

Research paper

## Effects of working memory training on cognitive, affective, and biological responses to stress in major depression: A novel cognitive bias modification protocol



Ellen Jopling<sup>a,\*</sup>, Ian H. Gotlib<sup>b,1</sup>, Joelle LeMoult<sup>a,1</sup>

<sup>a</sup> Department of Psychology, University of British Columbia, 2136 West Mall, Vancouver, BC V6T1Z4, Canada

<sup>b</sup> Stanford University, USA

### ARTICLE INFO

**Keywords:**

Cognitive bias modification  
Depression  
Rumination  
Biological stress response

### ABSTRACT

**Background:** Over 320 million individuals are living with Major Depressive Disorder (MDD), a leading cause of disability worldwide. Thus, there is a crucial need to identify processes that contribute to the maintenance of depressive episodes. Difficulty removing negative information from working memory (WM) is posited to exacerbate affective, cognitive, and biological dysregulation in Major Depressive Disorder (MDD), but this has not yet been tested empirically.

**Methods:** In this study we examined whether training depressed individuals to remove negative information from WM (RNI training) would reduce symptoms of depression and levels of rumination, and would be associated with attenuated biological responsivity to stress. Individuals diagnosed with MDD were randomly assigned to complete Real-RNI training or Sham-RNI training for six days.

**Results:** Across conditions, participants exhibited significant improvements from pre- to post-training in removing negative information from WM, symptoms of depression, and rumination. Furthermore, participants in the Real-RNI condition showed a more attenuated pattern of cortisol and respiratory sinus arrhythmia (RSA) responses to stress than did participants in the Sham-RNI training condition.

**Limitations:** We did not assess the long-term effects of training. It will be important for future research to examine whether the documented training-related effects persist across time.

**Conclusions:** This study is the first to examine the effects of RNI training on clinical symptoms and biological responses to stress in MDD, and it provides experimental evidence that training individuals with depression to remove negative information from WM can help to modulate the heightened biological responses to stress seen in depression.

### 1. Introduction

Major Depressive Disorder (MDD) is characterized by difficulty removing negative information from working memory (WM; [LeMoult and Gotlib, 2019](#); [World Health Organization, 2012](#)). Although researchers have posited that difficulty removing negative information from WM contributes to depressive symptoms, rumination, and exaggerated biological responses to stress ([Joormann, 2010](#); [LeMoult and Gotlib, 2019](#); [Nolen-Hoeksema et al., 2008](#)), there has been no research to date that experimentally examines the associations among these variables in the context of depression. Consequently, we do not fully understand the ways in which difficulty removing negative information from WM contributes to MDD.

To date, only one study has experimentally examined the effects of difficulty removing information from WM on symptoms of depression and levels of rumination ([Onraedt and Koster, 2014](#)). In that study, participants with MDD and high levels of trait rumination completed six sessions of training on a dual n-back task. Although performance on the dual n-back task significantly improved from pre- to post-training, this gain did not transfer to measures of depression, rumination, or alternative measures of WM. It is possible that [Onraedt and Koster \(2014\)](#) did not find transfer effects because participants were trained to remove *non-valenced* information from WM, which does not directly target the core difficulty underlying levels of rumination and depressive symptoms observed in MDD: difficulty removing *negatively valenced* information from WM (for reviews see [Joormann and Stanton, 2016](#);

\* Corresponding author.

E-mail address: [ellen.jopling@psych.ubc.ca](mailto:ellen.jopling@psych.ubc.ca) (E. Jopling).

<sup>1</sup> Equal contribution.

(LeMoult and Gotlib, 2019). While there is some evidence that affective WM training can result in improved control over affective information in non-clinical samples (Schweizer et al., 2011, 2013), the associations among removing negative information from WM, rumination, and depression have not been examined experimentally, and not within a sample of participants with MDD.

Although researchers have also not yet examined the association between difficulties in WM disengagement and dysregulated biological responses to stress, studies assessing constructs related to WM disengagement provide a degree of support for this association. For example, researchers have documented that ruminative responses to stress are associated with impaired recovery of both the neuroendocrine and autonomic nervous systems (Key et al., 2008), particularly for individuals with MDD (LeMoult and Joormann, 2014). For example, both MDD and ruminative responses to stress have been linked with excessive respiratory sinus arrhythmia (RSA) withdrawal in response to stress (Beauchaine, 2015; LeMoult et al., 2015). Given the association between difficulty disengaging from negative material in WM and rumination (LeMoult and Gotlib, 2019), there is reason to expect that difficulty disengaging from negative information in WM might underlie the dysregulated biological responses to stress documented in MDD. However, this possibility has not yet been experimentally examined.

The cognitive bias modification (CBM) literature highlights the importance of manipulating cognitive processes to test causal relations and to identify mechanisms that might underlie the onset of MDD (Hallion and Ruscio, 2011). Investigators have contended that the strongest advances in our understanding of how CBM paradigms achieve their effects will come from the assessment of training-related changes across multiple domains. Underscoring this point, previous studies using CBM paradigms have demonstrated that training individuals to alter the way they process information can result in changes in cognition, affect, and biology. These studies help to establish causal associations between cognitive biases and both affective and biological functioning (Hertel and Mathews, 2011). To date, much of the CBM literature has targeted attentional and interpretation biases in the context of anxiety disorders (Hallion and Ruscio, 2011; Macleod and Mathews, 2012). Thus, studies are needed that investigate the cognitive, affective, and biological effects of training participants with MDD to remove negative information from WM.

The present study was designed to extend the CBM literature by testing the effects of training depressed individuals to remove negative information (RNI training) from WM on cognitive, affective, and biological functioning. We assigned individuals diagnosed with MDD to either the Real-RNI or Sham RNI condition for six days. We measured individual differences in the ability to remove negative information from WM, symptoms of depression, and levels of rumination at both pre- and post-training sessions. In addition, at post-training, participants completed a standardized laboratory-based stressor, during which we measured biological responsivity. We predicted that, compared to participants in the Sham-RNI condition, participants in the Real-RNI condition would exhibit greater improvements from pre- to post-training in removing negative information from WM (Hypothesis 1). Further, we expected that, compared to participants assigned to the Sham-RNI condition, participants assigned to the Real-RNI condition would report greater pre- to post-training decreases in symptoms of depression (Hypothesis 2) and levels of rumination (Hypothesis 3), and would exhibit attenuated biological responses across the laboratory stressor as measured by cortisol (Hypothesis 4) and RSA (Hypothesis 5).

