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Augmenting Interpretative Cognitive Bias Modification Using Memory Reconsolidation Updating

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Augmenting Interpretative Cognitive Bias Modification Using Memory Reconsolidation Updating

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Abstract

Augmenting Interpretative Cognitive Bias Modification Using Memory Reconsolidation Updating

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Research suggests that interpretative cognitive biases can be attenuated by cognitive bias modification for interpretation (CBM-I). However, small effect sizes and a lack of follow-up data highlight a need to increase the potency and durability of CBM-I. Recent findings have suggested that reactivating a fear memory briefly before behavioral intervention may suppress later return of fear, through utilization of a process known as reconsolidation updating. The current experiment investigated the efficacy of a CBM-I augmentation that involved administering a brief fear reactivation procedure prior to CBM-I. 74 adults with clinical social anxiety were randomly assigned to give an impromptu speech either 10 minutes prior to interpretation bias training (CBM+FRT), 24 hours prior to training (CBM), or 24 hours prior to placebo training (CONTROL). Social anxiety symptomology and interpretation bias were assessed using self-report questionnaires and a behavioral task at baseline (BL), post-training (POST), 1-week follow-up (FU1), and 2-week (FU2) follow-up. Mixed effects regression models revealed that as hypothesized, the CBM+FRT group had significantly lower

interpretation bias than the CBM group at FU2, but not at POST or FU1. However, there were no significant between-group differences in self-reported anxiety symptoms at any assessment. Additionally, no difference in interpretation bias between CBM and CONTROL was found at POST. Findings provide support for continued investigation of brief fear network reactivation as a means of enhancing anxiety treatment. However, a failure to find effects of non-augmented CBM-I suggests that further scrutiny is necessary to determine CBM's clinical utility.

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Chapter 1: Introduction

COGNITIVE BIAS MODIFICATION

Over the past several decades, researchers have invested considerable effort into studying the relationship between anxiety disorders and various information processing biases. In doing so, they have attempted to answer questions such as whether anxiety is characterized by the presence of cognitive biases, what role biases have in the development and maintenance of psychopathology, and whether anxiety symptoms can be ameliorated or prevented by manipulating bias intensity.

It has been firmly established that interpretation bias, which describes a tendency to interpret ambiguous situations as overly threatening, exists in anxious populations (Mathews & MacLeod, 2005; Mobini, Reynolds, & Mackintosh, 2012). Furthermore, research suggests that this cognitive bias can be modified through procedures commonly referred to as cognitive bias modification for interpretation (CBM-I), and that these procedures also lead to significant reductions in anxiety-related indices (Beard & Amir, 2008; Mackintosh, Mathews, Yiend, Ridgeway, & Cook, 2006; MacLeod & Mathews, 2012; Mobini et al., 2014).

Despite these positive findings, the effects of CBM-I have been shown to be quite variable, with some studies failing to find training-induced reductions in bias or anxiety symptoms (Chan, Lau, & Reynolds, 2014; Nowakowski, Antony, & Koerner, 2015; Orchard, Apetroaia, Clarke, & Creswell, 2017). Effect sizes may be smaller than indicated from preliminary studies, and there has been a lack of follow-up data for these interventions, limiting the ability to draw conclusions about long-term effects (Cristea, Kok, & Cuijpers, 2015; Hallion & Ruscio, 2011; Menne-Lothmann et al., 2014). These

factors underscore the need to develop and test strategies for increasing the potency and durability of CBM-I.

Fear Extinction Augmentation

Approaches derived from other research programs into fear extinction and attenuation may provide insight into such strategies. Recently, promising findings have emerged from the translation of basic animal and human research, which suggest that reactivating a fear memory prior to pharmacological or behavioral intervention may mitigate later return of fear (Agren, Björkstrand, & Fredrikson, 2017; Brunet et al., 2011; Soeter & Kindt, 2015; Telch, York, Lancaster, & Monfils, 2017). Although this technique has primarily been used as an augmentation strategy for extinction of laboratory-acquired fear in animals and humans thus far, a recent study showed it to also be effective in enhancing exposure therapy for naturally acquired fear (Telch et al., 2017), hinting at its potential for broader use in clinical practice.

A strength of the fear reactivation procedure is its potential capacity to reduce symptom reemergence at follow-up, addressing the return of fear that is often seen after exposure therapy (Kindt, 2014). It is widely thought that this reemergence of fear is derived from a failure of extinction processes to eliminate preexisting fear memories, as extinction is based on the generation of new safety memories that outcompete original associations of danger (Bouton, Winterbauer, & Todd, 2012). Although new safety learning may inhibit the expression of fear under specific conditions, it is possible for fear to reemerge, as evidenced by the phenomena of spontaneous recovery, renewal, reinstatement, and reacquisition (Bouton, 2002).

Researchers have attempted to capitalize on the malleable nature of memory in order to enhance extinction durability. Newly acquired memories are initially labile and

susceptible to disruption, before being converted into a more durable long-term state through a protein-synthesis dependent process known as consolidation (McGaugh, 2000). Although a consolidated memory is resistant to interference, it is thought that reactivating the fear memory renders it temporarily susceptible to disruption before it reconsolidates into a stable state once more (Nader & Hardt, 2009; Nader, Schafe, & Le Doux, 2000). If no processes interfere with reconsolidation, it is expected that the memory will reconsolidate into permanence within a temporal window lasting no longer than six hours. However, disrupting the reconsolidation process during the critical timeframe, either with pharmacological agents (Kindt, Soeter, & Vervliet, 2009; Soeter & Kindt, 2010) or extinction procedures (Schiller et al., 2010), seems to overwrite original fear associations as opposed to simply creating a set of new inhibitory associations; the result is increased durability of fear extinction.

