Facing recovery: Emotional bias in working memory, rumination, relapse and recurrence of Major Depression- an experimental paradigm conducted five years after first episode of MDD

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Abstract

Identifying vulnerability factors for relapse of depression is essential in planning preventive interventions. Emotional face processing in Major depression (MDD) shows promise as a potential cognitive marker for depression. The current study investigates how working memory load (WM) in face processing relates to rumination and new episodes of MDD in a novel explorative paradigm. It was expected that history a of MDD is associated with reduction of the ability to process sad stimuli in high WM load conditions, and reduction of the ability to process happy stimuli in low WM conditions. It was further predicted that these relations are associated with rumination and risk for relapse.

The experiment was included as a cross sectional part in a follow-up study of a population that previously experienced first episode (FE) depression. The FE (N=23)-, and a healthy control group (N=22) completed a WM face processing task. In the task, three happy or sad faces were presented, processed in either a high or low WM taxing manner, followed by a target stimulus consisting of one of the previous pictures. Response time and accuracy were dependent variables. Rumination and number of relapses or recurrences were measured.

The FE group recalled the placement of significantly fewer happy faces in the low WM load condition, and significantly fewer sad faces, in the high WM load condition compared to controls. Significantly different scores between groups predicted trait rumination. Poor accuracy in the sad high WM load condition correlated with high degree of rumination. Relapse or recurrence was predicted by rumination.

The present study supports an emotional WM deficit in remitted MDD. This suggests that deficits in manipulation of sad faces could represent a trait bias related to rumination and depression.

Keywords

Major depression, first episode, Facial processing, Emotional working memory, Rumination, Relapse, Recurrence

Introduction

Major depression (MDD) is a leading cause of disability in the global burden of disease (Ferrari et al., 2013). Amongst those experiencing MDD, it is estimated that more than 50% will experience a relapse or recurrence (Vittengl, Clark, Dunn, & Jarrett, 2007). Given the remarkably high prevalence and considerable risk of relapse and recurrence of MDD, it is important to expand knowledge about potential markers and risk factors associated with this disorder. Research on emotional processing could expand the current knowledge in MDD.

Variables that appear important for the risk of relapse and recurrence of MDD, are number of previous episodes and the presence of residual symptoms (Hardeveld, Spijker, De Graf, Nolen, & Beekman, 2010; Richards, 2011), as well as impaired cognition, particularly with regards to working memory (WM) and executive functions (Lee, Hermens, Porter, & Redoblado-Hodge, 2012; Snyder, 2013). Schmid and Hammar (2013a, 2013b) found impairments in inhibition and semantic fluency in a population experiencing first episode (FE) MDD. Impaired inhibition persisted in remission in this group, and inhibition/switching predicted relapse during the following year (Schmid & Hammar, 2013b). Cognitive deficits could impact patients' daily functioning, even in remission (Jaeger, Berns, Uzelac, & Davis-Conway, 2006), which might complicate the return to everyday life (Hammar & Årdal, 2009). In addition, impaired cognition in MDD could have significant links to emotional dysregulation (Joormann & Vanderlind, 2014).

Gotlib and Joormann (2010) synthesize traditional cognitive theories of depressive biases with contemporary neurocognitive research. In line with Mathews and MacLeod (2005), they conclude that depression is characterized by selective impairments, including deficits in cognitive control when processing negative stimuli, difficulties in disengaging from negative material, elaborating on the same material, and a lack of ability in using positive

stimuli to alleviate depressive mood. Furthermore, Joormann and D'Avanzato (2010) suggest in a review a relation between maladaptive emotion regulation strategies such as rumination and biases in emotional and cognitive processing. The authors further suggest that this could be a risk factor for recurrence in MDD.

According to Nolen-Hoeksema, Wisco and Lyubomirsky (2008), rumination involves continuous and passive reflection on negative thoughts, their causes and consequences, without engaging a response to change these circumstances. Whitmer and Gotlib (2013) suggest that attentional bias and WM impairments might contribute to rumination. Nolen-Hoeksema (2000) postulated that higher levels of rumination are associated with higher levels of depressive symptoms over time, and that rumination can predict the onset of depressive disorders, and relapse to new episodes of depression. Rumination could thus be associated with emotional processing bias and influence MDD.

Some studies have found a relationship between rumination and emotional facial processing (FP) bias. A functional neuroimaging study found that rumination was correlated with increased reactivity to sad faces in a remitted MDD sample (Thomas et al., 2011). Furthermore, a study found a relationship between rumination and bias in judging emotional expressions in a depressed sample, even when controlling for depressive symptoms (Raes, Hermans, & Williams, 2006). If bias is independent of mood, it could suggest that impaired emotional processing is relatively independent of mood congruency effects and is related to rumination.

Rumination is also associated with bias in executive functions regarding emotional FP. A study on inhibition of angry faces in a student population found that rumination, but not symptoms of depression, was significantly related to deficits in inhibiting negative material (De Lissnyder, Koster, Derakshan, & De Raedt, 2010). Two studies supported a relation between bias in WM processing of angry faces and rumination: Here FP bias, but not

depression, was related to rumination, in both a dysphoric and nondysphoric sample, and in high and low ruminators (De Lissnyder, Koster & De Raedt, 2012; Koster, De Lissnyder, & De Raedt, 2013). Demeyer, De Lissnyder, Koster and De Raedt (2012) furthermore found that increased switching costs from angry to neutral faces predicted depressive symptoms one year after testing in a remitted population. This relationship however, was mediated by rumination. This could suggest a relationship between emotional WM FP bias and rumination, contributing in the development or maintenance of depressive symptoms, thus representing a risk factor for MDD.