## 2. Method

### 2.1. Participants

Adults between 18 and 60 years of age were eligible to participate in this study if they were fluent in English and met criteria for current MDD or had no past or current psychopathology (CTLs). We recruited

CTL participants in order to confirm that our sample of depressed participants had, at pre-training, significantly higher self-reported symptoms of depression and rumination, and significantly greater difficulty removing negative information from WM. Diagnostic status was determined using the Structured Clinical Interview for DSM-IV (SCID-IV; First et al., 1996). Participants were excluded if they had major medical conditions, head trauma, bipolar disorder, symptoms of psychosis, an alcohol or substance use disorder in the past 6 months, or conditions known to affect the neuroendocrine or autonomic nervous systems.

Of the 90 individuals (54 with MDD and 36 CTLs) who were eligible following the SCID-IV, seven participants with MDD did not complete the post-training session and five participants with MDD had substantial difficulties following directions (e.g., did not properly complete the baseline assessment or did not complete any at-home trainings). Thus, the final sample consisted of 78 participants (42 with MDD and 36 CTLs) who were between 19 and 55 years of age. The final sample of participants did not differ at pre-training from the 12 individuals without complete data on any clinical or demographic characteristics, all  $p > 0.05$ .

### 2.2. Working memory bias task

Difficulty eliminating positive and negative information from WM was assessed using the affective version of the Sternberg task (Joormann and Gotlib, 2008). The task consists of three blocks of 40 trials. Each trial consisted of a learning display, a cue display, and a probe-recognition display. During the learning display, participants viewed two sets of three words. Following the offset of the word sets, participants viewed a cue that indicated which set of words would be relevant for the probe-recognition display; this prompted participants to remove the other (irrelevant) set of words from WM. Of the 120 trials, 40% required that participants remove the positive word set and 40% required that participants remove the negative word set. The final 20% of trials were control trials, which included positive and negative words in both sets; these trials were included to ensure that participants did not learn to make decisions about the probe based on word valence. Finally, in the probe-recognition display, a single word was presented and participants were given 3000 ms to indicate as quickly and as accurately as possible whether the probe word was from the relevant word set. The probe word could be from the relevant set, the irrelevant set, or a novel word that was not included in either set. Consistent with previous research (Joormann and Gotlib, 2008), individual differences in the ability to remove irrelevant information from WM were modeled as decision latencies to words from the irrelevant set minus the decision latencies to new words of the same valence. These differences in response times are termed *intrusion effects* and were calculated separately for positive and negative words. Difficulty removing information from WM results in larger intrusion effects. Psychometric properties for the Sternberg were good: split-half reliability coefficients on critical trial RTs ranged from 0.78 to 0.96.

### 2.3. Working memory training

Using stratified random assignment based on their scores on the Beck Depression Inventory-II, participants with MDD were assigned to either the Real-RNI ( $n = 22$ ) or the Sham-RNI ( $n = 20$ ) condition. In both conditions, participants completed an at-home training session each day for six days. Training tasks were administered using E-Prime software version 2 on laptop computers provided to participants. Each training session lasted 15–20 min and performance files were stored on the computer until participants returned the laptop at their post-training session. Consistent with previous research, analyses were restricted to trials in which participants made correct responses and in which reaction times (RTs) were less than 3000 ms (Joormann and Gotlib, 2008). This resulted in the loss of 9.21% of trials at pre-training

and 7.86% of trials at post-training, which is consistent with previous studies (LeMoult, Yoon, and Joormann, 2015; LeMoult, and Joormann, 2014). Participants in the two conditions did not differ from each other in the percentage of trials lost at pre-training or post-training,  $p > 0.201$ .

### 2.3.1. Real RNI

Participants in the Real-RNI condition were presented with an adapted version of the original affective Sternberg Task that was completed during the pre-training session. The original and training tasks differed in length and in percentage of each type of trial. Of the 60 trials completed during each training session, 80% of trials required that participants remove the negative word set, 10% required that participants remove the positive word set (to ensure that participants had reason to continue learning both positive and negative word sets), and 10% were control trials.

### 2.3.2. Sham RNI

Participants in the Sham-RNI condition were presented with a modified lexical decision task. In each trial, participants were presented with a string of letters and were required to indicate whether the string formed a real word. Of the 360 trials, 50% of trials presented nonsense words, and 50% presented the same words that were used in the Real-RNI task. Thus, participants in the Real-RNI and Sham-RNI conditions were exposed to the same wordlists each day (additional details in the online supplement).

## 2.4. Psychosocial stressor

To examine participants' biological responses to stress, participants completed the Trier Social Stress Test (TSST; Kirschbaum et al., 1993) during the post-training lab session. The TSST is a standardized stressor that has been found to be effective in eliciting a biological stress response (Dickerson and Kemeny, 2004). It consists of four phases: baseline (20 min), anticipation (10 min), stressor (10 min), and recovery (30 min). Neuroendocrine (salivary cortisol) and autonomic (RSA) responses were measured throughout the task. See online supplement for further details.

### 2.4.1. Cortisol

Saliva samples were collected immediately before the baseline period (S1), immediately after the baseline period (S2), immediately after the stressor (S3), 15 min after stressor offset (S4), and 30 min after stressor offset (S5). This collection schedule is based on meta-analytic findings of the timing of cortisol reactivity and recovery (Dickerson and Kemeny, 2004). Cortisol values were winsorized to 2 standard deviations above the mean as is consistent with previous research (Doom et al., 2013; Gotlib et al., 2015).

