**Brief online intervention to modify interpretation biases in emotional disorders:
Study protocol for a randomized controlled trial**

Ines Nieto¹

Carmelo Vazquez¹

¹Department of Clinical Psychology
School of Psychology
Complutense University of Madrid

Running head: Online modification of interpretation biases

Correspondence: cvazquez@psi.ucm.es
School of Psychology, Complutense University of Madrid, 28223 Madrid (Spain)

Abstract: 230 words.

Abstract

Background: Cognitive biases seem to play an important role in the development and maintenance of emotional disorders such as depression and anxiety. Novel procedures, known as Cognitive Bias Modification (CBM), aim to reduce these dysfunctional information processing modes. This study aims to develop a brief online intervention program to modify biased interpretations in depression and anxiety overcoming some methodological issues that have been addressed in previous literature.

Methods: Volunteer participants will be recruited via social media, posters and universities. They will be randomly assigned to the experimental group or a waiting list control group. Both groups will attend two assessment sessions at the lab. The assessment will consist of questionnaires measuring cognitive and emotional variables as well as three experimental tasks to measure cognitive biases (i.e., attention, memory and interpretation). After the first assessment session only participants in the experimental group will receive a link to follow the four-sessions program at home. All participants will receive, via email, follow-up questionnaires two weeks and three months after the second assessment session.

Discussion: This study will test an online program potentially beneficial to modify cognitive variables in disorders such as depression and anxiety. Several limitations of previous CBM procedures are addressed and the impact of the program both on cognitive performance and clinical symptoms will be explored.

Trial registration: This trial was prospectively registered on June 17, 2019 with the ClinicalTrials.gov NCT03987477

Key words: Cognitive Bias Modification; Ambiguous Interpretations; Emotional Disorders

Background

Anxiety and mood disorders are the most common mental disorders in the population, showing an 18.1 % and 9.5% 12-month prevalence, respectively [1]. Both disorders are associated with high social and economic costs, as well as high rates of chronicity and relapse [2,3].

High patterns of comorbidity between anxiety and mood disorders are consistent across studies [1,4]. This comorbidity could be due, at least in part, to the fact that these disorders share transdiagnostic factors such as rumination [5], and are also likely to share some general risk factors [6]. Cognitive theories point out to dysfunctional thinking as one of the main variables related to the onset and maintenance of these emotional disorders [6–8]. According to these influential theories, depressed and anxious individuals show specific cognitive dysfunctions that can ultimately lead to symptom development [9]. Several types of dysfunctions have been distinguished in regard to the onset and maintenance of emotional disorders. A useful heuristic to clarify diverse types of cognitive activity intervening in psychopathology is the so-called “cognitive taxonomy”, initially proposed by Ingram & Kendall [10]. This taxonomy distinguishes between *structural* variables (i.e., broad cognitive schemas through which information is filtered, represented and organized); *operational* variables (i.e., the mechanisms, like attentional, interpretation, or memory biases, by which cognitive structures work); *product* variables (i.e., the tangible outputs, like thoughts, images, memories, with which clinicians typically work with their clients). In general, cognitive biases have been defined as errors or distortions related to the operational domain that occur systematically at different times and across situations, reflecting ‘irrational’ modes of perceiving and elaborating information [11,12].

Cognitive Bias Modification (CBM)

Cognitive Bias Modification (CBM) is a recent approach developed to alter cognitive biases and explore the link between them and symptoms development. CBM procedures have mainly been aimed at modifying attentional, memory, or interpretation biases. Besides their clinical utility, these procedures are theoretically ambitious as their rationale is that a causal link between cognition and emotion would be demonstrated if changes in cognition are accompanied by consequent changes in emotion. Thus, the efficacy of CBM would provide support to the etiological role of cognition in emotional disorders. Although it has been applied in different conditions, such as eating disorders, substance abuse or anger-related problems [13], the main focus has been in anxiety and depression [14–17].

Mathews and Mackintosh [18], in their pioneer study in the field of CBM for interpretation processes (CBM-I), used a paradigm to induce negative interpretation biases in healthy individuals and found a possible causal link to anxiety. Since then, studies using different training paradigms have found an association between change in interpretation bias and symptoms. Recent meta-analyses show evidence of correlation between change in interpretation bias and negative mood [19] and significant differences between CBM training and control groups in anxiety and depression measures [16]. Some transdiagnostic factors, such as rumination, have also been found to improve with CBM-I [20]. A review of 12 meta-analyses of CBM procedures [17] revealed that there was a significant effect in 8 out of 10 meta-analyses for anxiety and 3 out of 7 meta-analyses for depression. Authors also found significant changes in attention biases in 8 out of 9 meta-analyses of studies using Attentional Bias Modification procedures (ABM), and changes in interpretation biases in the three meta-analyses on CBM-I. All this evidence reflects a possible causal link between cognitive

biases and symptoms that, at least in the case of interpretation biases, might suggest the existence of a causal connection with depressed mood in particular [21].

Although results are promising, there are some limitations in current CBM procedures [22,23]. First of all, there are some variables that could affect efficacy of CBM but remain unexplored. For example, although there are some studies indicating that the use of mental imagery during CBM procedures could have a beneficial impact on CBM [24–26], it is still unclear whether this factor is relevant [16,19]. Also, most CBM procedures are based on the idea that repetitive exposure to a specific way of processing information leads to its automatic use later in daily life [27]. Yet, the theoretical support to this mechanistic and repetitive procedure (that typically involves hundreds or even thousands of trials) is not clear. In fact, it could be possible that CBM procedures focused on enhancing elaborative rather than automatic processing modes could be more beneficial for disorders like depression in which those elaborative mechanisms seem to be more affected than automatic ones [25].

Another methodological recommendation to improve CBM paradigms is the use of direct and indirect measures to evaluate cognitive change [13,21]. This involves asking participants to directly respond a series of interpretations (e.g. plausibility ranking or the scrambled sentence task) together with non-conscious measures of interpretations (e.g. reaction time, or jumping to conclusions measure). The evaluation of long term benefits, when participants may have faced possible stressors in real life, has also been encouraged by previous research [28]. Also, cognitive biases at different processing levels (attention, interpretation, and memory) have traditionally been studied independently from each other but some authors already state the need to know how they interact with each other [29,30].