Studies in both rodents (Jones, Ringuet, & Monfils, 2013; Lee, Haberman, Roquet, & Monfils, 2016; Olshavsky et al., 2013; Shumake & Monfils, 2015) and humans (James et al., 2015; Oyarzún et al., 2012; Schiller, Kanen, LeDoux, Monfils, & Phelps, 2013; Soeter & Kindt, 2015) have shown that subjects who are administered interventions during the reconsolidation window show reduced return of fear when compared to subjects who do not undergo a reactivation trial. Despite these promising results, other studies have not replicated these findings (Chan, Leung, Westbrook, & McNally, 2010; Golkar, Bellander, Olsson, & Öhman, 2012; Kindt & Soeter, 2013a; Schroyens, Beckers, & Kindt, 2017; Shiban, Brütting, Pauli, & Mühlberger, 2015) or have produced mixed results (Maples-Keller et al., 2017), leaving open the possibility that the reconsolidation update mechanism is not entirely robust, or that unknown moderating factors have masked its effects.

CURRENT STUDY

The current experiment investigated the efficacy of CBM-I augmentation using reconsolidation update techniques in conjunction with an interpretation bias training paradigm. Previous work has suggested that threat biases can be acquired in situations where the bias serves an adaptive purpose, and that the ease of acquiring this bias predicts elevated anxiety in response to a later stressor (Clarke, MacLeod, & Shirazee, 2008). Building from this work, it seems reasonable that biased cognitive processing styles (such as interpretation bias) are learned responses to certain contexts. If an individual tends to associate an anxiety-provoking situation with a given pattern of information processing, then interventions terminating this association should alter the cognitive processing response when the individual is later placed in the same context.

The study outlined in this paper examined whether (a) fear memory reactivation enhanced the efficacy of CBM-I in reducing the return of interpretation bias at follow-up; and (b) fear memory reactivation enhanced the efficacy of CBM-I in reducing the return of pathological social anxiety at follow-up. We hypothesized that subjects who engaged in fear reactivation 10 minutes prior to CBM would exhibit greater reductions in interpretation bias and clinical anxiety symptoms at follow-up, relative to a control group undergoing CBM.

Chapter 2: Methods

PARTICIPANTS

74 study participants were enrolled in the study; 67 from the pool of introductory psychology students attending the University of Texas at Austin, and 7 from the general Austin community. Community subjects were recruited using study flyers as well as online postings to craigslist.com, each of which advertised social anxiety treatment and entry into a cash prize drawing. All participants met the following criteria: (a) clinically significant levels of social anxiety, as determined by a Liebowitz Social Anxiety Scale score of at least 30 (LSAS, Fresco et al., 2001; Liebowitz, 1987); (b) significant levels of negative interpretation bias, as measured by Ambiguous Social Scenario Interpretation Questionnaire scores greater than 1.4[1] (Amir, Foa, & Coles, 1998); (c) no active suicidal ideation; and (d) between the ages of 18-65. Community participants were given the option of entering into a drawing for one of ten $100 prizes; subjects from UT Austin psychology classes were given course credit for their participation.

MATERIALS

Self-Report Questionnaires

Liebowitz Social Anxiety Scale (LSAS, Liebowitz, 1987)

This 24-item scale measures fear and avoidance behaviors concerning social interactions and performance situations, using a 0-3 rating scale. It is a commonly used measure of social anxiety that demonstrates strong psychometric properties such as sensitivity to pharmacological treatment effects, discriminant validity distinguishing it from general anxiety and depression, and high convergent validity with other measures of

[1] Pilot testing indicated that one third of participants score below this cutoff.

social anxiety such as the Social Interaction Anxiety Scale (r=.73), Social Phobia Scale (r=.61), and Fear of Negative Evaluation Scale (r=.49) (Heimberg et al., 1999).

Brief Fear of Negative Evaluation Scale (BFNE, Leary, 1983)

The BFNE scale is a 12-item measure assessing fear of negative evaluation by others. In a study using a clinical sample (Collins, Westra, Dozois & Stewart, 2003), the BFNE demonstrated inter-item reliability of α=0.97, two week test-retest reliability of r=0.94, and high discriminant validity when comparing a socially anxious population to either healthy individuals or to individuals with panic disorder. The instrument was also found to be sensitive to treatment effects induced by CBT.

Appraisal of Social Concerns (ASC, Telch et al., 2004)

The ASC is a 20-item self-report questionnaire assessing threat appraisals relevant to socially anxious patients. Schultz et al. (2006) validated the instrument on a clinical sample, finding the ASC to be significantly correlated with other social anxiety measures such as the BFNE (r=.591) and the Social Phobia Scale (r=.594), and also determining that the measure demonstrated strong discriminant validity, sensitivity to treatment, and internal consistency.

Brief State-Trait Anxiety Inventory-State (Brief STAI-S, Berg et al., 1998)

The State-Trait Anxiety Inventory for state anxiety (STAI-S, Spielberger, 1983) is a widely used instrument consisting of 20 items measuring state anxiety. The Brief STAI–S is comprised of six items selected from the STAI-S. The Brief STAI-S has demonstrated high correlation (r = 0.93) with the full 20-item STAI-S, as well internal consistency of α = 0.86 (Berg et al., 1998). Although the instrument evaluates current state anxiety levels, in the current study it was occasionally administered immediately after challenge tasks for the purpose of assessing peak anxiety during the challenge itself.