### 2.4.2. RSA

Autonomic data were recorded continuously using the Biopac system. ECG signals were transmitted using three electrodes positioned in a modified lead II configuration. Respiration was measured using a respiratory belt placed around the chest and the abdomen. RSA was scored in 1-minute epochs using AcqKnowledge 4.0 software, and was calculated as the natural log of the high frequency power (0.15–0.40 Hz). Consistent with Kircanski et al. (2016), we created the following segments: baseline (10 min), anticipation (5 min), speech task (5 min), arithmetic task (5 min), initial recovery (15 min), and final recovery (15 min).

## 3. Self-report measures

### 3.1. Symptoms of depression

The severity of participants' symptoms of depression was assessed

with the Beck Depression Inventory-II (BDI-II; Beck et al., 1996), a 21-item self-report questionnaire assessing depressive symptoms experienced in the previous two weeks. In addition, at the pre- and post-training sessions, participants completed a modified BDI-II scale (M-BDI-II) that assessed depressive symptoms in the previous three days. In the present study, there was excellent internal consistency in both the original and modified versions of the BDI-II ( $\alpha \geq 0.92$ ).

### 3.1.1. Rumination

Rumination was assessed with the Ruminative Responses Scale (Nolen-Hoeksema and Morrow, 1991), a 22-item self-report questionnaire designed to measure individual differences in the tendency to ruminate when feeling depressed. In addition, at the pre- and post-training session, participants completed a modified RRS (M-RRS) that assessed rumination in the previous three days. In the current study, there was excellent internal consistency in both the original and modified versions of the RRS ( $\alpha \geq 0.93$ ).

## 3.2. Procedure

The study was approved by the Stanford University Institutional Review Board. Following previous CBM studies (Hallion and Ruscio, 2011; Koster and Hoorelbeke, 2015), data were collected in a multi-session procedure. Participants first came into the lab to complete the SCID and self-report measures of symptoms of depression (BDI-II) and rumination (RRS). Eligible participants were invited to return to the lab within two weeks for the pre-training session, during which they completed the Sternberg Task and reported on their symptoms of depression (M-BDI-II) and rumination (M-RRS) within the past three days. Participants were then assigned to complete either Real-RNI or Sham-RNI training at home for the next six consecutive days. On the seventh day, participants returned to the lab for the post-training session, during which participants completed the same cognitive and self-report measures completed during the pre-training session, and the TSST.

## 3.3. Statistical analyses

To examine whether depressed individuals who were assigned to the Real-RNI condition exhibited greater improvements from pre- to post-training than did depressed individuals who were assigned to the Sham-RNI condition in removing negative information from WM (Hypothesis 1), we will conduct a three-way Condition (Real RNI, Sham RNI) by Valence (positive, negative) by Time (pre-training, post-training) repeated-measures analysis of variance (ANOVA) on intrusion effects. If the expected three-way interaction is significant, we will conduct follow-up two-way ANOVAs within each condition, for each valence, and at each time point, followed by paired or independent sample *t*-tests as indicated. To examine whether depressed individuals assigned to the Real-RNI condition exhibit greater improvements from pre- to post-training than depressed individuals assigned to the Sham-RNI condition in symptoms of depression (Hypothesis 2) and levels of rumination (Hypothesis 3), we will conduct a two-way Condition by Time repeated-measures ANOVAs on BDI-II and on RRS scores. If the expected two-way interaction is significant, we will conduct independent-samples *t*-tests at pre- and post-training, and paired-samples *t*-tests for participants in both the Real-RNI and Sham-RNI condition.

To examine whether depressed individuals assigned to the Real-RNI condition exhibited attenuated cortisol (Hypothesis 4) and RSA (Hypothesis 5) responses to stress than did depressed individuals assigned to the Sham-RNI condition, we will use hierarchical linear modeling (HLM; Raudenbush and Bryk, 2002). This approach allows us to model the repeated measurements of both cortisol and RSA within persons as a function of time, and permits the examination of unevenly spaced measurement occasions (Hruschka et al., 2005). Thus, the exact time of cortisol and RSA collection will be allowed to vary by individual, which provides a precise estimation of collection timepoints

**Table 1**  
Clinical and demographic characteristics.

Variable	Participants with MDD		Total	Controls
	Real RNI	Sham RNI		
Age, <i>M</i> ( <i>SD</i> )	28.00 (5.58)	29.50 (9.40)	28.71 (7.58)	29.71 (10.25)
Gender, % female	68.2	70.0	69.0	66.7
Racial background, % white	69.6	60.0	64.3	60.6
Marital status, % single	72.7	80.0	76.2	62.9
Years of education, <i>M</i> ( <i>SD</i> )	15.32 (3.58)	16.70 (2.62)	15.98 (3.20)	14.79 (3.58)
Number trainings completed, <i>M</i> ( <i>SD</i> )	5.82 (0.50)	5.95 (0.39)	5.88 (0.45)	—
BDI-II, <i>M</i> ( <i>SD</i> )	30.14 (11.30)	27.45 (9.34)	28.86 (10.38)	1.53 (2.36)
RRS, <i>M</i> ( <i>SD</i> )	62.55 (12.16)	58.45 (8.86)	60.60 (10.79)	30.44 (9.25)
Pre-Training				
M-BDI-II, <i>M</i> ( <i>SD</i> )	31.90 (10.31)	26.47 (9.14)	29.39 (10.05)	2.69 (3.20)
M-RRS, <i>M</i> ( <i>SD</i> )	56.46 (9.82)	52.32 (7.36)	54.54 (8.91)	27.80 (6.09)
Negative intrusion effects, <i>M</i> ( <i>SD</i> )	352.01 (220.87)	446.84 (218.32)	397.17 (222.20)	298.71 (199.04)
Positive intrusion effects, <i>M</i> ( <i>SD</i> )	397.44 (201.67)	411.78 (242.13)	404.27 (219.20)	382.84 (196.98)
Post-Training				
M-BDI-II, <i>M</i> ( <i>SD</i> )	28.14 (10.55)	22.50 (11.35)	25.45 (11.18)	—
M-RRS, <i>M</i> ( <i>SD</i> )	52.50 (11.02)	49.05 (9.76)	50.86 (10.46)	—
Negative intrusion effects, <i>M</i> ( <i>SD</i> )	297.24 (177.82)	301.87 (224.58)	299.44 (198.93)	—
Positive intrusion effects, <i>M</i> ( <i>SD</i> )	308.62 (208.71)	313.92 (323.18)	311.14 (265.93)	—