Objectives and hypotheses

The purpose of the study is to design a brief online intervention aimed at reducing interpretation negative emotional cognitive biases. The intervention will be applied to an experimental group to analyze its impact on cognitive and emotional variables in comparison to a waiting-list control group. More specifically, the intervention is framed within the field CBM-I but, instead of using a repetitive training, it is based on the techniques frequently used in cognitive-behavioral therapies (e.g. (31,32,33)). Thus, while original CBM studies (e.g. [18]) were designed to train participants to change cognitive interpretation biases in an automatic manner, the current intervention aims to teach participants the meaning and consequences of emotional cognitive biases, and how to modify them.

This study also aims to improve in several respects the procedures used in previous CBM procedures. First, based on previous evidence [34], mental imagery is used in order to shed some light into its role when modifying cognitive processes. Second, direct and indirect measures of cognitive performance are used to complement the information provided by self-report questionnaires. Moreover, these measures evaluate the three different domains proven to be affected by them (attention, interpretation and memory) [35], given the need to explore their interplay [36]. Finally, given that it is not clear the maintenance of CBM effects, a longitudinal follow-up was used to explore the maintenance of benefits in time and the dynamics of the different processing biases (attention, interpretation, and memory).

It is hypothesized that there will be a significant change in interpretation bias (less negative or more positive/neutral) from pre-intervention to post- intervention in the experimental group in comparison to the control group. It is also expected that changes

in interpretation biases will be also associated to significant changes in attention and memory biases (less negative or more positive/neutral) from pre-intervention to post-intervention in the experimental group in comparison to the control group. Finally, it is hypothesized that the intervention will help the experimental group to reduce symptoms of depression and anxiety and increase well-being from pre-intervention to post-intervention in comparison to the control group. Due to the lack of conclusive findings from previous studies, it is explored whether these changes are maintained over time (after 2 weeks and 3 months) and the temporal dynamics of the different cognitive bias processes (attention, interpretation, and memory).

Methods

Participants and recruitment

Sample size was calculated based on the estimated effect size of the change in interpretation bias before and after a CBM-I intervention ($d = .43$) according to a recent meta-analysis on the field [19]. Following G*Power calculations [37], the minimum sample size (α set at 0.05, power at 0.95) to find a difference in a repeated-measures multivariate analysis of variance with one within-subjects factor (two time points) and one between-subjects factor (two groups) was 73 participants. Twenty percent more participants will be recruited due to expected attrition [38].

Participants will be volunteer students of the Complutense University of Madrid recruited via social media associated to the university and posters at the Faculty of Psychology. They will be offered course academic credits in exchange of their participation. Exclusion criteria will include any form of visual and/or auditory disability that makes participants unable to follow online sessions and lack of Internet

access. No restriction will be placed regarding concomitant treatment during the study, although this information will be monitored during the assessment sessions.

This study is a randomized superiority trial with two parallel groups and a 1:1 allocation ratio. Participants will be randomly allocated (using an Excel macro) to the experimental group (cognitive bias intervention) or a control waiting list group. This control group was chosen due to the novelty of the intervention, for which waitlist is recommended to get a first impression of its effects [39]. The procedure has been approved by the university ethics committee (Ref. 2018/19-017) and has been registered (Clinical.gov). Moreover, it follows the recommendations for a clinical trial protocol [40].

Intervention: ‘Relearning to think’ program

This is a brief online intervention designed to modify negative emotional interpretation biases. The intervention is composed of four different sessions in audiovisual format with psychoeducational content, open-answer questions and exercises to be completed by users. Different cognitive biases, such as jumping to conclusions, mental filter, overgeneralization and negative attributions are targeted in each session following classical descriptions of biases [8,41]-see Figure 1. The organization of the sessions content was based on the Cognitive Error Rating Scales (CERS; [42], a manual created for therapists to evaluate cognitive errors during clinical sessions, and the CBM-errors [43], a clinical strategy to promote more benign interpretations following Beck’s theory [23].

Figure 1. Classification of the specific cognitive biases targeted in the four online sessions of the program.

Each session of ‘Relearning to think’ is composed of four different parts (see Figure 2). In part 1, participants receive information about specific interpretation biases and are given examples in video format. Some of these videos are daily life scenes where professional actors represent examples of cognitive biases (following clinical vignettes described elsewhere) [6]. During each video (before the resolution of the scene), and in order to increase active involvement, participants have to complete an open-ended question about what could happen in those ambiguous situations. In the second part, users are informed about the risks of using negative interpretations and it is followed by the explanation of the strategies to avoid them (part 3). These strategies are based on “the 4 questions technique” [44], widely used in clinical practice. This technique involves 4 steps to re-evaluate the negative interpretation of a given situation: finding evidence for the negative thoughts, uncovering the cognitive bias present in the situation, identifying the negative consequences and creating alternative ways of thinking. Finally, during part 4, participants have the opportunity to practice the

strategies in an exercise composed of an imagery training [45] followed by negative scenarios in audio format aimed to be reinterpreted. Figure 3 shows the steps of the exercise. It starts with an imaginary training [45] aimed to make scenarios more vivid to users. Participants are presented a screen saying ‘Close your eyes. Imagine’ for 1 second followed by a black screen during which a negative scenario is played in audio format with female voice (e.g. *Your partner travels to work by car and normally arrives home promptly every day. Today you notice that they are over an hour late. Your first thought is that there must have been a crash*). Audio scenarios are daily life situations where negative interpretations arise and participants are asked to imagine themselves in those situations. A beep is played for users to open their eyes and start with the exercise questions. First, they have to rate their mood (sadness, happiness, anxiety and anger) in a 10-point VAS scale based on the most frequent emotions experienced in daily life [46,47]. Then, they are guided to apply the 4 questions technique to each scenario. Finally, users evaluate the degree to which they believe in the new alternative thoughts and emotions generated by the new scenario (sadness, happiness, anxiety and anger).