During these instances, the wording of Brief STAI-S questions was adapted to reflect this timing.

Cognitive Tasks

Assessment of Interpretation Bias

Interpretation bias was assessed with a modified version[2] of the Ambiguous Social Scenarios Interpretation Questionnaire (ASSIQ) developed by Amir, Foa, & Coles (1998). At each assessment period (see Fig. 1), participants were presented via computer 14 hypothetical social scenarios with ambiguous meaning, each followed by three possible interpretations of the scenario (positive, neutral, and negative). Order of scenario presentation was randomized across subjects and across assessment periods. For each scenario, participants were instructed to rank-order the likelihood of the explanations. A negative interpretation bias score for a given set was derived by calculating the mean rank-order of the negative interpretation across the 14 scenarios.

Cognitive Bias Modification (CBM) Training

The CBM training paradigm was based on that of Matthews & Mackintosh (2000) via Belli and Lau (2014). It involved seating the participant at a computer and presenting a short paragraph relating to a social situation. Participants were instructed to visualize themselves in the presented scenario, and they advanced through the paragraph line by line by pressing a keyboard button. The scenario remained ambiguous in terms of how it was to be emotionally interpreted, until the final word of the paragraph was presented as a word fragment with several missing letters. Participants typed the first missing letter of the word fragment to complete the word, resolving the scenario's ambiguity in the

[2] Because previous experiments used quantities of stimuli that were insufficient for the current study, 56 original stimuli were developed during pilot testing, each consisting of an ambiguous scenario and three possible explanations. Stimuli were separated into 4 sets of 14 scenarios each.

process and also advancing them to the next screen. After doing this, a comprehension question was presented that reinforced the meaning of the training item, and then a feedback screen was shown based on the subject's comprehension question response. A single trial with the corresponding positive/negative word fragment completion might read as follows (Mathews & Mackintosh, 2000):

Your partner asks you to go to an anniversary dinner that their company is holding. You have not met any of their work colleagues before. Getting ready to go, you think that the new people you will meet will find you

[bo---g/fri----y]

(boring/friendly)

The follow-up comprehension question would read:

Will you be disliked by your new acquaintances? [yes/no]

Finally, the feedback screen would show one of the following:

Correct Answer / Wrong Answer

As demonstrated in this example, trials that actively worked to reduce negative interpretation biases included a final word that resolved the meaning of the vignette in a positive manner. However, it was also possible to have trials in which the word fragment completion was neutrally or negatively valenced, and so it either did not affect the

meaning of the scenario, or else it acted to increase negative interpretation bias. In an example of a neutral trial, the concluding sentence of the previous trial might read, "Getting ready to go, you think that you will meet many new pe--le [people].

Stimuli were derived from those used by Mathews and Mackintosh (2000), but were modified so that each positive training scenario had a corresponding neutral or negative counterpart, and wording was changed to be consistent with vernacular common to the Southwestern United States.

Fear Reactivation Task (FRT)

The fear reactivation task (FRT) was intended to briefly reactivate participants' social evaluative fear network, thus presumably making it more amenable to reconsolidation updating. Participants were informed that they had 30 seconds to prepare a speech about a time that they were proud of themselves, and then were led to a room with a video camera in a prominent location. After 30 seconds of preparation time, the participant delivered the speech to two uniformed research assistants of mixed gender, who were trained to maintain a neutral expression and provide no feedback to the participant. After one minute of speech time, participants were instructed to stop the speech. However, participants were not informed of this time limit in advance.

Chapter 3: Procedure

Recruitment and Screening

Community participants responding to study advertisements were provided study details and given an online version of the LSAS to complete at home. Those with LSAS scores of at least 30 were invited to participate in exchange for entry into a drawing for one of ten $100 cash prizes.

Participants from the University of Texas undergraduate psychology research pool who scored at least a 30 on the LSAS in a pre-screening survey were either emailed with study information and invited to participate, or else they self-enrolled into the study through their introductory psychology classes.

Baseline Assessment and Randomization

At the first lab visit, participants provided informed consent and took the full battery of measures described in Figure 2 (Measurement Battery 1). Exclusionary criteria of active suicidal ideation, age outside of 18-65 years old, scoring less than 1.4 on the ASSIQ, or scoring below 30 on the LSAS were assessed at this time. Baseline LSAS scores were reassessed during the initial lab visit (in addition to during pre-screening) to maintain contextual consistency across measurements.

Participants were stratified on high/low levels of baseline anxiety as measured by the LSAS, and high/low levels of baseline interpretation bias as measured by the ASSIQ, with median splits for stratification determined by pilot data. Stratification yielded four blocks of subjects: high anxiety/high bias, low anxiety/low bias, high anxiety/low bias, and low anxiety/high bias.

Within each block, subjects were randomized to one of three conditions: (a) CBM augmented by a brief pre-training fear reactivation trial within the critical memory

reconsolidation window, CBM + FRT; (b) CBM with a pre-training fear reactivation outside of the memory reconsolidation window, CBM; or (c) placebo CBM with a pre-training fear reactivation outside of the memory reconsolidation window, CONTROL. To increase statistical power to detect effects of the reconsolidation updating manipulation, twice as many subjects were randomized to the CBM+FRT and CBM conditions than to the CONTROL condition. Out of every 10 subjects, 4 were assigned to CBM + FRT, 4 were assigned to CBM, and 2 were assigned to CONTROL. Assignment was carried out using the Research Randomizer Version 4.0, available from http://www.randomizer.org (Urbaniak & Plous, 2014).