Note: BDI-II = Beck Depression Inventory-II, RRS = Ruminative Responses Scale, M-BDI-II = Modified Beck Depression Inventory-II (previous three days), M-RRS = Modified Ruminative Response Scale (previous three days).

for each participant. Linear, quadratic, and piecewise models will be evaluated for both cortisol and RSA. We will select the model that best fits the data based on the smallest value of Akaike's Information Criteria (AIC) and visual inspection of the data. Condition will be dummy-coded with the Sham-RNI condition as the referent group, and will be included at Level 2. Models will be fit using full information maximum likelihood for the calculation of deviance and AIC, and fit using restricted maximum likelihood for the estimation of model parameters. See supplement for all HLM equations.

## 4. Results

### 4.1. Differences between MDD and CTL groups

Clinical and demographic characteristics of participants are presented in Table 1. Participants with MDD did not differ significantly from CTLs with respect to age, gender, racial background, marital status, years of education, or income, all  $p > 0.05$ . As expected, however, at pre-training, participants with MDD had significantly higher levels of depressive symptoms,  $t(49) = -16.09$ ,  $p < .001$ ,  $g = 3.43$ , and rumination,  $t(71) = -15.46$ ,  $p < .001$ ,  $g = 3.42$ , than did CTLs. MDD participants also had significantly greater negative intrusions effects on the Sternberg task than did CTL participants,  $t(76) = -2.05$ ,  $p = .044$ ,  $g = 0.46$ , indicating that they had more difficulty removing negative information from WM.

### 4.2. Differences between depressed participants in the real-RNI and sham-RNI conditions

Participants with MDD who received Real-RNI training did not differ significantly from those who received Sham-RNI training with respect to age, gender, racial background, marital status, years of education, income, number of at-home training sessions completed, or baseline symptoms of depression, rumination, negative intrusion effects, or positive intrusion effects,  $p > 0.05$ .

### 4.3. Effects of RNI training

Pre- and post-training negative intrusions, symptoms of depression, and levels of rumination are presented in Table 1.

#### 4.3.1. Working memory biases (Hypothesis 1)

The three-way repeated-measures ANOVA yielded a significant main effect of time,  $F(1,40) = 10.84$ ,  $p = .002$ ,  $\eta^2 = 0.21$ ; participants with MDD significantly improved from pre- to post-training in removing positively and negatively valenced irrelevant information from WM. No other effects were significant,  $p > 0.302$ .<sup>1</sup> Including age as a covariate did not change the findings reported here. The main effect of age was not significant, and age did not interact significantly with time, valence, or condition to predict intrusion scores,  $p > 0.211$ .

#### 4.3.2. Depression (Hypothesis 2)

The repeated-measures ANOVA conducted on symptoms of depression yielded a main effect of time,  $F(1,39) = 6.97$ ,  $p = .012$ ,  $\eta^2 = 0.15$ , reflecting a significant decline from pre- to post-training in depressive symptoms. No other effects were significant,  $p > 0.078$ .

#### 4.3.3. Rumination (Hypothesis 3)

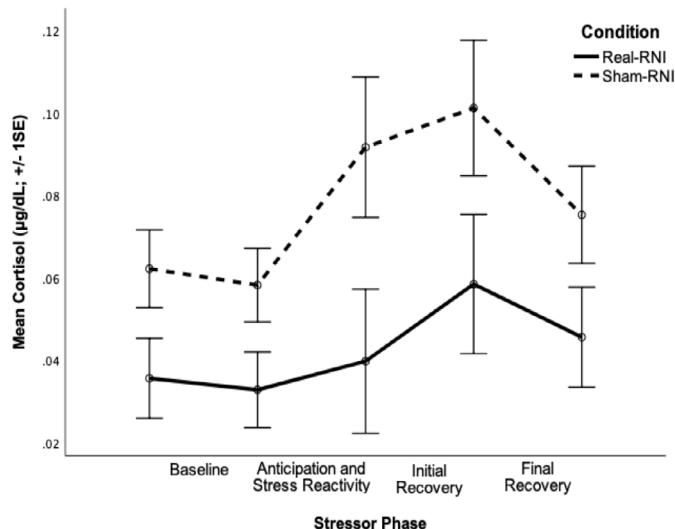
The repeated-measures ANOVA on rumination yielded a significant main effect of time,  $F(1,39) = 10.62$ ,  $p = .002$ ,  $\eta^2 = 0.21$ , reflecting a significant pre- to post-training decline in levels of rumination. No other effects were significant,  $p > 0.160$ .

#### 4.3.4. Cortisol responses to stress (Hypothesis 4)

Cortisol response to stress is presented by condition in Fig. 1 and all results can be found in Table S1 of the online supplement. Based on visual inspection of the data, deviance statistics, and the AIC value, the quadratic growth model best fit the pattern of cortisol production.

To examine the basic pattern of cortisol response to the TSST, we first ran a baseline model without any variables at Level 2. Participants' average cortisol level was significantly different than zero at baseline,  $B = -0.24$ ,  $t(38) = -2.32$ ,  $p = .026$ , and significantly increased in response to the stressor,  $B = 0.01$ ,  $t(38) = 2.27$ ,  $p = .029$ . Although the rate of change in cortisol level over time (i.e. the quadratic slope) was not significant,  $B = -0.00$ ,  $t(109) = -1.65$ ,  $p = .103$ , all estimates of variance components were significant (all  $p < 0.001$ ), indicating individual differences in the variation in cortisol levels at baseline and over time (linear and quadratic slopes).

