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Mood Reactivity Rather Than Cognitive Reactivity Is Predictive of Depressive Relapse: A Randomized Study With 5.5-Year Follow-Up

Gerard D. van Rijsbergen and Claudi L. H. Bockting
University of Groningen

Huibert Burger
University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

Philip Spinhoven
Leiden University and Leiden University Medical Center, Leiden, the Netherlands

Maarten W. J. Koeter
Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

Henricus G. Ruhé
University of Amsterdam and University Medical Center Groningen, Groningen, the Netherlands

Steven D. Hollon
Vanderbilt University

Aart H. Schene
Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

Objective: The current study examined whether cognitive reactivity, cognitive extremity reactivity, and mood reactivity following mood provocation predicted relapse in depression over 5.5 years. Additionally, this study was the 1st to examine whether changes in cognitive reactivity and mood reactivity following preventive cognitive therapy (PCT) mediated the preventive effect of PCT on relapse. ***Method:*** One hundred eighty-seven remitted recurrently depressed outpatients were randomized over treatment as usual (TAU) versus TAU + PCT with 5.5-year follow-up. Relapse in depression was assessed with the Structured Clinical Interview for *DSM–IV* Axis I Disorders (Spitzer, Williams, Gibbon, & First, 1990). ***Results:*** Mood reactivity predicted time to relapse over 5.5 years. We found no evidence that cognitive reactivity was a risk factor for relapse in depression. Moreover, unprimed dysfunctional beliefs predicted relapse directly. There was no indication of mediation by changes in cognitive reactivity (including extremity of the beliefs and unprimed beliefs) or mood reactivity on the preventive effect of PCT. Further, explorative analyses revealed that increases in cognitive and mood reactivity over time also predicted time to relapse. ***Conclusions:*** Our findings highlight a need to focus on mood reactivity instead of beliefs as a risk factor for relapse in depression. Similar to a previous study, we found no indications that cognitive therapy after remission reduced dysfunctional beliefs, cognitive reactivity, or extremity. Future studies should examine cognitive reactivity and mood reactivity in daily life as predictors of relapse.

Keywords: major depressive disorder, dysfunctional belief, cognitive reactivity, relapse prevention, working mechanism cognitive therapy

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Gerard D. van Rijsbergen and Claudi L. H. Bockting, Department of Clinical Psychology, University of Groningen, Groningen, the Netherlands; Huibert Burger, Department of Epidemiology and Interdisciplinary Center for Psychiatric Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; Philip Spinhoven, Institute of Psychology, Leiden University, Leiden, the Netherlands, and Department of Psychiatry, Leiden University Medical Center, Leiden, the Netherlands; Maarten W. J. Koeter, Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; Henricus G. Ruhé, Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands, and Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; Steven D. Hollon, Department of Psychology, Vanderbilt University; Aart H. Schene, Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands.

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Correspondence concerning this article should be addressed to Claudi L. H. Bockting, University of Groningen, Department of Clinical Psychology, Grote Kruisstraat 2-1, 9712 TS Groningen, the Netherlands. E-mail: c.l.h.bockting@rug.nl

Major depressive disorder (MDD) is a mood disorder with immense consequences for patients and society, and is associated with substantially reduced quality of life stretching out far beyond remission (Judd et al., 2000; Plaisier et al., 2010; ten Doesschate, Koeter, Bockting, & Schene, 2010). The World Health Organization (WHO) estimated that by 2030, MDD will rank second in most disabling conditions worldwide (Mathers & Loncar, 2006).

Part of MDDs disabling effect is due to its high risk of relapse that can rise to 80% in the absence of adequate treatment (Mueller & Leon, 1999). Several risk factors for relapse have been identified, for example, early onset, number of previous episodes, residual symptoms, and episode severity (Burcusa & Iacono, 2007; Judd et al., 1998; Kennedy & Paykel, 2004; Paykel, Ramana, Cooper, & Hayhurst, 1995). Potentially modifiable risk factors have been reported as well—including the impact of daily hassles and life events, specific coping styles, decentering, and dysfunctional beliefs (Beshai, Dobson, Bockting, & Quigley, 2011; Bockting, Spinhoven, Koeter, Wouters, & Schene, 2006; Burcusa & Iacono, 2007; Fresco, Segal, Buis, & Kennedy, 2007; Jarrett et al., 2012; ten Doesschate, Bockting, & Schene, 2009).