FEAR MEMORY NETWORK REACTIVATION

Prior to engaging in CBM training, subjects were administered the FRT. The FRT presumably allows the fear memory network to enter a temporary labile state, making it amenable to modification during a temporal window lasting no longer than 6 hours. CBM performed within this window was hypothesized to lead to more permanent treatment effects, when compared to CBM performed outside of the memory reconsolidation update window. As shown in Figure 2, two groups of subjects performed the FRT during the first laboratory visit (12-36 hours before the CBM task), and one group of subjects performed the FRT during the second laboratory visit (10 minutes prior to CBM training). State anxiety probes were deployed immediately before and after the FRT as a manipulation check.

COGNITIVE BIAS MODIFICATION FOR INTERPRETATION (CBM-I)

Participants completed CBM-I during lab visit 2. Participants first watched a 10-minute video about nature before CBM training.[3] All participants completed 84 trials, presented in seven blocks of twelve trials each. The relative percentages of positive/negative/neutral trials depended upon the participant's experimental group assignment. In the CBM and CBM + FRT conditions, 10 trials of every block contained positive resolutions, 1 trial contained a negative resolution, and 1 trial contained a neutral resolution. The purpose of the negative and neutral trials was to obfuscate the purpose of the task, thereby reducing demand characteristics. The control group, CONTROL, received an inactive version of the training task with 10 trials of each block containing a neutral resolution, 1 trial containing a negative resolution, and 1 trial containing a positive resolution. State anxiety probes were deployed immediately before and after CBM-I. After finishing bias training, participants completed post-training assessment of interpretation bias (see Fig 2).

FOLLOW-UP VISITS

Subjects returned to the lab for follow-up 1 (FU1) and follow-up 2 (FU2) at one and two weeks (+/- one day) after CBM-I, respectively. Follow-up visits involved administration of a measurement battery assessing interpretation bias (ASSIQ) and social anxiety symptoms (LSAS, BFNE, ASC). At the final visit, participants were fully debriefed about study objectives and were compensated either with entry into a cash drawing prize or course research credits.

[3] This procedure was included to allow mood to stabilize between all experimental groups before CBM training. A 10-minute duration was selected because prior research has indicated that this interval is sufficient to activate the reconsolidation update mechanism in humans (Kredlow, Unger, & Otto, 2016)

Chapter 4: Statistical Analyses

To assess the primary hypothesis that a brief pre-training fear reactivation trial would enhance the efficacy of CBM-I training, we obtained 4 assessments of the primary outcome variable (ASSIQ) over time: baseline, post-treatment, 1-week follow-up (FU1), and 2-week follow-up (FU2). No assessments were obtained during the treatment. In such situations, research suggests the use of mixed effects regression models (MRMs) have the advantage of allowing the means at each assessment to vary without fitting a specific growth curve (Liu, Rovine, & Molenaar, 2012). Such models more accurately reflect the true change that occurs and are less likely to result in false conclusions (Liu et al., 2012). Interpretation bias scores (ASSIQ) were treated as a three-level (post-training, 1-week follow-up, and 2-week follow-up) repeated measures factor: TIME. Baseline ASSIQ was entered as a covariate rather than as a level of the repeated measures independent variable (IV), because using it as a covariate more fully equates groups on baseline levels of the outcome, thus minimizing variance in the outcomes, increasing power, and more effectively handling potential problems with "regression to the mean" (Tabachnick & Fidell, 2007). The covariance matrix was modeled as auto-regressive, with heterogeneous variances at the three assessment time points. Two between subjects variables were entered: (1) a three-level treatment condition factor (CBM, CBM + FR, CONTROL), and (2) Z-transformed baseline ASSIQ score. All analyses were performed using SPSS mixed models.

To test our primary a priori hypothesis that CBM training combined with a brief pre-training fear reactivation trial would lead to greater change in interpretation bias at follow-up than CBM training alone, we performed separate a priori comparisons of CBM

vs. CBM + FR at post-training (POST) and each of the two follow-up assessments (FU1 and FU2), using simple effects from the MRM analysis.

We used a similar procedure to test our secondary hypothesis that CBM training combined with a brief pre-training fear reactivation trial would lead to greater change in social anxiety symptoms at follow-up relative to CBM training alone. However, a priori comparisons of CBM vs. CBM + FR were conducted for anxiety symptom measurements at FU1 and FU2 only, because the measures used (LSAS, BFNE, and ASC) were inappropriate for assessing changes from baseline to post-training on the following day.

To evaluate the effect of CBM versus placebo CBM on post-intervention interpretation bias, a repeated measures ANOVA was conducted for ASSIQ data, using a two-level within-subjects factor of TIME (Baseline, Post-Intervention), and a two-level between-subjects factor of condition (CBM, CONTROL).

Chapter 5: Results

Sample Characteristics

As presented in Figure 3, 74 participants were randomized to either the CBM + FRT (n=29), CBM (n=29), or CONTROL (n=16) conditions. Data from 13 participants was excluded due to invalid responding during bias assessments[4], resulting in 61 subjects whose data was analyzed. 1 participant was lost at the 1-week follow-up visit with no reason given, and 10 were lost at the 2-week follow-up visit due to scheduling difficulties. Between-group comparisons at baseline using one-way analyses of variance (ANOVAs) revealed no significant differences on any outcome measures (all p's > 0.2). Baseline demographic characteristics and outcome measures are presented in Tables 1 and 2.