Next, we tested variables shown to influence cortisol responses to stress as potential covariates: age, use of oral contraceptives, current use of psychotropic medication, past use of psychotropic medication, and engagement in exercise on the day of the session (Kudielka et al., 2004, 2009). Use of oral contraceptives and psychotropic medication



**Fig. 1.** Pattern of cortisol response to stress by condition.

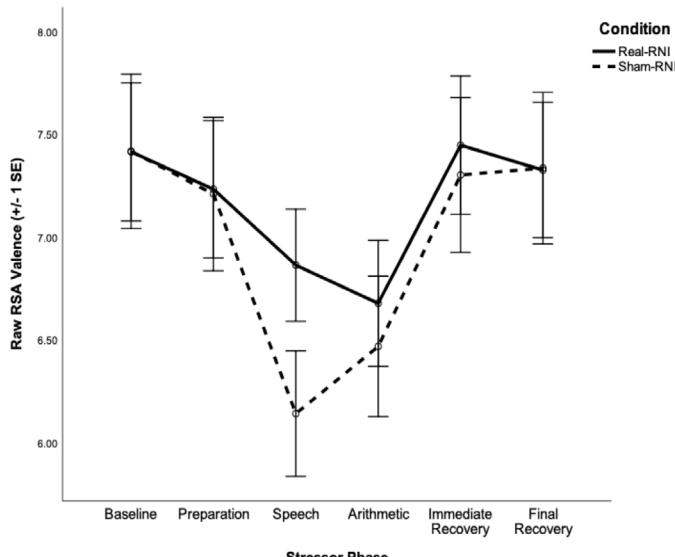
predicted baseline cortisol, and use of oral contraceptives predicted the rate of change in cortisol over time (i.e. the quadratic slope),  $ps < 0.049$ . Thus, we controlled for these variables in the corresponding Level 2 equation.

As expected, condition significantly predicted the quadratic slope,  $B = 0.0002$ ,  $t(107) = 2.00$ ,  $p = .048$ . Compared to participants in the Sham-RNI condition, individuals in the Real-RNI condition exhibited an accelerated rate of change in cortisol secretion, consistent with improved recovery from the stressor.

#### 4.3.5. RSA response to stress (Hypothesis 5)

RSA response to stress is presented by condition in Fig. 2 and all results can be found in Table S2 of the online supplement. Based on visual inspection of the data, deviance statistics, and the AIC value, RSA data were best fit with a piecewise linear growth model, which estimated the slope of RSA across baseline, anticipation, initial stress reactivity, subsequent stress reactivity, initial recovery, and final recovery phases of the stressor, as is consistent with previous work (Waugh et al., 2010).

A baseline model without any Level 2 predictors indicated that participants' level of RSA at baseline was significantly different from



**Fig. 2.** Pattern of RSA response to stress by condition.

zero,  $B = 7.43$ ,  $t(38) = 32.88$ ,  $p < .001$ , remained constant during the anticipation period,  $B = -0.02$ ,  $t(38) = -1.88$ ,  $p = .067$ , and then significantly declined during the initial stress reactivity period,  $B = -0.14$ ,  $t(38) = -5.28$ ,  $p < .001$ . Levels of RSA remained constant across the subsequent stress reactivity phase,  $B = 0.003$ ,  $t(38) = 0.33$ ,  $p = .742$ , significantly increased across the initial recovery period,  $B = 0.05$ ,  $t(38) = 8.37$ ,  $p < .001$ , and remained constant across the final recovery period,  $B = -0.003$ ,  $t(38) = -0.67$ ,  $p = .508$ .

Next, we tested variables shown to influence RSA response to stress as potential covariates: age, current use of psychotropic medication, past use of psychotropic medication, and engagement in exercise on the day of the session (Grossman et al., 2004; O'Regan et al., 2015; Voss et al., 2015). Both past and current use of psychotropic medication predicted the slope of RSA during the final recovery period,  $ps < 0.018$ . Consequently, these variables were included as covariates in the corresponding Level 2 equation.

As expected, participants in the Real-RNI condition exhibited a more attenuated pattern of RSA response to stress than did participants in the Sham-RNI condition. Specifically, compared to participants in the Sham-RNI condition, participants in the Real-RNI condition had less RSA withdrawal in response to the speech (initial stress reactivity),  $B = 0.15$ ,  $t(37) = 3.14$ ,  $p = .003$ , and less RSA augmentation in response to the arithmetic task (subsequent stress reactivity),  $B = -0.05$ ,  $t(37) = -2.63$ ,  $p = .012$ .

#### 4.4. Associations between change in negative intrusion effects and key outcomes

We conducted exploratory analyses to examine whether change in negative intrusions was associated with change in symptoms of depression, change in rumination, and degree of biological responses to stress, and to test whether these associations differed by condition. Analyses indicated that neither change in negative intrusions nor the interaction between condition and change in negative intrusions was associated with change in symptoms of depression or with change in levels of rumination,  $ps > 0.150$  (detailed results presented in Table S3 of the online supplement). Similarly, neither change in negative intrusions nor the interaction between condition and change in negative intrusions predicted cortisol responses to stress,  $ps > 0.435$  (detailed results presented in the text of the online supplement). However, a significant interaction between condition and change in negative intrusions predicted RSA trajectory across both the initial stress reactivity,  $B = 0.001$ ,  $t(35) = 3.24$ ,  $p = .003$ , and subsequent stress reactivity phase of the TSST,  $B = -0.0001$ ,  $t(35) = -2.13$ ,  $p = .040$ . Further, the interaction between condition and change in negative intrusion effects was significant at a trend level for baseline levels of RSA,  $B = -0.004$ ,  $t(35) = -2.00$ ,  $p = .053$ . Within the Real-RNI condition, greater change in negative intrusions was associated with a briefer RSA withdrawal during the anticipation period,  $B = -0.0001$ ,  $t(19) = -2.14$ ,  $p = .045$ , and with faster RSA recovery during the initial stress reactivity period,  $B = 0.0004$ ,  $t(19) = 2.73$ ,  $p = .013$ . Within the Sham-RNI condition, greater change in negative intrusions predicted higher levels of RSA at baseline,  $B = 0.003$ ,  $t(16) = 2.70$ ,  $p = .016$ , with greater pre- to post-training improvement in removing negative information from WM predicting higher levels of RSA at baseline. Detailed results are presented in the text of the online supplement.