Figure 2. Structure of each session of the program.

Figure 3. Practice exercise of each session of the program.

Primary outcome measures

Ambiguous Scenarios Test for Depression-II. The AST-D-II [48] is a self-report measure of interpretation biases. It consists of 15 ambiguous scenarios which participants have to rate on a scale from -5 (Very unpleasant) to 5 (Very pleasant). Participants are asked to imagine each scenario as vividly as possible and happening to them (e.g. *As you enter the room, the commission welcomes you and begins with the oral examination. After just few minutes you know intuitively how the examination will go*). Two parallel versions are used in counterbalanced order at baseline, post-treatment and in the follow-ups. Internal consistency has been shown to be good ($\alpha = 0.87$) for the general scale and its two short versions A ($\alpha = 0.77$) and B ($\alpha = 0.78$).

Depression, Anxiety and Stress Scale-21. The DASS [49] is a 21-item self-report questionnaire measuring symptoms of depression, anxiety and stress. Each of the three subscales contains 7 items and provide a different score for each construct. This

questionnaire has shown good reliability with the following α values for the Depression, Anxiety and Stress scales, respectively: 0.84, 0.70 and 0.82 [50].

Pemberton Happiness Index. The PHI [51] is a 11-item self-report questionnaire measuring general, eudaimonic, hedonic, and social well-being. It has shown to have a very good reliability ($\alpha = .92$).

Secondary outcome measures

a) Indirect measures

Mouse-based (gaze) contingent attention task (MCAT) [52]. A variant of the original Scrambled Sentence Test (SST, [53]) is used to measure interpretation bias while monitoring attention towards emotional stimuli, based on the same principles of action as in the eye-gaze contingent attention training (ECAT) [54]. At the beginning of the task, participants have to click a fixation cross at the left side of the screen to elicit natural left-to-right reading patterns. Then, the *reading screen* is presented with a 6-word emotional scrambled sentence (e.g., “am winner born loser a I”) where each word is hidden with a blank mask. Participants are instructed to move the mouse cursor over each mask to read the word hidden and mentally form a grammatically correct sentence using five of them. They are given a time limit of 14 seconds per sentence. This procedure is used to objectively measure attention biases toward emotional words (negative or positive). Then, the *answer screen* is presented with the six words unmasked for participants to click the order of the sentence they had mentally formed. In this section, participants are given a time limit of 7 seconds. The resulting ratio of correctly negative unscrambled sentences and correctly emotional unscrambled sentences is considered to be an index of automatic negative interpretation bias. To maximize the appearance of biases, at the beginning of the task participants are

presented a 6-digit number during 5 seconds and told to keep that number in mind during the entire task as they will be asked to retrieve it at the end of the task.

SST-Memory task. As a measure of memory biases, participants are given 5 minutes to freely remember the sentences they constructed during the SST. Following Everaert et al.'s procedure [30], the ratio of correctly recalled negative/positive scrambled sentences is a measure of memory bias.

Computerized beads task [55]. The beads task is a measure of probabilistic reasoning which was initially designed to measure jumping to conclusion (JTC) bias in schizophrenic patients [56]. The adapted version used in this study has two parts. The first one consists of presenting two jars with beads of two different colors in different ratios (e.g. 60 orange/40 purple, and 60 purple/40 orange) Participants are told that the program selects one of the jars to take beads randomly out of it and return them. The instruction is to decide which jar is being used, based on the number of beads of each color. The second part follows the same procedure with the difference that the beads are all in white but present two different ratios of positive and negative adjectives (60 positive/40 negative, and 60 negative/40 positive). The number of beads viewed before reaching a decision is an index of jumping to conclusion bias.

b) Direct measures

Dysfunctional Attitudes Scale. The DAS [57] is a scale of 40 sentences reflecting dysfunctional cognitive schemas. Participants have to rate each sentence from 0 (not applicable to me) to 3 (highly applicable to me). The sum of the scores is an index of stable dysfunctional attitudes (i.e., a measure of cognitive structures). The DAS has been found to be a predictor of major depression [58] and it has shown to have good reliability $\alpha = .70$ [59].

Ruminative Responses Scale The RRS [60](Nolen-Hoeksema & Morrow, 1991) is composed of two subscales measuring rumination cognitive style. For the present study, only the 5-item brooding subscale will be used in order to measure the tendency to ruminate about negative events. The scale has shown good reliability ($\alpha = .93$) [61].

Other measures

Patient Health Questionnaire-9. The PHQ-9 [62] is a 9-item self-report questionnaire to assess possible present episodes of depression according to the DSM-IV diagnostic criteria. Each item is rated in frequency on a four-point scale from 1 (Not at all) to 4 (Nearly every day). Diagnosis is made if participants select a frequency of 3 or 4 in four or more items, including anhedonia and depressed mood. This questionnaire has shown good reliability with a Cronbach's α of 0.89 [63].

GAD-7 [64] is a 7-item self-report questionnaire to assess present episodes of anxiety according to the DSM-IV diagnostic criteria. Each item is rated on a four-point scale from 0 (Not at all) and 3 (Nearly every day), being the final score between 0-21. Level of severity can be evaluated according to the following categories: minimal (0-4), mild (5-9), moderate (10-14) and serious (14-20).

The scale for mood assessment-EVEA [65] is a measure of current mood that participants take right before and after each of the sessions of the program. It is included to reflect some possible reactions to the cognitive training procedure. Participants have to rate, from 0 to 10, their current level of anger, happiness, anxiety, depression, and boredom. Scores of each subscale (4 items each) are summed up providing an index of emotional change during the session.

Credibility and expectancy questionnaire The CEQ [66] is a 6-item measure used to assess the expectancy and rationale credibility of participants regarding the

online program they are offered before they start it. It consisting of two subscales that measure credibility based on cognition (*what you think*) and treatment expectancy based on affect (*what you feel*). Both subscales have shown to have good internal consistency ($\alpha = .86$ for credibility, $\alpha = .90$ for expectancy).