Rumination as a risk factor for MDD is supported by study of the effect of mindfulness based cognitive theraphy on depression. Here, the authors found that rumination predicted relapse to MDD in subjects over a one year period (Michalak, Hölz, & Teismann, 2011). A recent review elaborates on the suspected role of rumination in relapse and recurrence in MDD. Here the authors propose that a two factor model were rumination contribute to dysphoric elaboration, which together with dysphoric attention, puts individuals at risk for depression (Farb, Irving, Anderson, & Segal, 2015).

In the last decade emotional FP has received increased attention in the investigation of biases in depression (Bistricky, Ingram, & Atchley, 2011; Bourke, Douglas, & Porter, 2010). Bourke et al. (2010) suggest that abnormal FP in MDD directly causes some of the social- and affective symptoms experienced in this condition. Furthermore, the authors mention that changes in emotional processing could potentially help predict the course of, and inform on the treatment progress of MDD. The former is in line with studies showing that FP bias could predict depression (Bouhuys, Geerts, & Gordijn, 1999; Hale, 1998). Furthermore, Harmer, Cowen, and Goodwin, (2011) have suggested that biased FP normalizes in antidepressant treatment *before* symptom reduction, and therefore could serve as an efficacy marker in

psychopharmacological studies. Thus FP bias, like rumination, could be of particular clinical relevance and represent an ecologically valid variable in MDD research.

Studies of FP in depression point to several biases: In general, depressive- and at-risk populations seem to attend to a stronger degree to negative expressions and steer away from positive expressions, along with recalling more sad than happy faces (Bourke et al., 2010; Bistricky et al., 2011; Leppänen, 2006). In a metaanalysis, Kohler et al. (2011) reported moderate effect sizes for impaired identification and differentiation of emotional facial expressions. Depression seems to be associated with altered FP regarding memory, attention, recognition and higher cognitive functions like executive functions and WM.

There seems to be an impairment of emotional FP related to rumination, even in remission of MDD (Demeyer et al., 2012). Levens and Gotlib (2010) found that depressed participants had difficulties in updating emotional WM, tending to keep sad faces in WM longer and happy faces shorter, compared to controls. These findings were also replicated in a remitted population, and may indicate that emotional WM bias is a trait in this group that potentially contributes to relapse in MDD (Levens & Gotlib, 2015). Given the mounting evidence for emotional WM deficits in depression and for how these may relate to rumination, as well as for the potential clinical and social relevance of FP bias, studies with paradigms combining these methods could contribute to new insights into the underlying etiological aspects of MDD. The current study employs a novel explorative paradigm to investigate these matters, investigating how emotional WM FP is related to rumination, relapse and recurrence in a remitted MDD group.

The current study is based on a lexical study of emotional WM, which found a deficit in manipulation of negative material related to rumination. Joormann, Levens and Gotlib (2011) conducted a study on differences in WM manipulation of emotional lexical stimuli between a depressed and a control group. The former showed longer response times (RT) in a

WM loading condition, with strongest effects in the negative condition. This could suggest difficulties with WM processing of negative material in the depression group. *Only RT in the negative WM loading condition correlated with measures of rumination in the MDD group.* This could suggest that WM deficits in cognitive control of negative material could be related to rumination. The current study will employ a novel, modified paradigm of the one used in Joormann et al. (2011) to investigate whether emotional FP will yield the same result as that of emotional words in a remitted MDD group. It will further investigate if this is related to rumination and depression in this group.

The aim of the present study was to investigate WM processing load of emotional facial stimuli in relation to rumination and depression, specifically to see if rumination and biased processing of emotional stimuli were a risk factor in depression. In a five-year follow-up study, a formerly depressed group was tested on emotional FP paradigm as a cross-sectional part of a longitudinal study.

An explorative task was employed in order to investigate emotional bias in a WM paradigm. The paradigm was designed to investigate differences between the FE group and a control group (CG) in accuracy (AC) and RT, relative to WM load (Low WM load: Maintain. High WM load: Manipulate), and emotional valence (sad, happy). Given the FP bias reported in the literature (Bourke et al., 2010; Bistricky et al., 2011; Leppänen, 2006) it was expected that subjects from the FE group would attend to negative- and away from positive stimuli, thus recalling the placement of more sad, and less happy faces, in the low WM loading conditions. In line with previous findings of Joormann et al. (2011), it was expected that in a high WM loading condition, subjects with depressive biases would perform worse than controls on negative material. We furthermore expected biases in WM to be associated with rumination (Whitmer & Gotlib, 2013), relapse and recurrence in MDD. The study investigated the following three hypotheses:

First, the FE group will accurately recall the placement of significantly more sad-, and fewer happy faces in a low WM load condition compared to controls, and show shorter RT for sad than happy faces, reflecting a bias towards sad, and away from positive stimuli.

Secondly, it is hypothesized that the FE group will show longer RT and lower AC compared to controls in the sad high WM load condition, due to deficits in cognitive control of negative material, with these measures correlating with rumination.

Thirdly, rumination will significantly differ between groups, and together with FP bias predict relapse or recurrence of MDD.