#### 5. Discussion

This study is the first to experimentally examine the effects of training depressed individuals to remove negative information from WM on cognition, affect, and biological responses to stress. Previous WM training paradigms have focused predominantly on non-valenced stimuli (Course-Choi et al., 2017; Onraedt and Koster, 2014; Owens et al., 2013); this study is the first to examine the effects of affective WM training with a clinically depressed sample. Using

multiple indicators of biological functioning, we found that depressed individuals assigned to the Real-RNI training condition exhibited less biological reactivity in response to the stressor than did depressed individuals assigned to the Sham-RNI training condition. In addition, contrary to our hypotheses, all participants significantly improved in their ability to remove negative information from WM and reported significant decreases in both symptoms of depression and levels of rumination. In other words, there was no significant effect of Real-RNI compared to Sham-RNI training on pre- to post-training change in negative intrusions, symptoms of depression, or levels of rumination.

Unexpectedly, participants in both conditions significantly improved from pre- to post-training in removing emotional information from WM. There are several possible explanations for this finding. First, the lexical decision task completed by participants in the Sham-RNI condition may have engaged the neural systems involved in WM, such as subregions of the prefrontal cortex (Courtney et al., 1997; Curtis and D'Esposito, 2003). Indeed, there is evidence to suggest that both lexical decision tasks and verbal WM tasks are associated with increased activation of regions such as the anterior cingulate gyrus and left inferior frontal gyrus (Chen and Desmond, 2005; Phan et al., 2005; Zhang et al., 2003). Thus, it is possible that the real and sham tasks may have been activating structures in the same neural system (McNamara and Altarriba, 1988). However, it is important to note that the lexical decision task does not involve the same degree of active engagement that is required by the modified Sternberg task (Roediger, 1990). Reviews of the CBM literature argue that, while training and control conditions may involve exposure to identical stimuli, the critical difference between conditions is whether the stimuli are actively processed in a manner that is transfer-appropriate to the variables of interest (Hertel and Mathews, 2011). This argument is supported by a number of empirical studies demonstrating that active training (beyond stimulus exposure) is required for successful modification of cognitive processes (Hoppitt et al., 2010; Mathews and Mackintosh, 2000). It is also possible that participants in both conditions improved significantly from pre- to post-training in negative intrusions, symptoms of depression, and levels of rumination because of a regression to the mean or because of natural temporal fluctuations in these phenomena (Barnett et al., 2005). The equivalent changes across conditions could also be attributed to our use of an active control group, which may have served as a form of behavioral activation, as participants in both conditions completed cognitive tasks daily. To test for this possibility, future work should consider the use of a wait-list control condition, which could allow us to gain a better understanding of the reasons why individuals in the control condition improved on both affective and cognitive measures. Finally, all participants completed the affective Sternberg task at baseline: this single training session may have been sufficient to improve participants' ability to control the contents of WM. Consistent with this possibility, researchers have found training-related effects to emerge after a single session of cognitive bias modification training in samples of depressed individuals (Cohen et al., 2015; Tran et al., 2011; Yiend et al., 2014).

Importantly, we found that biological responses to stress at post-training differed by training condition. Compared to participants in the Sham-RNI condition, participants in the Real-RNI condition exhibited attenuated cortisol and RSA responses to stress. Moreover, for individuals who completed Real-RNI training, greater pre- to post-training improvement in removing negative information from WM was associated with more flexible RSA withdrawal and augmentation across the preparation and initial stress reactivity periods. Among participants who completed Sham-RNI training, greater pre- to post-training improvement in removing negative information from WM was associated with higher levels of RSA at baseline. Thus, the current study provides evidence that difficulty removing negative information from WM is associated with exaggerated biological responses to stress. This finding is particularly important given the effects of chronic biological dysregulation on neural, cardiovascular, autonomic, and immune systems

(Golbidi et al., 2015; McEwen, 2008), and on risk for the recurrence of depressive episodes (Appelhof et al., 2006; Morris et al., 2012; Yaroslavsky et al., 2014). It is interesting to speculate why we might have found significant differences between training conditions in biological responses to stress, but *not* in negative intrusions, depression, or rumination. One possibility is that the benefits of CBM protocols are not fully realized until participants encounter stress. Indeed, this proposition is consistent with results from the meta-analysis conducted by Hallion and Ruscio (2011), in which they found more robust effects of CBM procedures following a stressor. However, in light of the finding that participants in the Real-RNI and Sham-RNI training conditions did not differ in pre- to post-training changes in working memory biases, symptoms of depression, or levels of rumination, it is important to acknowledge that the observed group differences in biological responses to stress could reflect false positive results. Thus, it is critical to replicate the findings reported here.

Two limitations of the present study warrant discussion. First, all participants completed the affective Sternberg task at pre-training. Researchers have suggested that exposing a control group (i.e. Sham-RNI condition) to tasks similar to those used in active training has the potential to improve their WM performance (Onraedt and Koster, 2014). Thus, future work should use different tasks for assessment and training. Second, a long-term follow-up was not included in the present study. Although we did document training-related effects, it will be important for future work to assess long-term changes in memory performance following RNI training.

The present study extends the CBM literature by manipulating a cognitive process that is central to depression and by examining the effects of this manipulation on cognitive, affective, and biological functioning. Contrary to our hypotheses, we found that participants in both the Real-RNI and Sham-RNI training conditions improved from pre- to post-training in negative intrusions, symptoms of depression, and levels of rumination. However, our results do provide preliminary experimental evidence that cognitive control deficits contribute to dysregulated biological responses to stress, a finding that is critical given the prospective association between dysregulated biological responses to stress and trajectories of illness in MDD (Morris and Rao, 2014; Morris et al., 2012). Indeed, the present study is the first to experimentally test the associations among difficulties removing negative information from WM, symptoms of depression, levels of rumination, and biological responses to stress in depressed individuals. It is critical that investigators continue to conduct research in this area. In particular, future research should investigate whether the effects of training observed in the current study persist across time. Further, it will be important for future studies to examine the neural mechanisms underlying RNI training to elucidate precisely the ways in which CBM paradigms achieve their beneficial effects.