The Working Alliance Inventory for Internet interventions (WAI-I) [67] is a self-report measure to assess alliance in Internet interventions. In this study, only the 8-item subscale of Task and goal agreement with program was used in order to measure the level of concordance of the program with participants' interests. This measure was used at the end of the program to know if participants were satisfied with the result. An example of an item is 'Through the online program I have become clearer about the things I need to do to help improving my situation'. Chronbach's α for this subscale has been shown to be good ($\alpha = .84$).

Stressful Events Questionnaire (SE) [68] is a self-report scale to measure stressful situations that happen to participants between the second assessment and the follow-ups (2 weeks and 3 months). The scale includes positive and negative ratings of high impact events as well as daily events related to different contexts (social, emotional, academic/occupational, and 'other').

Procedure

Figure 4 shows the schedule of enrolment, intervention and assessment following the recommendations for clinical trials [40]. The main investigator will run an Excel macro for the randomization of participants to the experimental and control groups. This method assigns of a sequence of numbers with different codification for each group. In any case participants will be aware of the codification meaning. Participants will receive the questionnaires for the first assessment the day before the

first assessment session in the lab together with the consent form and an information file about the online program. During this session, the main investigator will explain the rationale of the intervention ‘Relearning to think’ and will provide participants with the instructions to complete the program. They will need to log into an online platform created for the purpose of this study and create their own account and password to access the material. Information will be coded with the participant’s number and only the main researchers will have access to data. This data will be monitored by the main investigator as adherence control. The first time participants access the platform, they will find the first session available and only 24 hours later they will be allowed to complete the second one. This time lag between sessions aims to increase participants learning and avoid cognitive overload and boredom.

After briefing on the intervention, participants will sign the informed consent (explaining their right to discontinue the study at any moment and with no consequences) and complete some demographic information and the three experimental tasks (MCAT, computerized beads task, and SST recall task). At the end of this first assessment, participants will be cited again after approximately 10 days for a second assessment session and the experimental group will be receiving via email the link to start the intervention online. The control group will be given the opportunity to complete the intervention right after the second assessment. To improve adherence, both groups will receive a reminder for the second assessment session the day before the date. Finally, those participants who agree will be sent some selected questionnaires for the follow-ups (after 2 weeks and after 3 months). To increment adherence during the follow-ups, participants will be sent up to a maximum of three reminders to complete questionnaires. Both groups will have the opportunity to complete a ‘feedback question’

to give their opinion about the intervention. This question will be included in the post-assessment for the experimental group and at the follow-ups for the control group.

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close-out
TIMEPOINT	$-t_1$	0 (Pre)	10 days	Post	Follow-up (2w)	Follow-up (3m)
ENROLMENT:						
Informed consent	X					
Allocation	X					
INTERVENTIONS:						
Online program for the experimental group			↔			
Waiting time for the control group			↔			
ASSESSMENTS:						
Ambiguous Scenarios Test for Depression-II (AST-D-II)		X		X	X	X
Depression, Anxiety and Stress Scale-21 (DASS21)		X		X	X	X
Pemberton Happiness Index (PHI)		X		X	X	X
Mouse-based (gaze) contingent attention task (MCAT)		X		X		
Scrambled Sentence Task-Memory (SST-M)		X		X		

<i>Computerized beads task</i>		X		X		
<i>Dysfunctional Attitudes Scale (DAS)</i>		X		X		
<i>Ruminative Responses Scale (RRS)</i>		X		X		
<i>Patient Health Questionnaire-9 (PHQ-9)</i>		X				
<i>Generalized Anxiety Disorder-7 (GAD-7)</i>		X				
<i>The scale for mood assessment-EVEA</i>			X			
<i>Credibility and expectancy questionnaire</i>		X				
<i>The Working Alliance Inventory for Internet interventions (WAI-I)</i>				X		
<i>Stressful Events Questionnaire</i>					X	X

Figure 4. Schedule of enrolment, interventions, and assessments.

Analytic plan

Demographic data and pre-treatment measures will be analyzed to test for group differences with analysis of variance and chi squared test for nominal variables.

Complete-case analyses will be conducted for those participants who complete all 4 online sessions and attend pre- and post-assessment evaluation sessions. A series of 2 (group: Experimental, Control) x 2 (time: pre-training, post-training) analyses of

variance will be performed to evaluate the change between groups. Depression and anxiety symptoms will also be included in the analyses to explore their influence in the results. Intention-to-treat (ITT) analyses will be conducted with all participants, regardless of session or outcome measure completion. ITT mixed models (restricted maximum likelihood (REML) estimation) will be used to account for missing data [69]. Binary logistic regression will be used to evaluate the assumption that data is Missing at Random (MAR). Exploratory analyses will be conducted to study the interplay between the different cognitive bias scores. Finally, follow-up assessments will be included a series of analyses of variance to evaluate group differences in time. All analyses will be performed in SPSS Statistics 20 with an α level of 0.05.

Discussion

The current study will test the efficacy of a brief online intervention to target emotional negative cognitive biases. Although traditional CBM interventions are designed to change this type of dysfunctional processing in an automatic way [16], the rationale of ‘Relearning to think’ is to increase participants’ awareness of their own thought processes and guide them to change these processes, in a more effortful way, by following a clinically-oriented working frame.

The study uses a transdiagnostic conceptualization of the role of cognitive biases in psychopathology. Given the high comorbidity between anxiety and mood disorders [1], having intervention tools that can tap both problems could be clinically useful. Some of the video scenarios designed for the program were based on examples proposed by previous transdiagnostic approaches [6] and the content is suitable for different common psychopathologies in which cognitive biases may play a role.