Acute-phase cognitive therapy (A-CT) as well as preventive cognitive therapy (PCT) focus on presumed cognitive vulnerability factors of relapse, that is, underlying dysfunctional beliefs that are presumed to be latent in the remitted phase, but are easily activated by sad mood and thereby a trigger for depressive relapse. Cognitive therapy (CT) after remission, including mindfulness based cognitive therapy (MBCT), has shown to be an effective strategy in preventing relapse in depression (Guidi, Fava, Fava, & Papakostas, 2011; Piet & Hougaard, 2011; Vittengl, Clark, Dunn, & Jarrett, 2007). Relative risk reduction (RR) of relapse when CT after remission and MBCT were compared to non-active controls has been documented (RR reduction CT: 36% in 232 patients; RR reduction MBCT: 34% in 408 patients) and was especially prominent in patients with three or more previous major depressive episodes (MDEs; Piet & Hougaard, 2011; Vittengl et al., 2007). Enduring effects of CT that start after remission have been reported up to almost 6 years (Bockting, Spinhoven, Wouters, Koeter, & Schene, 2009; Fava et al., 2004).

Since dysfunctional beliefs appeared to be dependent on mood, both the *differential activation* hypothesis of Teasdale (1988) and the *mood state* hypothesis of Miranda and Persons (1988) shifted the focus from unprimed dysfunctional beliefs toward mood-linked activation of these beliefs (i.e., cognitive reactivity [CR]) as a risk factor for relapse in depression. Several studies have found support for the prediction of relapse by cognitive reactivity after remission from MDD (233 patients; Kuyken et al., 2010; Segal, Gemar, & Williams, 1999; Segal et al., 2006). Though, one recent study found no evidence for cognitive reactivity in patients remitted from MDD (Jarrett et al., 2012), whereas Lethbridge and Allen (2008) were unable to corroborate the predictive validity of cognitive reactivity (52 patients). Unfortunately methodological constraints limit the interpretation of these results. Only one of Segal's studies (Segal et al., 2006) randomized patients over treatment conditions. Moreover, interpretation of true mediation by change in cognitive reactivity is limited; both Segal et al. (1999) and Segal et al. (2006) were unable to examine pretreatment cognitive reactivity as they used currently depressed patient samples, and Kuyken et al. (2010) only measured post-treatment cognitive reactivity as well in their sample of remitted patients.

Besides reactivity of thought content, a dichotomous "black and white" thinking style (i.e., cognitive extremity [CE]) has also been related to relapse in depression (Beevers, Keitner, Ryan, & Miller, 2003; Petersen et al., 2007; Teasdale et al., 2001). Cognitive extremity predicted relapse during continuation phase and was found to increase the risk of relapse by a factor of 2.5 (Teasdale et al., 2001). However, other studies failed to find cognitive extremity to predict relapse (Beevers et al., 2003; Jacobs et al., 2010). Although we are unaware of any studies that investigated mood-linked change in cognitive extremity (i.e., cognitive extremity reactivity [CER]), mood-linked changes in explanatory flexibility (i.e., the flexibility or rigidity of assigning causes to certain events) have been examined (Fresco, Heimberg, Abramowitz, & Bertram, 2006; Fresco, Rytwinski, & Craighead, 2007). Following mood-provocation, explanatory flexibility decreased in participants with a history of MDD (Fresco et al., 2006).

In addition, changes in mood itself following mood provocation (i.e., mood reactivity [MR]) also appear to be related to relapse in depression (Ehring, Fischer, Schnülle, Bösterling, & Tuschen-Caffier, 2008; Ehring, Tuschen-Caffier, Schnülle, Fischer, & Gross, 2010; Lethbridge & Allen, 2008). This implies that the inability to effectively regulate affect during emotional or stressful events could signal the return of depressive symptomatology. Remitted patients who failed to show an adequate reduction in self-rated happiness after a sad mood provocation were at increased risk of relapse over 12 months (Lethbridge & Allen, 2008). This so called emotion context insensitivity (ECI) has been associated with poor psychosocial functioning and depression status later in time (Peeters, Berkhof, Rottenberg, & Nicolson, 2010; Rottenberg, Kasch, Gross, & Gotlib, 2002). Mood reactivity appears to reflect underlying stress susceptibility (Britton, Shahar, Szepsenwol, & Jacobs, 2012), in that mood reactivity to stressful events appears to be related to the onset of depressive symptoms (Cohen, Gunthert, Butler, O'Neill, & Tolpin, 2005).