## Funding

This research was supported by National Institute of Mental Health (NIMH) Grants R21-MH101545 (to IHG), F32-MH102013 (to JL), and by the Brain & Behavior Research Foundation (formerly NARSAD) Young Investigator Award 22,337 (to JL). These funding sources had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

## CRediT authorship contribution statement

**Ellen Jopling:** Formal analysis, Writing - original draft. **Ian H. Gotlib:** Funding acquisition, Writing - review & editing. **Joelle LeMoult:** Conceptualization, Funding acquisition, Writing - review & editing.

## Declaration of Competing Interest

None.

## Acknowledgments

We thank Christina Schreiner, Emily Livermore, and Brooke Gilbert for their assistance in scheduling and running the participants.

## Supplementary materials

Supplementary material associated with this article can be found in the online version, at [doi:10.1016/j.jad.2020.01.007](https://doi.org/10.1016/j.jad.2020.01.007).

## References

- Appelhof, B.C., Huyser, J., Verweij, M., Brouwer, J.P., Van Dyck, R., Fliers, E., Schene, A.H., 2006. Glucocorticoids and relapse of major depression (dexamethasone/corticotropin-releasing hormone test in relation to relapse of major depression). *Biol. Psychiatry* 59 (8), 696–701.
- Barnett, A.G., van der Pol, J.C., Dobson, A.J., 2005. Regression to the mean: what it is and how to deal with it. *Int. J. Epidemiol.* 34 (1), 215–220.
- Beauchaine, T.P., 2015. Respiratory sinus arrhythmia: a transdiagnostic biomarker of emotion dysregulation and psychopathology. *Curr. Opin. Psychol.* 3, 43–47.
- Beck, A.T., Steer, R.A., Brown, G.K., 1996. Manual for the Beck Depression Inventory-II. Psychological Corporation, San Antonio, TX.
- Chen, S.H.A., Desmond, J.E., 2005. Cerebrocerebellar networks during articulatory rehearsals and verbal working memory tasks. *Neuroimage* 24 (2), 332–338.
- Cohen, N., Mor, N., Henik, A., 2015. Linking executive control and emotional response: a training procedure to reduce rumination. *Clin. Psychol. Sci.* 31 (1), 15–25.
- Course-Choi, J., Saville, H., Derakshan, N., 2017. The effects of adaptive working memory training and mindfulness meditation training on processing efficiency and worry in high worriers. *Behav. Res. Ther.* 89, 1–13.
- Courtney, S.M., Ungerleider, L.G., Keil, K., Haxby, J.V., 1997. Transient and sustained activity in a distributed neural system for human working memory. *Nature* 386 (6625), 608.
- Curtis, C.E., D'Esposito, M., 2003. Persistent activity in the prefrontal cortex during working memory. *Trends. Cogn. Sci. (Regul. Ed.)* 7 (9), 415–423.
- Dickerson, S.S., Kemeny, M.E., 2004. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. *Psychol. Bull.* 130 (3), 355–391.
- Doom, J.R., Cicchetti, D., Rogosch, F.A., Dackis, M.N., 2013. Child maltreatment and gender interactions as predictors of differential neuroendocrine profiles. *Psychoneuroendocrinology* 38 (8), 1442–1454.
- First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1996. Structured Clinical Interview For DSM-IV Axis I disorders-Clinician Version (SCID-CV). American Psychiatric Press, Washington.
- Golbidi, S., Frisbee, J.C., Laher, I., 2015. Chronic stress impacts the cardiovascular system: animal models and clinical outcomes. *Am. J. Physiol. Heart Circulat. Physiol.* 308 (12), H1476–H1498.
- Gotlib, I.H., Lemoult, J., Colich, N.L., Foland-Ross, L.C., Hallmayer, J., Joormann, J., Wolkowitz, O.M., 2015. Telomere length and cortisol reactivity in children of depressed mothers. *Mol. Psychiatry* 20 (5), 615.
- Grossman, P., Wilhelm, F.H., Spoerle, M., 2004. Respiratory sinus arrhythmia, cardiac vagal control, and daily activity. *Am. J. Physiol. Heart Circulat. Physiol.* 287 (2), H728–H734.
- Hallion, L.S., Ruscio, A.M., 2011. A meta-analysis of the effect of cognitive bias modification on anxiety and depression. *Psychol. Bull.* 137 (6), 940–958.
- Hertel, P.T., Mathews, A., 2011. Cognitive bias modification: past perspectives, current findings, and future applications. *Perspect. Psychol. Sci.* 6 (6), 521–536.
- Hoppitt, L., Mathews, A., Yiend, J., Mackintosh, B., 2010. Cognitive bias modification: the critical role of active training in modifying emotional responses. *Behav. Ther.* 41 (1), 73–81.
- Hruschka, D.J., Kohrt, B.A., Worthman, C.M., 2005. Estimating between- and within-individual variation in cortisol levels using multilevel models. *Psychoneuroendocrinology* 30 (7), 698–714.
- Joormann, J., 2010. Cognitive inhibition and emotion regulation in depression. *Curr. Dir. Psychol. Sci.* 19 (3), 161–166.
- Joormann, J., Gotlib, I.H., 2008. Updating the contents of working memory in depression: interference from irrelevant negative material. *J. Abnorm. Psychol.* 117 (1), 182–192.
- Joormann, J., Stanton, C.H., 2016. Examining emotion regulation in depression: a review and future directions. *Behav. Res. Therapy*, 86 35–49.
- Key, B.L., Campbell, T.S., Bacon, S.L., Gerin, W., 2008. The influence of trait and state rumination on cardiovascular recovery from a negative emotional stressor. *J. Behav. Med.* 31 (3), 237–248.
- Kircanski, K., Waugh, C.E., Camacho, M.C., Gotlib, I.H., 2016. Aberrant parasympathetic stress responsivity in pure and co-occurring major depressive disorder and generalized anxiety disorder. *J. Psychopathol. Behav. Assess* 38 (1), 5–19.