The study also addresses some of the questions that remain unanswered regarding CBM efficacy. It combines subjective (e.g. AST-D) along with objective measures (e.g. JTC measure, MCT) to assess cognitive biases. The present study was aimed to complement both self-report and behavioral measures to avoid potential biases of respondents. Mental imagery is also used following the proposal that it may enhance CBM-I performance [13]. Holmes, et al. [45] found that mental imagery of emotional content have a beneficial impact in cognitive change. ‘Relearning to think’ includes an imagery training with the aim to potentiate vividness of the scenarios and promote interpretation change.

Furthermore, explores in an innovative manner whether changes in interpretation biases may be associated to concomitant changes in attention and memory. There is very scarce basic research on the interrelation between different types of biases in emotional disorders [30] and this study will offer a unique opportunity to explore whether a specific intervention designed to change interpretation of ambiguous scenarios may also affect other domains of information processing.

Finally, there is an increasing interest in the use of online interventions and many researchers wonder if this format is also beneficial for individual with clinical problems. The extant evidence suggests that psychological treatments delivered online can be as effective as face-to-face therapies [70,71] and seem to overcome some of the limitations traditional therapies present [72]. For example, online sessions can be taken by the individual at any time, there is no need to wait to schedule dates, stigma is reduced and individuals increase their self-efficacy [73]. Specifically, CBM interventions seem to be highly suitable for the online format due to its flexibility in application or the minimal requirement of supervision, in comparison to traditional therapies [74]. CBM could even be used in a self-management way, so that it could be

applied to patients waiting for treatment or presenting vulnerability factors [27]. In sum, we expect that this study will offer new responses to some of the challenges CBM procedure face to make them more feasible, more efficient, and also more able to provide answers to some theoretical issues related to the complex relations between emotion, cognition, and clinical psychology.

Trial status

The trial was registered on 17th June 2019, with ClinicalTrial.gov NCT03987477. The study is actively recruiting participants and ongoing.

Date and version identifier

Issue date: 17 June 2019

Protocol amendment number: Original

Authors: IN, CV

Revision chronology: No other revision

List of abbreviations

ABM: Attentional Bias Modification; AST-D-II: Ambiguous Scenarios Test for Depression-II; CBM: Cognitive Bias Modification; CBM-I: Cognitive Bias Modification of Interpretations; CEQ: Credibility and Expectancy Questionnaire; DAS: Dysfunctional Attitudes Scale; DASS-21: Depression, Anxiety and Stress Scale-21; ECAT: Eye-gaze Contingent Attention Training; EVEA: Scale for mood; GAD-7: Generalized Anxiety Disorder Scale-7; ITT: Intention-To-Treat; JTC: Jumping To Conclusions; MANOVA: Multivariate Analysis Of Variance; MAR: Missing At Random; MCAT: Mouse-based (gaze) Contingent Attention Task; PHI: Pemberton Happiness Index; PHQ-9: Patient Health Questionnaire-9; REML: Restricted Maximum Likelihood; RRS: Ruminative Responses Scale; SE: Stressful Events Questionnaire; SST: Scrambled Sentence Test; WAI-I: The Working Alliance Inventory for Internet interventions.

Declarations

Ethics approval and consent to participate

This project has been approved by the School of Psychology Ethics Committee on June 17, 2019 (Ref. 2018/2019-017). All participants will provide informed consent before starting the first study session. To ensure anonymity, we will replace the names of participants with code numbers to process and analyze the data.

Consent for publication

All participants are asked for their consent to report on the results in publications.

Availability of data and materials

Not applicable

Acknowledgements

We thank Irene-López for her initial thoughts on the conceptualization of the study and Marta Miragall, Simon Blackwell, Alvaro Sánchez and Vanesa Peinado for their valuable contributions to the contents of the study. We also thank Víctor García and Alvaro Franco for their technical support in implementing the online program, Elena Robles and Eva Moreno for their help in several stages of the study, and all the students who voluntarily took part in the pilot study of the program (Ada Arteaga, Elena Castello, Andrea Cuesta, Beatriz Estefanía, and Juan José Rodrigo Apio).

Funding

This work was supported by CT17/17-CT18/17 UCM grant to IN and a MINECO grant PSI2015-69253-R to CV. This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Authors' contributions

IN and CV developed the study concept and study design. Testing and data collection will be performed by IN. Data analysis and interpretation will be performed by IN under the supervision of CV. IN drafted the manuscript and was corrected and expanded by CV. Both authors approved the final version of the manuscript for submission.

Any modifications to the protocol which may impact the potential benefit of the patient or may affect patient safety will be notified to the university ethics committee. Administrative changes and minor corrections will be agreed by both authors.

Competing interest

The authors declare that they have no competing interest.

Authors' details

Carmelo Vázquez, Faculty of Psychology, Complutense University of Madrid, 28223 Madrid (Spain)
Inés Nieto, inenieto@ucm.es, Faculty of Psychology, Complutense University of Madrid, 28223 Madrid (Spain)