Effect of Fear Reactivation Procedure on Interpretatation Bias

Table 2 presents means and standard deviations of the ASSIQ at post-treatment, 1-week follow-up, and 2-week follow-up. Results from the MRM analysis revealed a main effect of time ($F(2,69)=3.65$, $p=.031$, $d=.573$), indicating a general decrease in bias over time, regardless of condition. Results also revealed a main effect of condition ($F(1,50)=4.13$, $p=.048$, $d=.61$), such that participants receiving CBM + FRT had lower levels of interpretation bias overall than participants receiving CBM alone. A priori comparisons at each time point indicated that interpretation bias did not significantly differ between CBM + FRT and CBM conditions at post-training ($F(1,47)=.208$, $p=.650$, $d=.122$) or at 1-week follow-up ($F(1,45)=1.642$, $p=.207$, $d=.342$). However, the CBM + FRT group had significantly lower interpretation bias than the CBM group at 2-week follow up ($F(1,37)=8.031$, $p=.007$, $d=.757$). Hence, combining CBM-I with a brief pre-

[4] Excluded participants had a mean response latency of less than five seconds from stimulus presentation until initial response during each trial of the ASSIQ task.

training fear reactivation trial led to a greater decrease in interpretation bias at 2-week follow-up than CBM-I alone (see Fig. 4).

Effect of Fear Reactivation Procedure on Social Anxiety Symptoms

Table 2 presents means and standard deviations of social anxiety measures at 1-week and 2-week follow-up. Results from the MRM analysis revealed a main effect of time on self-reported anxiety measured by the BFNE ($F(1,35)=6.427$, $p=.016$, $d=.76$), indicating that BFNE scores decreased over time, irrespective of condition. However, no main effect of time was found for anxiety reported on either the LSAS ($F(1,36)=2.700$, $p=.109$, $d=.493$) or the ASC ($F(1,35)=3.17$, $p=.083$, $d=.534$). No main effect of condition was found for any measure of anxiety symptoms [LSAS: ($F(1,47)=1.992$, $p=.165$, $d=.423$), BFNE: ($F(1,44)=.419$, $p=.521$, $d=.194$), ASC: ($F(1,43)=1.487$, $p=.229$, $d=.366$)]. A priori comparisons from the MRM analysis indicated that anxiety symptoms did not significantly differ between CBM + FRT and CBM conditions at 1-week follow-up [LSAS: ($F(1,46)=1.900$, $p=.175$, $d=.413$), BFNE ($F(1,46)=.041$, $p=.841$, $d=.061$), ASC ($F(1,46)=3.055$, $p=.087$, $d=.524$)], or at the 2-week follow-up [LSAS ($F(1,44)=1.549$, $p=.220$, $d=.373$), BFNE ($F(1,41)=.935$, $p=.339$, $d=.290$), ASC ($F(1,40)=.558$, $p=.460$, $d=.224$)]. Overall, results indicated that there were no significant between-group differences in self-reported anxiety symptoms during the 1-week and 2-week follow-up assessments.

Effect of CBM Training on Interpretation Bias

A repeated measures ANOVA using ASSIQ data revealed a statistically significant main effect of time ($F(1,38)=16.79$, $p<.001$, $d=1.39$), reflecting an overall decrease in interpretation bias from baseline to post-training, regardless of condition. However, there was no significant Time x Condition interaction ($F(1,38)=1.60$, $p=.21$,

η_p^2=.040), indicating that the group receiving active CBM did not exhibit a statistically significant difference in interpretation bias when compared to the placebo control group.

Chapter 6 : Discussion

The current study is the first to test the utility of using a brief fear memory network reactivation procedure as an augmentative strategy for CBM-I training, among a population presenting with naturally acquired social anxiety. Socially anxious participants who underwent a brief fear network reactivation procedure 10 minutes prior to CBM training demonstrated greater reductions in interpretation bias at two-week follow-up than individuals who had undergone an identical fear reactivation outside of the memory reconsolidation window (one day prior to CBM). Importantly, these improvements were observed at the 2-week follow-up period but at not post-training, consistent with hypothesized results. Our findings are in line with emerging literature demonstrating the ability of a brief fear memory reactivation to enhance extinction learning (Agren et al., 2017; 2012; Oyarzún et al., 2012; Schiller et al., 2013; Telch et al., 2017), but in contrast to other studies that have not found such an effect (Drexler, Merz, & Hamacher-Dang, 2014; Golkar et al., 2012; Kindt & Soeter, 2013b; Shiban et al., 2015; Soeter & Kindt, 2011). Results provide initial evidence that memory reconsolidation updating can strengthen efforts to rewrite cognitive processing styles, and is not restricted to modifying isolated fear memories.

Although the current findings are consistent with reconsolidation interference, alternative explanations may also account for observed results. Neubauer et al. (2013) considered the possibility that activation of relevant fear-schemata during training is necessary for CBM to be effective. This perspective is supported by a study from Kuckertz et al. (2014), which suggested that engaging in an anxiety-provoking task immediately prior to CBM for attention bias (CBM-A) facilitated reductions in social anxiety symptoms. It is possible that the fear-reactivation procedure of the current study

potentiated relevant interpretation biases during the retraining period instead of invoking the reconsolidation mechanism. However, this hypothesis would predict immediate, post-training bias reduction, as opposed to bias reduction observed at follow-up. Furthermore, state anxiety probes deployed immediately prior to CBM revealed no significant between-group differences on an independent samples t-test ($p=.78$), suggesting that differences in state anxiety (and presumably interpretation bias) during training cannot readily account for our findings.