- Kirschbaum, C., Pirke, K.M., Hellhammer, D.H., 1993. The 'Trier social stress test'-a tool for investigating psychobiological stress responses in a laboratory setting. *Neurosci Biobehav Rev* 28 (1–2), 76–81.
- Koster, E.H.W., Hoorelbeke, K., 2015. Cognitive bias modification for depression. *Curr. Opin. Psychol.* 4, 119–123.
- Kudielka, B.M., Buske-Kirschbaum, A., Hellhammer, D.H., Kirschbaum, C., 2004. HPA axis responses to laboratory psychosocial stress in healthy elderly adults, younger adults, and children: impact of age and gender. *Psychoneuroendocrinology* 29 (1), 83–98.
- Kudielka, B.M., Hellhammer, D.H., Wüst, S., 2009. Why do we respond so differently? reviewing determinants of human salivary cortisol responses to challenge. *Psychoneuroendocrinology* 34 (1), 2–18.
- LeMoult, J., Gotlib, I.H., 2019. Depression: a cognitive perspective. *Clin. Psychol. Rev.* 69, 51–66.
- LeMoult, J., Joormann, J., 2014. Depressive rumination alters cortisol decline in major depressive disorder. *Biol. Psychol.* 100 (1), 50–55.
- LeMoult, J., Yoon, K.L., Joormann, J., 2015. Rumination and cognitive distraction in major depressive disorder: an examination of respiratory sinus arrhythmia. *J. Psychopathol. Behav. Assess.* 38 (1), 20–29.
- Macleod, C., Mathews, A., 2012. Cognitive bias modification approaches to anxiety. *Ann. Rev. Clin. Psychol.* 11, 189–217.
- Mathews, A., Mackintosh, B., 2000. Induced emotional interpretation bias and anxiety. *J. Abnorm. Psychol.* 109 (4), 602–615.
- McEwen, B.S., 2008. Central effects of stress hormones in health and disease: understanding the protective and damaging effects of stress and stress mediators. *Eur. J. Pharmacol.* 583 (2–3), 174–185.
- McNamara, T.P., Altarriba, J., 1988. Depth of spreading activation revisited: semantic mediated priming occurs in lexical decisions. *J. Mem. Lang.* 27 (5), 545–559.
- Morris, M.C., Rao, U., 2014. Cortisol response to psychosocial stress during a depressive episode and remission. *Stress* 17 (1), 51–58.
- Morris, M.C., Rao, U., Garber, J., 2012. Cortisol responses to psychosocial stress predict depression trajectories: social-evaluative threat and prior depressive episodes as moderators. *J. Affect. Disord.* 143 (1–3), 223–230.
- Nolen-Hoeksema, S., Morrow, J., 1991. A prospective study of depression and posttraumatic stress symptoms after a natural disaster: the 1989 loma prieta earthquake. *J. Pers. Soc. Psychol.* 61 (1), 115.
- Nolen-Hoeksema, S., Wisco, B.E., Lyubomirsky, S., 2008. Rethinking rumination. *Perspect. Psychol. Sci.* 3 (5), 400–424.
- O'Regan, C., Kenny, R.A., Cronin, H., Finucane, C., Kearney, P.M., 2015. Antidepressants strongly influence the relationship between depression and heart rate variability: findings from the Irish longitudinal study on ageing (TILDA). *Psychol. Med.* 45 (3), 623–636.
- Onraedt, T., Koster, E.H.W., 2014. Training working memory to reduce rumination. *PLoS ONE* 9 (3), e90632.
- Owens, M., Koster, E.H.W., Derakshan, N., 2013. Improving attention control in dysphoria through cognitive training: transfer effects on working memory capacity and filtering efficiency. *Psychophysiology* 50 (3), 297–307.
- Phan, K.L., Fitzgerald, D.A., Nathan, P.J., Moore, G.J., Uhde, T.W., Tancer, M.E., 2005. Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. *Biol. Psychiatry* 57 (3), 210–219.
- Raudenbush, S.W., Bryk, A.S., 2002. Hierarchical linear models: applications and data analysis methods. *Adv. Quant. Techn. Social Sci.* 1 (2nd).
- Roediger, H.L., 1990. Implicit memory: retention without remembering. *Am. Psychol.* 45 (9), 1043.
- Schweizer, S., Grahn, J., Hampshire, A., Mobbs, D., Dalgleish, T., 2013. Training the emotional brain: improving affective control through emotional working memory training. *Ann. Intern. Med.* 158 (3), 5301–5311.
- Schweizer, S., Hampshire, A., Dalgleish, T., 2011. Extending brain-training to the affective domain: increasing cognitive and affective executive control through emotional working memory training. *PLoS ONE* 6 (9), e24372.
- Tran, T.B., Hertel, P.T., Joormann, J., 2011. Cognitive bias modification: induced interpretive biases affect memory. *Emotion* 11 (1), 145.
- Voss, A., Schroeder, R., Heitmann, A., Peters, A., Perz, S., 2015. Short-term heart rate variability - Influence of gender and age in healthy subjects. *PLoS ONE* 10 (3), e0118308.
- Waugh, C.E., Panage, S., Mendes, W.B., Gotlib, I.H., 2010. Cardiovascular and affective recovery from anticipatory threat. *Biol. Psychol.* 84 (2), 169–175.
- Yaroslavsky, I., Rottenberg, J., Kovacs, M., 2014. Atypical patterns of respiratory sinus arrhythmia index an endophenotype for depression. *Dev. Psychopathol.* 26 (4), 1337–1352.
- Yiend, J., Lee, J.S., Tekes, S., Atkins, L., Mathews, A., Vrinten, M., Shergill, S., 2014. Modifying interpretation in a clinically depressed sample using "cognitive bias modification-errors": a double blind randomised controlled trial. *Cognit. Ther. Res.* 38 (2), 146–159.
- Zhang, J.X., Leung, H.C., Johnson, M.K., 2003. Frontal activations associated with accessing and evaluating information in working memory: an fMRI study. *Neuroimage* 20 (3), 1531–1539.
- World Health Organization. (2012). Depression: fact sheet no. 369. Retrieved from <http://www.who.int/mediacentre/factsheets/fs369/en/index.html>.