References

1. Kessler, R. C., Chiu, W. T., Demler, O., Walters EE. Prevalence, severity, and

- comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62:617–27.
2. Whiteford, H. A., Degenhardt, L., Rehm, J., Baxter, A., Ferrari, A. J., Erskine, H. E., Vos T. Global burden of disease attributable to mental and substance use disorders: Findings from the Global Burden of Disease Study 2010. *Lancet*. 2013;382:1575–86.
 3. Collins PY, Patel V, Joestl SS, March D, Insel TR, Daar AS, et al. Grand challenges in global mental health. *Nature* [Internet]. 2011;475:27–30. Available from: <http://www.nature.com/articles/475027a>
 4. Wittchen H-U. Generalized anxiety disorder: Prevalence, burden, and cost to society. *Depress Anxiety* [Internet]. 2002;16:162–71. Available from: <http://doi.wiley.com/10.1002/da.10065>
 5. McLaughlin KA, Nolen-Hoeksema S. Rumination as a transdiagnostic factor in depression and anxiety. *Behav Res Ther* [Internet]. 2011;49:186–93. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S000579671000255X>
 6. Barlow, D. H., Farchione, T. J., Fairholme, C. P., Ellard, K. K., Boisseau, C. L., Allen, L. B., Ehrenreich-May J. Protocolo unificado para el tratamiento transdiagnóstico de los trastornos emocionales. Madrid: Alianza Editorial; 2015.
 7. Beck AT. Depression: Clinical, experimental, and theoretical aspects. Pennsylvania: University of Pennsylvania Press; 1967.
 8. Beck AT. Cognitive therapy and the emotional disorders. New York: Meridian; 1976.
 9. Mineka S, Watson D, Clark LA. Comorbidity of anxiety and unipolar mood disorders. *Annu Rev Psychol* [Internet]. 1998;49:377–412. Available from: <http://www.annualreviews.org/doi/10.1146/annurev.psych.49.1.377>
 10. Ingram, R. E., Kendall PC. Cognitive clinical psychology: Implications of an information processing perspective. In: Ingram RE, editor. *Inf Process approaches to Clin Psychol*. Orlando, FL: Academic Press; 1986. p. 3–21.
 11. Haselton, M.G., Nettle, D. Andrews PW. The evolution of cognitive bias. In: D. M. Buss, editor. *Handb Evol Psychol*. Hoboken, NJ, US: John Wiley & Sons Inc.; 2005. p. 724–746.
 12. Kahneman D. Thinking, fast and slow. Barcelona: Penguin Random House Editorial Group; 2012.
 13. MacLeod C, Koster EHW, Fox E. Whither cognitive bias modification research? Commentary on the special section articles. *J Abnorm Psychol* [Internet]. 2009;118:89–99. Available from: <http://doi.apa.org/getdoi.cfm?doi=10.1037/a0014878>
 14. Hakamata Y, Lissek S, Bar-Haim Y, Britton JC, Fox NA, Leibenluft E, et al. Attention Bias Modification treatment: A meta-analysis toward the establishment of novel treatment for anxiety. *Biol Psychiatry* [Internet]. 2010;68:982–90. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0006322310007663>
 15. Hallion LS, Ruscio AM. A meta-analysis of the effect of cognitive bias modification on anxiety and depression. *Psychol Bull* [Internet]. 2011;137:940–58. Available from:

<http://doi.apa.org/getdoi.cfm?doi=10.1037/a0024355>

16. Cristea IA, Kok RN, Cuijpers P. Efficacy of cognitive bias modification interventions in anxiety and depression: Meta-analysis. *Br J Psychiatry* [Internet]. 2015;206:7–16. Available from: https://www.cambridge.org/core/product/identifier/S0007125000237318/type/journal_article
17. Jones EB, Sharpe L. Cognitive bias modification: A review of meta-analyses. *J Affect Disord* [Internet]. 2017;223:175–83. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0165032717310960>
18. Mathews A, Mackintosh B. Induced emotional interpretation bias and anxiety. *J Abnorm Psychol* [Internet]. 2000;109:602–15. Available from: <http://doi.apa.org/getdoi.cfm?doi=10.1037/0021-843X.109.4.602>
19. Menne-Lothmann C, Viechtbauer W, Höhn P, Kasanova Z, Haller SP, Drukker M, et al. How to boost positive interpretations? A meta-analysis of the effectiveness of cognitive bias modification for interpretation. Voracek M, editor. *PLoS One* [Internet]. 2014;9:e100925. Available from: <https://dx.plos.org/10.1371/journal.pone.0100925>
20. Hertel P, Mor N, Ferrari C, Hunt O, Agrawal N. Looking on the dark side: Rumination and cognitive-bias modification. *Clin Psychol Sci* [Internet]. 2014;2:714–26. Available from: <http://journals.sagepub.com/doi/10.1177/2167702614529111>
21. Everaert J, Podina IR, Koster EHW. A comprehensive meta-analysis of interpretation biases in depression. *Clin Psychol Rev* [Internet]. 2017;58:33–48. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0272735817303963>
22. Koster EHW, Bernstein A. Introduction to the special issue on Cognitive bias modification: Taking a step back to move forward? *J Behav Ther Exp Psychiatry* [Internet]. 2015;49:1–4. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0005791615000737>
23. Lee J-S, Mathews A, Shergill S, Yiu Chan DK, Majeed N, Yiend J. How can we enhance cognitive bias modification techniques? The effects of prospective cognition. *J Behav Ther Exp Psychiatry* [Internet]. 2015;49:120–7. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0005791615000373>
24. Holmes EA, Lang TJ, Moulds ML, Steele AM. Prospective and positive mental imagery deficits in dysphoria. *Behav Res Ther* [Internet]. 2008;46:976–81. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0005796708000910>
25. Duque A, López-Gómez I, Blanco I, Vázquez C. Modificación de Sesgos Cognitivos (MSC) en depresión: Una revisión crítica de nuevos procedimientos para el cambio de sesgos cognitivos. *Ter psicológica* [Internet]. 2015;33:103–16. Available from: http://www.scielo.cl/scielo.php?script=sci_arttext&pid=S0718-48082015000200005&lng=en&nrm=iso&tlng=en
26. Hitchcock C, Werner-Seidler A, Blackwell SE, Dalgleish T. Autobiographical episodic memory-based training for the treatment of mood, anxiety and stress-related disorders: A systematic review and meta-analysis. *Clin Psychol Rev* [Internet]. 2017;52:92–107. Available from:

<https://linkinghub.elsevier.com/retrieve/pii/S0272735816301969>

27. Schartau PES, Dalgleish T, Dunn BD. Seeing the bigger picture: Training in perspective broadening reduces self-reported affect and psychophysiological response to distressing films and autobiographical memories. *J Abnorm Psychol* [Internet]. 2009;118:15–27. Available from: <http://doi.apa.org/getdoi.cfm?doi=10.1037/a0012906>
28. Vazquez C, Blanco I, Sanchez A, McNally RJ. Attentional bias modification in depression through gaze contingencies and regulatory control using a new eye-tracking intervention paradigm: Study protocol for a placebo-controlled trial. *BMC Psychiatry* [Internet]. 2016;16:439. Available from: <http://bmcpsy psychiatry.biomedcentral.com/articles/10.1186/s12888-016-1150-9>
29. Sanchez A, Duque A, Romero N, Vazquez C. Disentangling the interplay among cognitive biases: Evidence of combined effects of attention, interpretation and autobiographical memory in depression. *Cognit Ther Res* [Internet]. 2017;41:829–41. Available from: <http://link.springer.com/10.1007/s10608-017-9858-5>
30. Everaert, J., Duyck, W., Koster EH. Attention, interpretation, and memory biases in subclinical depression: A proof-of-principle test of the combined cognitive biases hypothesis. *Emotion*. 2014;14:331–40.
31. Beck, A.T., Rush, A.J., Shaw, B.F., Emery G. *Terapia cognitiva de la depresión*. Bilbao: Desclee de Brower; 1983.
32. Greenberger, D., Padesky CA. *Mind over mood: Change how you feel by changing the way you think*. 2nd ed. New York: Guilford Press; 2015.
33. Leahy RL. *Cognitive therapy techniques, second edition: A practitioner's guide*. 2nd ed. New York: Guilford Publications; 2017.
34. Lang TJ, Blackwell SE, Harmer CJ, Davison P, Holmes EA. Cognitive Bias Modification using mental imagery for depression: Developing a novel computerized intervention to change negative thinking styles. *Eur J Pers* [Internet]. 2012;26:145–57. Available from: <http://doi.wiley.com/10.1002/per.855>
35. Gotlib IH, Joormann J. Cognition and depression: Current status and future directions. *Annu Rev Clin Psychol* [Internet]. 2010;6:285–312. Available from: <http://www.annualreviews.org/doi/10.1146/annurev.clinpsy.121208.131305>
36. Everaert J, Koster EHW, Derakshan N. The combined cognitive bias hypothesis in depression. *Clin Psychol Rev* [Internet]. 2012;32:413–24. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0272735812000499>
37. Faul F, Erdfelder E, Buchner A, Lang A-G. Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behav Res Methods* [Internet]. 2009;41:1149–60. Available from: <http://link.springer.com/10.3758/BRM.41.4.1149>
38. Crutzen R, Viechtbauer W, Spigt M, Kotz D. Differential attrition in health behaviour change trials: A systematic review and meta-analysis. *Psychol Health* [Internet]. 2015;30:122–34. Available from: <http://www.tandfonline.com/doi/abs/10.1080/08870446.2014.953526>

39. Gold SM, Enck P, Hasselmann H, Friede T, Hegerl U, Mohr DC, et al. Control conditions for randomised trials of behavioural interventions in psychiatry: A decision framework. *The Lancet Psychiatry* [Internet]. Elsevier Ltd; 2017;4:725–32. Available from: [http://dx.doi.org/10.1016/S2215-0366\(17\)30153-0](http://dx.doi.org/10.1016/S2215-0366(17)30153-0)
40. Chan A-W, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: Guidance for protocols of clinical trials. *BMJ* [Internet]. 2013;346:e7586–e7586. Available from: <http://www.bmj.com/cgi/doi/10.1136/bmj.e7586>
41. Burns, D. D., Beck AT. *Feeling good: The new mood therapy*. New York: Avon; 1999.
42. Drapeau, M., Perry, J. C., Dunkley, D., Blake E. *Cognitive Errors Rating Scales*. Canada: McTavish; 2010.
43. Lester KJ, Mathews A, Davison PS, Burgess JL, Yiend J. Modifying cognitive errors promotes cognitive well being: A new approach to bias modification. *J Behav Ther Exp Psychiatry* [Internet]. 2011;42:298–308. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0005791611000024>
44. Beck, A.T., Emery, G., Greenberg R. *Anxiety and phobias: A cognitive approach*. New York: Basic Books; 1985.
45. Holmes EA, Lang TJ, Shah DM. Developing interpretation bias modification as a ‘cognitive vaccine’ for depressed mood: Imagining positive events makes you feel better than thinking about them verbally. *J Abnorm Psychol* [Internet]. 2009;118:76–88. Available from: <http://doi.apa.org/getdoi.cfm?doi=10.1037/a0012590>
46. Trampe D, Quoidbach J, Taquet M. Emotions in everyday life. Avenanti A, editor. *PLoS One* [Internet]. 2015;10:e0145450. Available from: <https://dx.plos.org/10.1371/journal.pone.0145450>
47. Cowen AS, Keltner D. Self-report captures 27 distinct categories of emotion bridged by continuous gradients. *Proc Natl Acad Sci* [Internet]. 2017;114:E7900–9. Available from: <http://www.pnas.org/lookup/doi/10.1073/pnas.1702247114>
48. Rohrbacher H, Reinecke A. Measuring change in depression-related interpretation bias: Development and validation of a parallel ambiguous scenarios test. *Cogn Behav Ther* [Internet]. 2014;43:239–50. Available from: <http://www.tandfonline.com/doi/abs/10.1080/16506073.2014.919605>
49. Lovibond PF, Lovibond SH. The structure of negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. *Behav Res Ther* [Internet]. 1995;33:335–43. Available from: <https://linkinghub.elsevier.com/retrieve/pii/000579679400075U>
50. Bados A, Solanas A, Andrés R. Psychometric properties of the Spanish version of Depression, Anxiety and Stress Scales (DASS). *Psicothema*. 2005;17:679–83.
51. Hervás G, Vázquez C. Construction and validation of a measure of integrative well-being in seven languages: The Pemberton Happiness Index. *Health Qual Life Outcomes* [Internet]. 2013;11:66. Available from: <http://hqlo.biomedcentral.com/articles/10.1186/1477-7525-11-66>