Method

Participants

The original sample consisted of 30 patients experiencing MDD for the first time, approximately 6 years prior. MDD was defined as a score of ≥ 20 on the Montgomery Åsberg Depression rating scale (MADRS; Montgomery & Åsberg, 1979). The group can be defined as at-risk of MDD having experienced at least one episode of MDD (Bhagwagar & Cowen, 2008). Subjects were recruited through the cooperation of physicians and psychologists in primary healthcare, and the student healthcare program at the University of Bergen. Participants were first contacted by mail, then by phone. Exclusion criteria were a history of psychosis, brain damage, electroconvulsive treatment, and alcohol or substance abuse. Of the 30 original participants, 23 were available for follow-up for the present study. Although this was initially a FE depression group, subjects differed in how their depression had developed since first testing (see table 1).

To measure depressive symptoms, all participants in the FE group were screened with MADRS (Montgomery & Åsberg, 1979). The FE group as a whole was not depressed as measured by mean group score (MADRS < 13). Five participants were above the cut-off. FE

participants completed the International Neuropsychiatric Interview (MINI; Leiknes, Leganger, Malt, & Malt, 1999) to investigate additional psychopathology.

Table 1

Participant Characteristics

	FE group (N = 23)		**CG (N = 22)**	
Male/Female	11/12		10/12	
	M	*SD*	*M*	*SD*
Age	30.50	5.83	30.14	6.09
IQ*	119.05	8.45	119.76	8.32
Education	15.27	2.37	16.48	1.94
RRS	48.43	13.31	31.05	9.65
MADRS score	8.32	7.88	*	*
FE variables	Frequency	%		
Comorb. (MINI)	9	39.5	*	*
Relapse**	17	73.91	*	*

*IQ measured at first testing **Relapse/recurrence in since last testing in the First episode (FE) group. Control group (CG) and FE group mean (M) age and standard deviations (SD), Ruminative Responses Scale (RRS), Frequency refers to number of participants with comorbid diagnoses and relapse

We used the National Institute of Mental Health prospective Life Chart Methodology (NIMH LCM; Denicoff et al., 2000) concurrently to investigate whether patients had experienced relapse or recurrence of MDD since last testing.

The CG group originally consisted of 31 subjects; of these, 20 participated in this study. For the present study they were contacted by mail, and then by telephone. We had to recruit two new controls to sufficiently match groups, due to dropout from the original population. The CG was recruited through internal announcement at the University of Bergen, and through acquaintances of employees of The Department of Biological and Medical

Psychology of The University of Bergen. The CG was matched with the FE group in terms of the following variables (see Table 1): Gender, age, and years of education (+- 2 years).

Before including controls in the current experiment, we interviewed them by administering a structured questionnaire to ascertain whether they met exclusion criteria. For controls, exclusion criteria included a history of mental illness including a history of depression, brain damage, serious somatic illness, and alcohol or substance abuse.

All subjects received a gift certificate worth 400 NOK (approximately 50 USD) as compensation for participation. The study was conducted according to the guidelines of the Helsinki Declaration (World Medical Association, 2008), and was approved by the regional committee for medical and health research (REK) in Norway.

Stimuli

The paradigm used 40 black and white pictures of emotional faces retrieved from The Karolinska Directed Emotional Faces stimuli set (Lundqvist, Flykt, & Öhman, 1998). These consisted of male and female actors facing forward, displaying sad or happy emotions. The pictures were composed in a controlled fashion, using the same background, same clothing, same light conditions and so forth. Picture stimuli were sequentially and randomly sampled from four lists of 10 pictures containing sad male, happy male, sad female and happy female pictures, so that all pictures had the same probability of being presented across the conditions, except when they had been presented in previous trials.

Procedure

Before testing began, participants signed an informed consent form. A trained psychologist then administered clinical tests to the depression group. Both the FE group and the CG completed the Ruminative Responses Scale (RRS; Treynor, Gonzalez, & Nolen-Hoeksema, 2003) to investigate trait tendency to ruminate. After taking part in an extended neuropsychological test battery, the subjects completed the experimental paradigm of the

current study. All testing was performed at the neuropsychological clinic at the Department of Biological and Medical Psychology, University of Bergen, and took approximately 3 hours in all.

The experiment was run on a DELL laptop (Lattitude E6430, running Windows 7, 32 bit true color, 1600 x 900 resolution, computer screen refresh rate = 60 Hz), and data on AC and RT were automatically collected using E-prime (Version 2.0; Schneider, Eschman, & Zuccolotto, 2002).

Figure 1

Participants were presented with a series of three either sad or happy female or male faces. See figure 1 for description. The faces appeared on the screen for 1,000 ms each, and the first picture was preceded by a 250 ms fixation display, while the other two were preceded by two 750 ms fixation displays. The series of three pictures was followed by another 1,000 ms fixation, then followed by the cue "forwards" or "backwards" presented for 500 ms. The cue instructed participants to either recall the pictures as they were sequentially presented (i. e. "forwards") or in the opposite order ("backwards"). This was followed by a 4,000 ms delay period, in which participants either maintained (low WM load) or manipulated (high WM load) the sequential ordering of the stimuli in WM. Following this, a probe stimulus consisting of one of the previously shown pictures was presented. Participants were asked to indicate where in the previous sequence the probe picture was placed by pressing the number-key option "1", "2" or "3".

Sequence of correct order were counterbalanced so that the probability of pressing "1", "2" or "3" was equal across conditions. Dependent variables were RT and AC. To make sure that participants understood the task, two initial example trials were presented, one for the "forwards"-, and one for "backwards" condition. In order for the experiment to continue, a correct response was required. The example tasks were followed by a practice block of four

trials, after which the participants could ask the experimenter questions if necessary. The paradigm consisted of two blocks of 24 trials. The conditions were presented in random order, thus resulting in a total of 48 trials; 12 in the negative "forwards" maintain, and 12 in the negative "backwards" manipulate conditions, and 12 in both of the positive maintain and manipulate conditions. The experimental paradigm lasted approximately 15 minutes including practice trials.

