (2011). The effect of mindfulness-based cognitive therapy for prevention of relapse in recurrent major depressive disorder: a systematic review and meta-analysis. *Clinical psychology review*, *31*(6), 1032-1040.

Segal, Z. V., Williams, J. M. G., & Teasdale, J. (2013). *Mindfulness-based cognitive therapy for depression: A new approach to preventing relapse*. Guilford Publications.

Selig, J. P., & Preacher, K. J. (2009). Mediation models for longitudinal data in developmental research. *Research in human development*, *6*(2-3), 144-164.

Southworth, F., Grafton, B., MacLeod, C., & Watkins, E. (2017). Heightened ruminative disposition is associated with impaired attentional disengagement from negative relative to positive information: support for the "impaired disengagement" hypothesis. *Cogn Emot*, *31*(3), 422-434. https://doi.org/10.1080/02699931.2015.1124843

Teasdale, J. D., Segal, Z. V., Williams, J. M. G., Ridgeway, V. A., Soulsby, J. M., & Lau, M. A. (2000). Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy. *Journal of consulting and clinical psychology*, *68*(4), 615.

Van Aalderen, J., Donders, A., Giommi, F., Spinhoven, P., Barendregt, H., & Speckens, A. (2012). The efficacy of mindfulness-based cognitive therapy in recurrent depressed patients with and without a current depressive episode: a randomized controlled trial. *Psychological Medicine*, *42*(5), 989-1001.

van der Velden, A. M., Kuyken, W., Wattar, U., Crane, C., Pallesen, K. J., Dahlgaard, J., Fjorback, L. O., & Piet, J. (2015). A systematic review of mechanisms of change in mindfulness-based cognitive therapy in the treatment of recurrent major depressive disorder. *Clinical psychology review*, *37*, 26-39.