We also cannot exclude the possibility that the fear reactivation indiscriminately enhanced memory, as opposed to altering only reactivated memory traces. Such an account might also predict significant facilitation of bias reduction by the end of training, which was not observed. Still, future studies would benefit from the addition of memory assessments to rule out the possibility of global memory enhancement extending beyond social-evaluative threats.

The failure to find an effect of non-augmented CBM-I training on interpretive bias also deserves comment. A recent review (Cristea et al., 2015) found no overall effect of CBM in reducing cognitive biases for social anxiety disorder, after accounting for outlier studies and publication bias (although effect sizes were larger for CBM-I than for CBM-A). As such, current results may reflect a genuine lack of potency of CBM.

Experimental considerations may also account for these null findings. Steinman and Teachman (2015) found that beneficial effects of CBM training are lost beyond a threshold of task difficulty. They modulated the difficulty of the CBM task by varying the number of missing letters in a word fragment that participants needed to solve. Results indicated that for highly anxious individuals, interpretations were modified when 0, 1, or 2 letters were missing, but not when individuals were required to solve fragments with 3 missing letters. Because the current study required subjects to solve for an

average of 3.23 missing letters per word fragment (SD=1.09), the non-augmented version of CBM may have been too difficult to yield effects, particularly considering that an anxious sample of participants was used. Although the strength of conclusions in the current study would have been bolstered by a finding that unaugmented CBM outperformed neutral control, the fact that augmented CBM outperformed each of the other conditions suggests that adding a fear reactivation procedure to CBM can result in increased efficacy even under suboptimal conditions, and can modify biases that might otherwise have remained unchanged.

Caution is warranted in interpreting findings, particularly in regards to evaluating the broader impacts of CBM-I. Although the reactivation procedure successfully decreased interpretation bias, this was not reflected in subsequent measures of self-reported anxiety and social threat appraisals, and is consistent with several previous studies obtaining similar results (Fu, Du, Au, & Lau, 2013; Salemink & Wiers, 2012; Salemink, van den Hout, & Kindt, 2009; Teachman & Addison, 2007). Because modification of interpretations is only useful insofar as it can reduce anxiety symptoms, the current findings suggest that further scrutiny is necessary to determine the clinical utility of CBM, and to delineate the conditions under which its effects extend to anxiety symptomology.

Several limitations should be considered. First, the sample size was relatively small, and replication with a larger sample is needed. Second, the two-week follow up period was relatively brief, and precludes assessment of long-term outcomes. It is possible that a longer follow-up period is necessary to capture reductions in social anxiety symptoms which may lag behind reductions in bias, as discussed by Schmidt et al. (2009). Finally, missing data at follow-up visits was less than optimal (9.5%),

although there was no pattern to missingness, and the analytic methods used are well equipped to handle missing data.

In conclusion, the current study provides the first evidence that a brief fear reactivation can be used to enhance the effects of cognitive bias modification for interpretive bias, and calls for further investigation into the clinical utility of this strategy for enhancing other psychological treatments for anxiety-related disorders.

Tables and Figures

Table 1: Demographics and Baseline Characteristics

	CBM + FRT (N=21)		CBM (N=26)		CONT (N=14)	
Mean Age (SD)	19.81 (1.72)		19.92 (3.11)		19.50 (0.85)	
	N	%	N	%	N	%
Gender (Female)	15	71.43	14	53.85	10	71
Race						
Non-Hispanic White or Euro-American	8	38.1	11	42.3	7	50.0
Black, Afro-Caribbean, or African American	0	0	4	15.4	1	7.1
Latino or Hispanic American	3	14.3	5	19.2	4	28.6
East Asian or Asian American	6	28.6	8	30.8	0	0
South Asian or Indian American	4	19.0	0	0	0	0
Middle Eastern or Arab American	1	4.8	0	0	0	0
Native American or Alaskan Native	0	0	0	0	0	0
Other	0	0	1	3.8	0	7.1

Table 2: Means and standard deviations of outcome measures

	Baseline M (SD)			Post-Treatment M (SD)			1-Week Follow-Up M (SD)		2-Week Follow-Up M (SD)	
	CBM+ FRT (N=21)	CBM (N=26)	CONT (N=14)	CBM+ FRT (N=21)	CBM (N=26)	CONT (N=14)	CBM+ FRT (N=21)	CBM (N=26)	CBM+ FRT (N=17)	CBM (N=20)
Interpretation Bias										
ASSIQ	1.85 (.32)	1.98 (.33)	2.02 (.38)	1.69 (.41)	1.83 (.47)	1.73 (.43)	1.60 (.20)	1.74 (.55)	1.402 (.263)	1.75 (.43)
Social Anxiety Symptom Measures										
LSAS	60.86 (18.87)	61.19 (24.02)	62.14 (16.62)	-	-	-	57.33 (22.19)	54.76 (22.82)	54.18 (22.55)	58.11 (22.95)
BFNE	41.86 (7.95)	43.73 (10.22)	45.29 (9.38)	-	-	-	39.95 (9.52)	41.16 (11.04)	37.76 (8.00)	39.28 (12.35)
ASC	84.19 (39.29)	88.85 (38.35)	91.71 (35.77)	-	-	-	82.30 (37.21)	73.67 (44.58)	69.31 (36.59)	76.21 (44.27)