Data scoring and Analysis Participant means on AC and RT in the different conditions were calculated in E-data aid (Version 2.0; Schneider et al., 2002) and exported to a statistical program. We treated RT in the extreme (> 10000 ms) as outliers, and removed them from the analysis. Furthermore, we only used RT from correct trials as in Joormann et al. (2011). All subsequent data analysis was performed in IBM SPSS statistics (version 20.0). AC scores over three standard errors from the mean were treated as missing data.

Results

Independent t-tests were used to compare groups on age, IQ, and education level. An alpha level of $p < 0.05$ was used for all statistical tests. Given the relatively small sample size one way ANOVA tests were used to look at the conditions relevant for hypotheses.

Independent sample t-tests found no significant differences between the groups on age; t (41) = .644, p = .845, IQ; t (41) = -.280, p = .781, or level of education; t (41) = - 1.815, p = .077, two tailed (for means see Table 1). A paired sample t-test was used to determine differences between the low- and high WM loading conditions maintain and manipulate on overall RT and AC. Subjects spent significantly longer time in the manipulate conditions (M = 2589.35 SD = 1167.16) compared to the maintain conditions (M = 2239.75 SD =1167.17) t (44) = 4.7, p < .000. Subjects showed higher AC in the maintain- (M = .7584 SD = .1138) than the manipulate (M = .7307 SD = .1394) conditions, however this difference was not significant t (44) = 1.608 p = .115.

Figure 2

To test our first hypothesis, one-way ANOVAs were conducted on the means for the happy and sad low WM condition, see figure 2 for means. The FE group recalled the placement of significantly fewer happy faces than controls in the low WM load condition F (1, 43) = 8.558, $p < .005$. The FE group, however, did not recall the placement a significantly larger number of sad faces in the low WM load condition F (1, 43) = 1.124, $p = .259$, and there were no significant differences in RT in the conditions.

To test hypothesis two, a one-way ANOVA in the sad high WM load condition was performed. Results showed that the FE group recalled significantly fewer placements of sad faces than controls F (1, 43) = 4.577, $p < .038$.

To investigate the relationship between bias and rumination, we performed a linear regression analysis with RRS score as dependent variable, and significant difference scores between groups as predictors, namely AC in the happy low WM load condition and sad high WM load condition. There was one missing response on RRS. None of the predictors violated multicollinearity (< .70 r). This was supported by Tolerance values < .10 and VIF values < 10. A visual inspection of the normal p-p plot of regression-standardized residuals revealed that the dots roughly followed the diagonal line, indicating that assumptions of normality were met. In the scatterplot, standardized residuals was roughly rectangularity distributed, with most scores centered, and no score exceeding 3.3 or preceding -3.3, indicating that assumptions for this test were met. This was also supported by a Cooks distance < 1. The linear regression was conducted with all variables that were significantly different between the groups, thus *potentially reflecting a depressive bias*, as predictors of trait RRS (Treynor et al., 2003). The model significantly explained 9.9 % (Adjusted R square) of the variance in RRS score F (2, 41) = 3,36, $p < .044$. The sad high WM load AC score showed the greatest contribution to the model. The predictor, however, only approached significance (*beta* = -.305

$p < .071$). This indicates that a low AC score in the sad high WM load condition is associated with a higher score on RRS. A Pearson product-moment correlation coefficient supported this relationship. There was a moderate negative correlation between the AC in the sad high WM load condition and RRS, $r = -.352$, $n = 45$, $p < .018$. To investigate if this relationship was mediated by current depression symptom score a Pearson product-moment correlation coefficient was conducted between AC score in the sad high WM load condition and MADRS score in the FE group. The relationship was not significant.

To investigate hypothesis three, a one-way ANOVA testing differences in RRS between groups were performed. The FE group scored significantly higher on rumination than controls $F(1, 42) = 24.195$, $p < .01$. To test the relationships between processing bias, rumination, and depression, we performed a logistic regression analysis with AC in the happy low WM load condition, and the sad high WM load condition and rumination, predicting relapse and recurrence of MDD in the population as a whole. The model containing all predictors was statistically significant χ^2 (3, N = 44) = 24.38. $p < .001$, indicating that the model could distinguish between those participants who experienced relapse and those who did not. The model as a whole explained between 42.5% (Cox & Snell R Square) and 57.7% (Nagelkerke R Square) of the variance in relapse, and correctly classified 81.8% of cases. Of the predictor variables, only the rumination score on RRS was a statistically significant contributor to the model with an odds ratio of 1.16, indicating that ruminators were 1.16 times more likely to experience relapse or recurrence of MDD. A blockwise comparison model comparing RRS to RRS in addition to bias scores showed that AC in the happy low WM load condition and the sad high WM load condition did not significantly contribute to prediction, and that RRS alone was superior in predicting relapse and recurrence.

Discussion

The aim of the present study was to investigate emotional FP in WM and determine how it relates to rumination, relapse and recurrence of MDD. Several of the hypotheses were supported.

Firstly, there were significant differences between groups in the low WM load condition, with the FE group recalling significantly fewer placements of happy faces than the controls, in the low WM load condition. However, the predicted negative bias in the FE group occurred neither on AC nor on RT. There were no significant differences in RT between groups.