Few studies have focused on the underlying mechanism of preventive CT after remission from MDD, and those that did focused on MBCT. Two studies had inconsistent results in examining rumination as a mediator of the effect of MBCT on depressive symptoms (Bieling et al., 2012; Shahar, Britton, Sbarra, Figueredo, & Bootzin, 2010). To date, only one study directly tested mediation by cognitive reactivity on the preventive effect of CT on relapse (Kuyken et al., 2010), which was unable to demonstrate that MBCT exerted its effects on relapse through post-treatment cognitive reactivity. One limitation of this study is the absence of baseline cognitive reactivity, limiting the interpretation of possible mediating effects. Finally, a recent study demonstrated partial mediation on the effect of MBCT on depressive symptoms by emotional reactivity following the Trier Social Stress Task (Britton et al., 2012). The current study is the first to examine whether changes in cognitive reactivity and mood reactivity mediate the preventive effect of PCT on relapse.

The present study is a secondary analysis of a randomized trial that investigated the effectiveness of PCT in preventing relapse in MDD up to 5.5 years after remission (Bockting et al., 2005, 2009). This study aims to examine whether (a) unprimed (latent) baseline cognitive vulnerability is predictive for relapse over 5.5 years; (b) cognitive reactivity, cognitive extremity reactivity, and mood reactivity are predictive for relapse over 5.5 years; (c) this reactivity is modifiable by brief PCT; and (d) changes in reactivity

following treatment mediate the effect of PCT on reducing risk of relapse.

Method

Participants

In order to participate in the current study, patients had to have (a) experienced two or more MDEs in the previous 5 years; (b) current remission of the last MDE for at least 10 weeks but no longer than 2 years, both defined according to the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM–IV*; American Psychological Association, 1994) and assessed with the Structured Clinical Interview for *DSM–IV* Axis I Disorders (SCID-I; Spitzer, Williams, Gibbon, & First, 1990) administered by trained interviewers; and (c) a current score of <10 on the Hamilton Depression Rating Scale ($HDRS_{17}$; Hamilton, 1960). Exclusion criteria were as follows: current mania, hypomania, a history of bipolar illness, any psychotic disorder (current and previous), organic brain damage, current alcohol or drug abuse, predominant anxiety disorder, recent electroconvulsive therapy (ECT), recent cognitive treatment or CT at the start of the study, or current psychotherapy with a frequency of more than twice a month. The protocol was approved by the institutional ethics review committees. See Bockting et al. (2005, 2009) for more details.

Design

Participants were screened for eligibility using the telephone version of the SCID-I. Current and past depressive episodes were checked at baseline and at five follow-up assessments (3, 12, 24, 36, and 66 months). Participants who met the inclusion criteria were randomly allocated to (a) treatment as usual (TAU) or (b) TAU + PCT. Randomization was performed using randomly permuted blocks in strata of study location and type of aftercare (general practitioner/psychiatric center/no aftercare).

Treatment

Preventive cognitive therapy. Participants in the experimental condition received eight weekly 2-hr sessions of PCT in groups of 7–12 patients. PCT is based on Beck, Rush, Shaw, and Emery's (1979) acute-phase CT (Bockting et al., 2005) and focused mainly on identification of negative thoughts and dysfunctional attitudes, and subsequent challenging of these attitudes using different cognitive techniques including Socratic dialogue (Bockting, 2009). Moreover, participants were encouraged to practice with alternative attitudes. They were also asked to keep a diary of positive experiences in order to enhance specific memories of positive experiences. In the final three sessions, relapse prevention strategies were formulated individually. Nine specifically trained psychologists, all fully trained as cognitive behavior therapists (minimum 5 years of training), delivered the intervention. All intervention group sessions were audiotaped to enable treatment integrity evaluation, using a checklist of all particular interventions. Treatment adherence was monitored between sessions, and any adherence or competence issues were resolved with the therapist prior to the subsequent session. This occurred only once, following an overlooked homework assignment.

Treatment as usual (TAU). TAU involved "naturalistic" care, that is, standard treatment (including primary care, specialty care and no treatment). There was no restriction on the use of antidepressant medication (ADM) during the period from entry through follow-up; however, actual ADM use was monitored.