Figure 1: Examples of stimuli used in the Ambiguous Social Scenarios Interpretation Questionnaire

A group of people starts laughing as you pass by them

A) They were laughing at a funny comment that you made

B) They were laughing at a joke that somebody in the group told just before you passed

C) They were laughing because they think you are strange

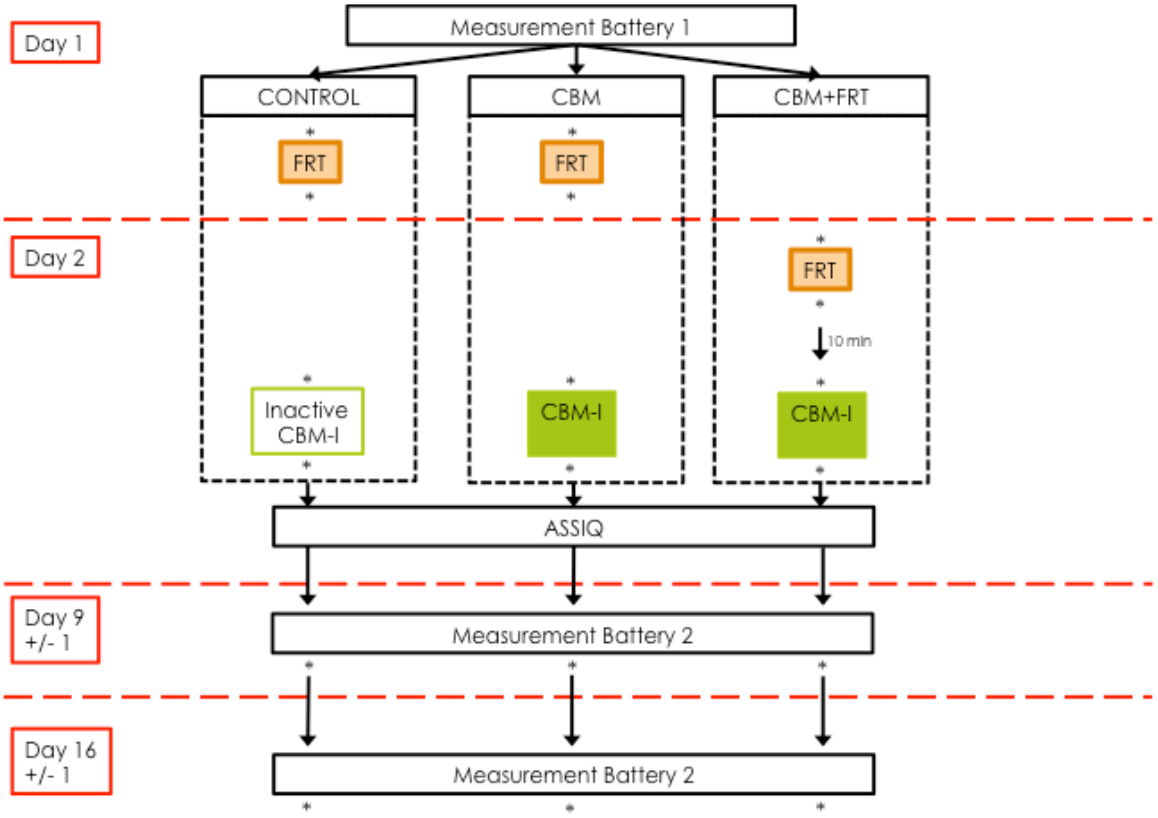
Your neighbors see you outside the police station

A) They think you are turning in property you found

B) They think you are passing by

C) They think you are being arrested for some crime

Figure 2: Experimental Design and Timeline



Assessment	Instrument(s) Administered
*	Brief STAI - State Anxiety
Measurement Battery 1	Demographics, ASSIQ, LSAS, BFNE, ASC
Measurement Battery 2	ASSIQ, LSAS, BFNE, ASC