Secondly, a difference between groups in AC was found in the high WM load condition. As predicted, these differences manifested themselves in the processing of sad faces, with the FE group recalling placements of significantly fewer sad faces than controls. In addition to this, bias scores in AC significantly predicted rumination; with AC in the sad high WM load condition as the strongest predictor, however only approaching significance. Furthermore, AC in the sad high WM load condition showed a significant negative correlation with rumination. There was a significant difference between groups in RRS score.

In conclusion, a model consisting of bias scores together with rumination predicted relapse and recurrence, thus supporting our final hypothesis. In this model however, only the rumination score was a statistically significant predictor, and bias scores did not contribute to prediction.

The current study did not find any significant differences between groups on measures of RT. This could be due to the low variance in RT and that current paradigm is not sensitive on differences in RT. In addition, it could be that the AC scores reflect the bias more correctly.

The results support that the high WM load condition was more taxing than the low WM load condition. Analysis of WM load on overall RT and AC in the low WM load and

high WM load conditions were conducted. Here we found a significant difference between overall RT in both WM load and conditions. Although the subjects overall had higher AC in the low WM load condition, this difference was not significant. Differences between conditions in AC and RT are used to indicate difficulty in other WM tasks like the N-Back task (Meule, 2017).

Our first hypothesis predicted differences in AC and RT, on sad and happy faces, between the FE group and the CG in the low WM load condition. These differences were evident in the happy face stimuli. This finding is opposed to findings suggested by Bistricky et al. (2011) and Bourke et al. (2010), supporting a memory and attention bias for sad facial stimuli. However, no sad face bias was found in neither AC nor RT scores in the current low WM load condition. This could be explained by bias in measures of memory and attentional paradigms differ from the current paradigm. Importantly, findings showed a significant difference between the groups in AC for happy faces, where the FE group recalled the placement of significantly fewer happy faces than the CG. A bias in processing of positive stimuli could potentially lessen the amount of positive stimuli a remitted person experiences (Levens & Gotlib, 2015) and contribute to diminished levels of positive affect (Joormann & Vanderlind, 2014). Impaired ability to process positive stimuli could also potentially contribute to depression (Levens & Gotlib, 2010). The CG AC score in the happy low WM loading condition shows a bias for happy faces. Some studies support a happy face bias in a healthy population (Putman, Van Honk, Kessels, Mulder, & Koppeschaar, 2004; Ridout et al., 2003). These studies, however, investigated long-term memory. The current study indicated that a positive bias could hold true for short-term WM processes as well. Our results could suggest that healthy controls show positive bias for a low WM load condition and correct sequential placing of happy faces, and that a population at risk of depression shows an decreased positivity bias relative to the CG, which also could contribute to depression.

Our second hypothesis predicted differences between groups in AC and RT on sad faces in the high WM load condition. There were no differences in RT as discussed above. The FE group recalled the placement of significantly fewer sad faces compared to the controls in this condition. This could be due to a deficit in cognitive control over negative material. Moreover, the impaired AC in the sad high WM load condition showed a significant negative correlation with rumination, thus supporting the second hypothesis. Interestingly, in the regression model predicting rumination, only bias for WM processing of sad faces in the high WM load condition approached significance. The result makes theoretical sense in that only the bias for processing of sad faces when the WM load is high, is related to rumination. This could further support that a bias in a high WM load condition, requiring cognitive control of negative material, contributes to-, or is associated with-, rumination. This is supported by Joormann et al. (2011) who also found a relationship between manipulation of sad stimuli and rumination. There are several differences, however, between the findings of the current study and Joormann et al. (2011). For instance, the authors found differences in measures of RT, but no significant differences between groups in AC score. This is probably due to different paradigms, populations, and statistical analysis.

Whitmer and Gotlib (2013) in a review on rumination stated that rumination is associated with the following cognitive processes: Trait rumination can lead to difficulties in updating WM, impaired ability to disengage from or forget no longer relevant information, while state rumination is associated with impaired cognitive control. Koster, De Lissnyder, Derakshan & De Raedt (2011) proposed an impaired disengagement hypothesis, where processing of negative self-referent material is due to impaired ability to disengage from negative self-referent information. Here, rumination is linked to neurocognitive processes like attentional bias and lack of cognitive control. The present study, together with Joormann et al. (2011), further suggests that difficulties in WM manipulation of negative information, and

cognitive control, could be associated with rumination. The negative relationship between rumination and AC scores in the sad high WM loading condition is noteworthy; it could suggest WM deficit in cognitive control when manipulating negative stimuli could contribute to deficits in lexical and facial processing, as well as in ruminative processes. The lack of relationship between MADRS score and AC score could suggest that the relationship between RSS and AC scores in the sad high WM loading condition is relatively independent of other depressive symptoms.

Our final hypothesis was that rumination and bias in FP in emotional WM would significantly predict relapse or recurrence of MDD in a statistical model. The present study could suggest that difficulties in manipulating sad faces in WM could constitute a bias in a partly remitted group, and that that bias is related to rumination. The ultimate aim of this study was to investigate whether FP bias in the FE group was associated with relapse or recurrence of MDD. The model predicting relapse was significant, but only rumination showed a significant contribution to the model. Blockwise analysis of models showed that a model with bias scores in addition did not contribute to prediction over RRS alone.