52. Sanchez-Lopez A, De Raedt R, van Put J, Koster EHW. A novel process-based approach to improve resilience: Effects of computerized mouse-based (gaze)contingent attention training (MCAT) on reappraisal and rumination. *Behav Res Ther* [Internet]. 2019;118:110–20. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0005796719300695>
53. Wenzlaff RM, Bates DE. Unmasking a cognitive vulnerability to depression:How lapses in mental control reveal depressive thinking. *J Pers Soc Psychol* [Internet]. 1998;75:1559–71. Available from: <http://doi.apa.org/getdoi.cfm?doi=10.1037/0022-3514.75.6.1559>
54. Sanchez A, Everaert J, Koster EHW. Attention training through gaze-contingent feedback: Effects on reappraisal and negative emotions. *Emotion* [Internet]. 2016;16:1074–85. Available from: <http://doi.apa.org/getdoi.cfm?doi=10.1037/emo0000198>
55. Huq SF, Garety PA, Hemsley DR. Probabilistic judgements in deluded and non-deluded subjects. *Q J Exp Psychol Sect A* [Internet]. 1988;40:801–12. Available from: <http://journals.sagepub.com/doi/10.1080/14640748808402300>
56. Garety PA, Freeman D, Jolley S, Dunn G, Bebbington PE, Fowler DG, et al. Reasoning, emotions, and delusional conviction in psychosis. *J Abnorm Psychol* [Internet]. 2005;114:373–84. Available from: <http://doi.apa.org/getdoi.cfm?doi=10.1037/0021-843X.114.3.373>
57. Weissman A, Beck A. The Dysfunctional Attitude Scale: A preliminary investigation. *Pap Present Annu Meet Am Educ Res Assoc* [Internet]. 1978. p. 1–33. Available from: <https://eric.ed.gov/?id=ED167619>
58. Rude SS, Durham-Fowler JA, Baum ES, Rooney SB, Maestas KL. Self-report and cognitive processing measures of depressive thinking predict subsequent major depressive disorder. *Cognit Ther Res* [Internet]. 2010;34:107–15. Available from: <http://link.springer.com/10.1007/s10608-009-9237-y>
59. Sanz, J., Vázquez C. Adaptación española de la Escala de Actitudes Disfuncionales (DAS) de Beck: propiedades psicométricas y clínicas. *Análisis y Modif Conduct*. 1993;67:705–50.
60. Nolen-Hoeksema S, Morrow J. A prospective study of depression and posttraumatic stress symptoms after a natural disaster: The 1989 Loma Prieta earthquake. *J Pers Soc Psychol* [Internet]. 1991;61:115–21. Available from: <http://doi.apa.org/getdoi.cfm?doi=10.1037/0022-3514.61.1.115>
61. Hervás Torres G. Adaptación al castellano de un instrumento para evaluar el estilo rumiativo. *Rev Psicopatología y Psicol Clínica*. 2008;13.
62. Spitzer, R.L., Kroenke, K., Williams, J. B. PHQPCSG. Validation and utility of a self-report version of PRIME-MD: The PHQ primary care study. *JAMA* [Internet]. 1999;282:1737–44. Available from: <http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.282.18.1737>
63. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: Validity of a brief depression severity measure. *J Gen Intern Med* [Internet]. 2001;16:606–13. Available from:

<http://link.springer.com/10.1046/j.1525-1497.2001.016009606.x>

64. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder. *JAMA Intern Med* [Internet]. 2006;166:1092-1097.

Available from:

<http://archinte.jamanetwork.com/article.aspx?doi=10.1001/archinte.166.10.1092>

65. Sanz J. Un instrumento para evaluar la eficacia de los procedimientos de inducción de estado de ánimo: La “Escala de Valoración del Estado de Ánimo” (EVEA). *Análisis y Modif Conduct*. 2001;27:71–110.

66. Devilly GJ, Borkovec TD. Psychometric properties of the credibility/expectancy questionnaire. *J Behav Ther Exp Psychiatry* [Internet]. 2000;31:73–86. Available from:

<https://linkinghub.elsevier.com/retrieve/pii/S0005791600000124>

67. Gómez Penedo JM, Berger T, grosse Holtforth M, Krieger T, Schröder J, Hohagen F, et al. The Working Alliance Inventory for guided Internet interventions (WAI-I). *J Clin Psychol* [Internet]. 2019;jclp.22823. Available from:

<https://onlinelibrary.wiley.com/doi/abs/10.1002/jclp.22823>

68. Hernangomez L. Vulnerabilidad cognitiva a la depresión: Relación entre sesgos atencionales, auto-representación y síntomas depresivos. Universidad Complutense de Madrid; 2012.

69. Salim A, Mackinnon A, Christensen H, Griffiths K. Comparison of data analysis strategies for intent-to-treat analysis in pre-test–post-test designs with substantial dropout rates. *Psychiatry Res* [Internet]. 2008;160:335–45. Available from:

<https://linkinghub.elsevier.com/retrieve/pii/S0165178107002880>

70. Cuijpers P, Smit F, Oostenbrink J, de Graaf R, ten Have M, Beekman A. Economic costs of minor depression: a population-based study. *Acta Psychiatr Scand* [Internet]. 2007;115:229–36. Available from: <http://doi.wiley.com/10.1111/j.1600-0447.2006.00851.x>

71. Holmes EA, Ghaderi A, Harmer CJ, Ramchandani PG, Cuijpers P, Morrison AP, et al. The Lancet Psychiatry Commission on psychological treatments research in tomorrow’s science. *The Lancet Psychiatry* [Internet]. 2018;5:237–86. Available from:

<https://linkinghub.elsevier.com/retrieve/pii/S2215036617305138>

72. Kazdin AE, Blase SL. Rebooting psychotherapy research and practice to reduce the burden of mental illness. *Perspect Psychol Sci* [Internet]. 2011;6:21–37. Available from:

<http://journals.sagepub.com/doi/10.1177/1745691610393527>

73. Andersson G. Internet-Delivered Psychological Treatments. *Annu Rev Clin Psychol*. 2016;12:157–79.

74. Yiend J, Lee J-S, Tekes S, Atkins L, Mathews A, Vrinten M, et al. Modifying interpretation in a clinically depressed sample using ‘Cognitive Bias Modification-Errors’: A double blind randomised controlled trial. *Cognit Ther Res* [Internet]. 2014;38:146–59. Available from: <http://link.springer.com/10.1007/s10608-013-9571-y>