Figure 3: CONSORT Flow Diagram

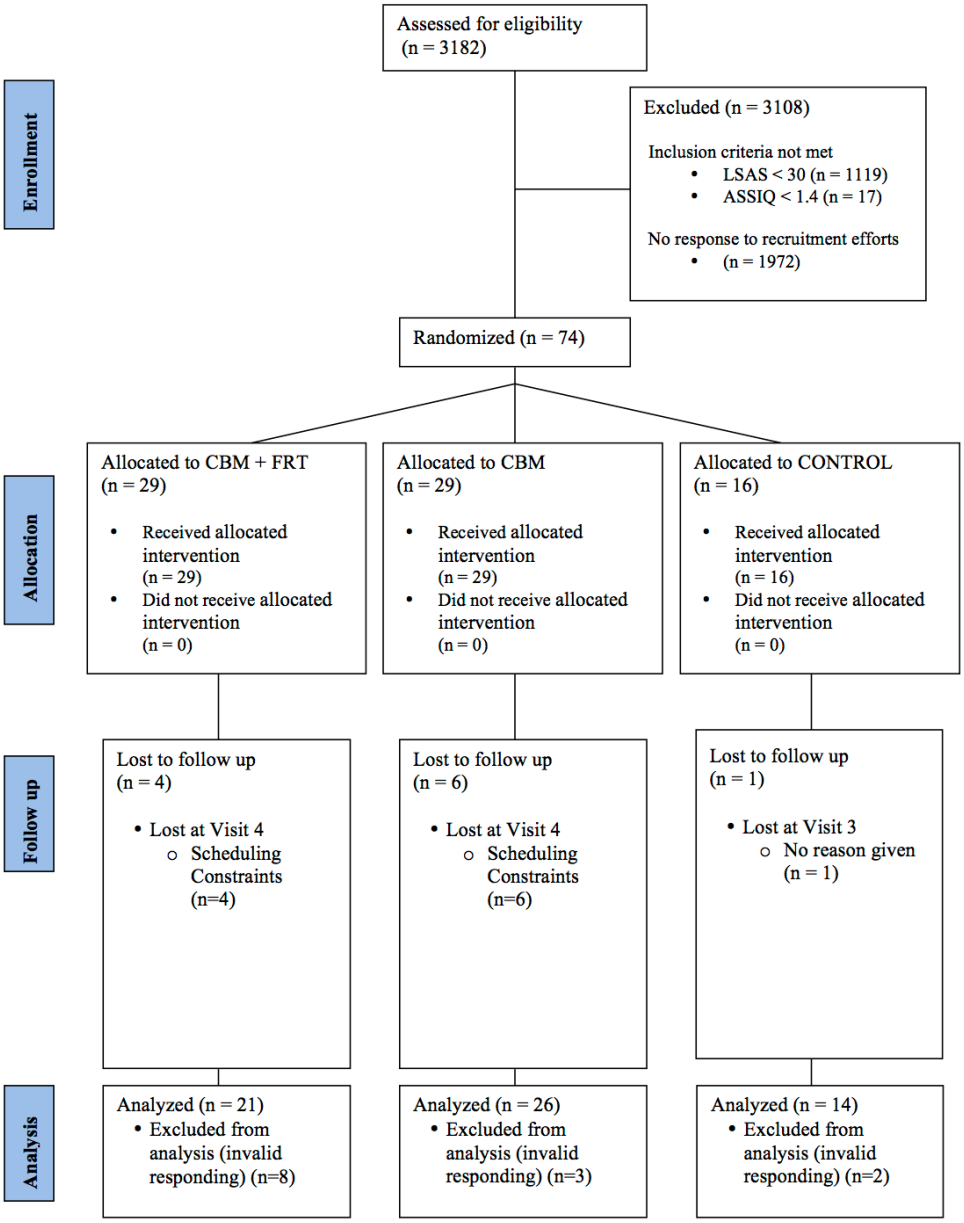
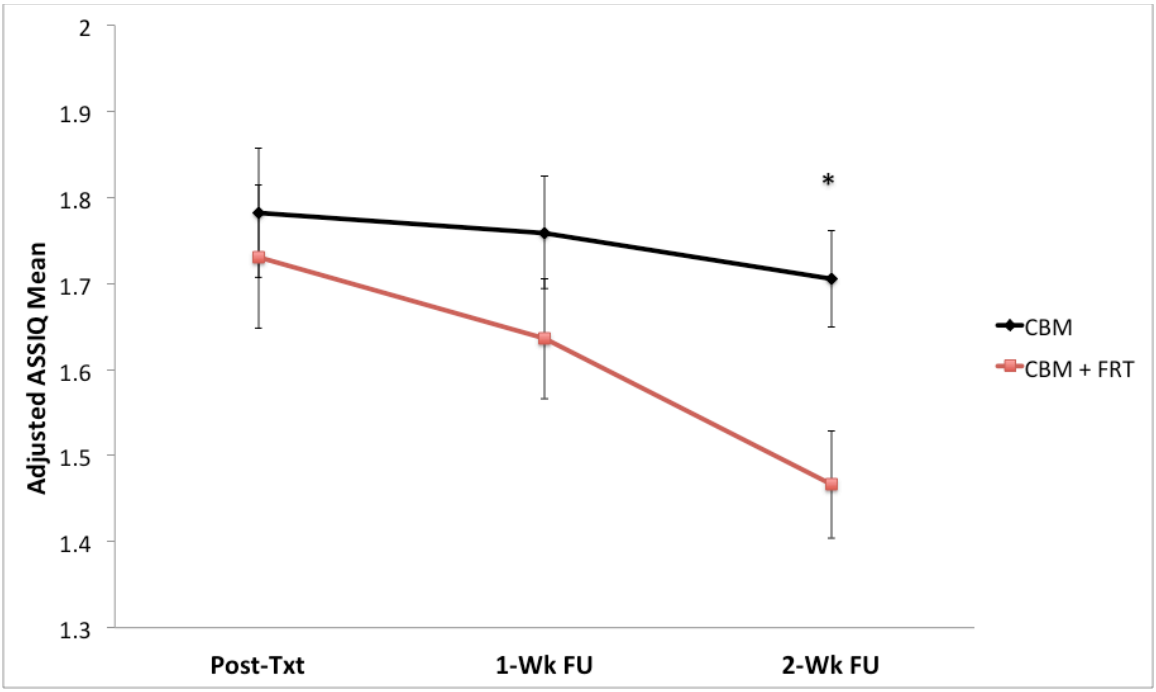


Figure 4: Interpretation Bias Score



Notes: Adjusted mean interpretation bias score immediately following CBM (Post-Txt), at 1-week follow-up (1-Wk FU), and at 2-week follow-up (2-Wk FU), controlling for baseline bias. CBM + FRT = cognitive bias modification administered 10 minutes after fear reactivation; CBM = cognitive bias modification administered one day after fear reactivation. Error bars represent +/- 1 standard error. *$p \leq 0.05$

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