The failure to establish a clear relationship between biases and relapse and recurrence could be because rumination mediates the emotional WM bias effect on depressive symptoms. Thomas et al. (2011) for instance, found that automatic emotional face processing biases, but not depressive symptoms, correlated with RRS in remission. Demeyer et al. (2012) found that emotional bias in cognitive control in switching between angry and neutral faces predicted depressive symptoms after one year in a remitted sample. Rumination score, however, mediated this effect, and it could therefore be argued that emotional WM bias could contribute to rumination that leads to depressive symptoms.

To our knowledge, this is the third study to suggest a relationship between risk of relapse and recurrence in MDD, and FP bias (Hale, 1998; Bouhuys et al., 1999). This is

remarkable, considering the growing interest in FP in MDD (Bourke et al., 2010; Bistricky et al., 2011; Harmer et al., 2011; Stuhrmann, Suslow, & Dannlowski, 2011). The lack of studies on emotional bias as a predictor for depression might reflect a general lack of longitudinal studies of depressive phenomena illustrating the need for such studies. Furthermore, we are not aware of any studies that show rumination as a significant predictor for risk of recurrence in a remitted FE MDD group. The study, however, support the findings of Michalak, Hölz, and Teismann (2011) on rumination as a risk factor for relapse in MDD. It also partly supports the two factor model of relapse and recurrence (Farb et al., 2015).

A central issue regarding cognitive deficits and emotional biases in depression is whether these phenomena represent states or traits (Bistricky et al., 2011; Kohler et al., 2011; Lee et al., 2012; Stuhrmann et al., 2011). The present study, together with recent studies like Levens and Gotlib (2015), suggests that emotional FP bias in WM is a trait, relatively independent of current depressive symptoms. The performance of the groups in the current study differed despite being matched on important variables. The literature on emotional FP biases is diverse and utilizes a wide range of paradigms and populations (Bistricky et al., 2011; Bourke et al., 2010). It can thus be difficult to draw conclusions as to how, and in what form, biased FP and WM may constitute a trait in depression, and how it can be a risk factor for relapse and recurrence.

Limitations

The FE population in the current study had become relatively heterogeneous since experiencing their first depressive episode. In the population of the present study, more than 70% had experienced relapse. Several in the FE group had comorbid psychological disorders, mainly anxiety disorders, which according to Sunslow et al. (2004) and Mathews and MacLeod (2005), could elicit different FP biases than depression alone. In addition, considerable dropout has affected the overarching study. It is hard to know if the current

sample has different characteristics than the original sample because of this. For instance dropout rates in the CG could be due to participants experiencing depression. The study, despite heterogeneity, did produce significant findings, suggesting that more selected populations could show results that are even more robust. Furthermore the relationship between MADRS scores and rumination in the CG remains unknown.

Furthermore, the relatively small heterogeneous sample probably affected the power of statistical analyses as described above and made it feasible to do hypothesis testing by one way ANOVAs instead of more complex designs. The present results should therefore be replicated in a larger population, and be interpreted with caution. The current results could be random due to overall between group effects, but has backing in theoretical and statistical findings, most notably the relationship found between sad WM bias and rumination. The relative young age of participants should also be taken into account, and the results of this study regarding cognitive deficits and depression, can probably not be generalized to the literature on mild cognitive impairment (MCI) and depression in the elderly (Blazer, 2003). Participant characteristics could thus limit external validity and should be taken into account when generalizing the current results to other populations.

Another major limitation was that data used to predict relapse were collected *after* participants had experienced one or more episodes of depression. A statistical model was used to predict relapse and recurrence from the current data, thus any future predictive value is merely speculative, although not without merit. Having data on relapse and recurrence history in this population is a major strength compared to other studies (Levens & Gotlib, 2015).

This is the first study that employed the current experimental paradigm; more studies are needed to assess the validity and reliability of the present experimental task. However, the tendency for impairment when manipulating sad stimuli and a relationship with rumination,

was in some ways replicated from a similar lexical paradigm (Joormann et al., 2011), thus supporting reliability.

Further research

The literature on WM FP bias in depression is scarce and divergent. A standardization of paradigms and experimental procedures could serve to strengthen validity and generalizability of results from such studies. Furthermore, a relationship between the literature on neuropsychological cognitive deficits, rumination, and emotional bias in MDD should be established. Lastly, if FP bias is hereditary, as Joormann and Gotlib (2007) suggest the relationship between depressive genotypes and FP phenotypes should be investigated. Emotional WM FP holds the potential for seminal contributions to the understanding of MDD. Therefore, controlled longitudinal studies into the nature and consequences of these phenomena seem warranted.

If a cognitive emotional bias puts certain populations at risk of MDD and exacerbate symptoms of this disorder, interventions normalizing bias should be developed (Koster, Fox, & MacLeod, 2009). For example, computerized positive mental imagery has been used to treat depression with promising results (Lang, Blackwell, Harmer, Davison, & Holmes, 2012). Cognitive remediation of depression holds promise as an effective and helpful intervention in treatment and prevention of this disorder (Porter, Bowie, Jordan, & Malhi, 2013). Longitudinal investigation on cognitive remediation of cognitive deficits and emotional biases in MDD could be a potentially effective intervention against the alarming rate of relapse and recurrence in this disorder.

Conclusion

Impaired cognition has emerged as a central feature of MDD. Recently, the focus has shifted from general deficits to more specific emotional biases in relation to this disorder. The present study suggests a bias in processing emotional faces: Having experienced depression

was associated with recalling the placement of fewer happy faces in a low WM loading condition, and the correct placement of fewer sad faces in a high WM loading condition. Rumination was significantly and uniquely related to manipulation of sad stimuli. Rumination predicted relapse and recurrence of depression. A WM deficit in cognitive control for negative material could thus contribute to ruminative processes, which constitute a risk factor for MDD. The present results indicate that WM biases for processing of emotional faces *could* be a trait marker, and significant factor in the pathogenesis of depression. Emotional WM could be of clinical and theoretical importance in depression, and FP has particular ecological validity social relevance. Emotional WM FP as a risk factor for depression thus warrants further research.

References

Bhagwagar, Z. U. B. I. N., & Cowen, P. J. (2008). 'It's not over when it's over': persistent neurobiological abnormalities in recovered depressed patients. *Psychological medicine*, *38*(03), 307-313.

Bistricky, S. L., Ingram, R. E., & Atchley, R. A. (2011). Facial affect processing and depression susceptibility: Cognitive biases and cognitive neuroscience. *Psychological bulletin*, *137*(6), 998.

Blazer, D. G. (2003). Depression in late life: review and commentary. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *58*(3), M249-M265.

Bouhuys, A. L., Geerts, E., & Gordijn, M. C. (1999). Depressed patients' perceptions of facial emotions in depressed and remitted states are associated with relapse: a longitudinal study. *The Journal of nervous and mental disease*, *187*(10), 595-602.

Bourke, C., Douglas, K., & Porter, R. (2010). Processing of facial emotion expression in major depression: a review. *Australian and New Zealand Journal of Psychiatry*, *44*(8), 681-696.

Demeyer, I., De Lissnyder, E., Koster, E. H., & De Raedt, R. (2012). Rumination mediates the relationship between impaired cognitive control for emotional information and depressive symptoms: A prospective study in remitted depressed adults. *Behaviour research and therapy*, *50*(5), 292-297.

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

De Lissnyder, E., Koster, E. H., & De Raedt, R. (2012). Emotional interference in working memory is related to rumination. *Cognitive Therapy and Research*,*36*(4), 348-357.

Denicoff, K. D., Leverich, G. S., Nolen, W. A., Rush, A. J., McElroy, S. L., Keck, P. E., ... & Post, R. M. (2000). Validation of the prospective NIMH-Life-Chart Method (NIMH-LCMTM-p) for longitudinal assessment of bipolar illness. *Psychological Medicine*, *30*(06), 1391-1397.

Farb, N. A., Irving, J. A., Anderson, A. K., & Segal, Z. V. (2015). A two-factor model of relapse/recurrence vulnerability in unipolar depression. Journal of abnormal psychology, 124(1), 38.

Ferrari, A. J., Charlson, F. J., Norman, R. E., Patten, S. B., Freedman, G., Murray, C. J., ... & Whiteford, H. A. (2013). Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS medicine*, *10*(11),e1001547.

Gotlib, I. H., & Joormann, J. (2010). Cognition and depression: current status and future directions. *Annual review of clinical psychology*, *6*, 285.

Hale III, W. W. (1998). Judgment of facial expressions and depression persistence. *Psychiatry research*, *80*(3), 265-274.

Hammar, Å., & Årdal, G. (2009). Cognitive functioning in major depression–a summary. *Frontiers in human neuroscience*, *3*.

Hardeveld, F., Spijker, J., De Graf, R., Nolen, W.A., & Beekman A. (2010). Prevalence and predictors of recurrence of major depressive disorder in the adult population. *Acta Psychiatrica Scandinavica, 122,* 184–191.

Harmer, C. J., Cowen, P. J., & Goodwin, G. M. (2011). Efficacy markers in depression. *Journal of Psychopharmacology*, *25*(9), 1148-1158.

Jaeger, J., Berns, S., Uzelac, S., & Davis-Conway, S. (2006). Neurocognitive deficits and disability in major depressive disorder. *Psychiatry research*, *145*(1), 39-48.

Joormann, J., & D'Avanzato, C. (2010). Emotion regulation in depression: Examining the role of cognitive processes: Cognition & Emotion Lecture at the 2009 ISRE Meeting. *Cognition and Emotion*, *24*(6), 913-939.

Joormann, J., Levens, S. M., & Gotlib, I. H. (2011). Sticky thoughts depression and rumination are associated with difficulties manipulating emotional material in working memory. *Psychological science*, *22*(8), 979-983.

Joormann, J., & Vanderlind, W. M. (2014). Emotion Regulation in Depression The Role of Biased Cognition and Reduced Cognitive Control. *Clinical Psychological Science*, *2*(4), 402-421.

Kohler, C. G., Hoffman, L. J., Eastman, L. B., Healey, K., & Moberg, P. J. (2011). Facial emotion perception in depression and bipolar disorder: a quantitative review. *Psychiatry research*, *188*(3), 303-309.

Koster, E. H., De Lissnyder, E., Derakshan, N., & De Raedt, R. (2011). Understanding depressive rumination from a cognitive science perspective: The impaired disengagement hypothesis. *Clinical psychology review*, *31*(1), 138-145.

Koster, E. H., De Lissnyder, E., & De Raedt, R. (2013). Rumination is characterized by valence-specific impairments in switching of attention. *Acta psychologica*, *144*(3), 563-570.

Koster, E. H., Fox, E., & MacLeod, C. (2009). Introduction to the special section on cognitive bias modification in emotional disorders. *Journal of Abnormal Psychology*, *118*(1), 1.

Lang, T. J., Blackwell, S. E., Harmer, C. J., Davison, P., & Holmes, E. A. (2012). Cognitive bias modification using mental imagery for depression: developing a novel

computerized intervention to change negative thinking styles. *European Journal of Personality*, *26*(2), 145-157.

Lee, R. S., Hermens, D. F., Porter, M. A., & Redoblado-Hodge, M. A. (2012). A meta-analysis of cognitive deficits in first-episode major depressive disorder. *Journal of affective disorders*, *140*(2), 113-124.

Leiknes, K. A., Leganger, S., Malt, E. A., & Malt, U. (1999). Mini internasjonalt neuropsykiatrisk intervju. In D. Sheehan, J. Janavs, J. Baker, K. Harnett-Sheenan, E. Knapp, & M. Sheehan(Eds.), Mini international neuropsychiatric interview. Tampa, FL: University of South Florida.

Leppänen, J. M. (2006). Emotional information processing in mood disorders: a review of behavioral and neuroimaging findings. *Current Opinion in Psychiatry*, *19*(1), 34-39.

Levens, S. M., & Gotlib, I. H. (2010). Updating positive and negative stimuli in working memory in depression. *Journal of Experimental Psychology: General*, *139*(4), 654.

Levens, S. M., & Gotlib, I. H. (2015). Updating emotional content in recovered depressed individuals: Evaluating deficits in emotion processing following a depressive episode. *Journal of behavior therapy and experimental psychiatry*,*48*, 156-163.

Lundqvist, D., Flykt, A., & Öhman, A. (1998). The Karolinska Directed Emotional Faces - KDEF, CD ROM from Department of Clinical Neuroscience, Psychology section, Karolinska Institutet, ISBN 91-630-7164-9.

Mathews, A., & MacLeod, C. (2005). Cognitive vulnerability to emotional disorders. *Annu. Rev. Clin. Psychol.*, *1*, 167-195.

Meule, A. (2017). Reporting and interpreting working memory performance in n-back tasks. *Frontiers in Psychology*, *8*.

Michalak, J., Hölz, A., & Teismann, T. (2011). Rumination as a predictor of relapse in mindfulness-based cognitive therapy for depression. *Psychology and Psychotherapy: Theory, Research and Practice*, *84*(2), 230-236.

Montgomery, S. A., & Åsberg, M. (1979). A new depression scale designed to be sensitive to change. *British Journal of Psychiatry, 134*, 322-389.

Nolen-Hoeksema, S. (2000). The role of rumination in depressive disorders and mixed anxiety/depressive symptoms. *Journal of abnormal psychology*, *109*(3), 504.

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

Porter, R. J., Bowie, C. R., Jordan, J., & Malhi, G. S. (2013). Cognitive remediation as a treatment for major depression: A rationale, review of evidence and recommendations for future research. *Australian and New Zealand Journal of Psychiatry*, *47*(12), 1165-1175.

Putman, P., Van Honk, J., Kessels, R. P., Mulder, M., & Koppeschaar, H. P. (2004). Salivary cortisol and short and long-term memory for emotional faces in healthy young women. *Psychoneuroendocrinology*, *29*(7), 953-960.

Raes, F., Hermans, D., & Williams, J. M. G. (2006). Negative bias in the perception of others' facial emotional expressions in major depression: The role of depressive rumination. *The Journal of nervous and mental disease*, *194*(10), 796-799.

Ridout, N., Astell, A., Reid, I., Glen, T., & O'Carroll, R. (2003). Memory bias for emotional facial expressions in major depression. *Cognition & Emotion*, *17*(1), 101-122.

Richards, D. (2011). Prevalence and clinical course of depression: a review. *Clinical psychology review*, *31*(7), 1117-1125.

Schmid, M., & Hammar, Å. (2013a). A follow-up study of first episode major depressive disorder. Impairment in inhibition and semantic fluency—potential predictors for relapse?. *Frontiers in psychology*, *4*

Schmid, M., & Hammar, Å. (2013b). Cognitive function in first episode major depressive disorder: poor inhibition and semantic fluency performance. *Cognitive neuropsychiatry*, *18*(6), 515-530.

Schneider, W., Eschman, A., & Zuccolotto, A. (2002). *E-Prime reference guide*. Psychology Software Tools, Incorporated.

Snyder, H. R. (2013). Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. *Psychological bulletin*, *139*(1), 81.

Stuhrmann, A., Suslow, T., & Dannlowski, U. (2011). Facial emotion processing in major depression: a systematic review of neuroimaging findings. *Biol Mood Anxiety Disord*, *1*(10).

Suslow, T., Dannlowski, U., Lalee-Mentzel, J., Donges, U. S., Arolt, V., & Kersting, A. (2004). Spatial processing of facial emotion in patients with unipolar depression: a longitudinal study. *Journal of affective disorders*, *83*(1), 59-63.

Thomas, E. J., Elliott, R., McKie, S., Arnone, D., Downey, D., Juhasz, G., ... & Anderson, I. M. (2011). Interaction between a history of depression and rumination on neural response to emotional faces. *Psychological medicine*, *41*(09), 1845-1855.

Treynor, W., Gonzalez, R., & Nolen-Hoeksema, S. (2003). Rumination reconsidered: A psychometric analysis. *Cognitive Therapy and Research*, *27*(3), 247-259.

Vittengl, J. R., Clark, L. A., Dunn, T. W., & Jarrett, R. B. (2007). Reducing relapse and recurrence in unipolar depression: a comparative meta-analysis of cognitive-

behavioral therapy's effects. *Journal of consulting and clinical psychology*, *75*(3), 475.

Whitmer, A. J., & Gotlib, I. H. (2013). An attentional scope model of rumination. *Psychological Bulletin*, *139*(5), 1036.