Measures

Visual Analogue Scale (VAS). Patients rated their current mood on a Visual Analogue Scale (VAS) measuring 100 mm. The left end of the scale was labeled "happy," and the right end was labeled "sad."

Dysfunctional Attitude Scale (DAS). The 40-item Dutch adaptation of the DAS (Douma, 1991; Weissman, 1979) was used to examine levels of dysfunctional beliefs (e.g., rigid schemes or attitudes). Patients rated their agreement with the 40-items on a 7-point scale that ranged from *totally agree* to *totally disagree*. Two versions of the DAS (A and B) were used in the current study, and have previously been shown to have good reliability ($\alpha = .86$ and .87, respectively; Dozois, Covin, & Brinker, 2003). In the current study, both demonstrated excellent internal consistency ($\alpha = .94$) and were highly correlated ($r = .85$).

Mood provocation procedure. Patients completed a mood provocation procedure as described by Segal et al. (1999, 2006) following inclusion in the study. Patients listened to a piece of music by Prokofiev called "Russia under the Mongolian Yoke" from the movie Alexander Nevsky. The orchestral introduction of this musical piece was played at half speed on a tape recorder and patients were instructed to recall a time in their life when they felt sad. Patients first completed a VAS rating of sad mood and the DAS-A after which Prokofiev's piece was played for 10 min. Immediately thereafter, patients again completed a VAS rating and the DAS-B. An average mood change of at least 10% on the VAS is considered to indicate successful mood provocation (Martin, 1990; Segal et al., 2006). This procedure was repeated for all patients 3 months later.

Relapse/recurrence. Relapse has been defined as the re-emergence of the index episode of depression within 6 months after initial remission, whereas a recurrence is proposed to represent a new episode occurring after 12 months of recovery (Hollon, Stewart, & Strunk, 2006). Since we included patients in remission for at least 10 weeks but no longer than 2 years, we chose to adopt a conservative approach. Therefore, and for sake of readability, relapse refers to the return of a depressive episode. The main outcome measure, time to relapse, was assessed with the SCID-I. At the five follow-up assessments, current and MDEs preceding the follow-up point were checked for all patients. To keep the assessors blind to treatment condition, we instructed participants not to reveal this information to the interviewers. Kappa (κ) for interrater agreement on relapse between the interviewers and an independent psychiatrist, assessed over the follow-up period, ranged from .94 to .96, indicating excellent agreement.

Construct operationalization. Endorsement of dysfunctional beliefs (unprimed) was calculated by the sum score of all items on the baseline DAS. Extremity of these beliefs was the total number of *totally agree* and *totally disagree* responses on the DAS. Following mood provocation, cognitive reactivity was the change in DAS scores, cognitive extremity reactivity was the change in extreme responses, and mood reactivity was the change in score on

the VAS. On an exploratory basis, we examined the course of reactivity over time by subtracting pretreatment from post-treatment reactivity scores.

Statistical analyses. To examine the prediction of relapse by baseline unprimed dysfunctional beliefs (DAS-A) and cognitive extremity on the DAS-A (CE), we used survival analysis (i.e., Cox regression) with time to first relapse as main outcome. All analyses were done on an intention to treat (ITT; including all randomized patients) and completers (patients attending ≥5 PCT sessions) basis. Patients who dropped-out during follow-up or who did not relapse within 5.5 years were treated as censored in ITT and completers analyses, meaning that their information was usefully taken into account by the Cox model.

These analyses were then repeated separately with cognitive-, cognitive extremity- and mood-reactivity as predictors of relapse. We analyzed baseline, post-treatment and, on an exploratory basis, the course of reactivity measurements following PCT (posttreatment–pretreatment) in order to assess the mediating effect of PCT. In line with Segal et al. (2006), we used the saved standardized residuals (ZresDAS, ZresVAS, ZresExtremeResponses) from the linear regression of pre-induction on post-induction scores as the independent variable in the survival analysis to reduce the impact of baseline variability.

To assess whether PCT moderated the relation between the predictors and relapse, we examined Condition × Predictor interactions and Condition × Predictor × Previous MDEs interactions for all predictors, since in a previous study the number of previous MDEs was a moderator in the prediction of relapse (Bockting et al., 2005, 2009). If PCT was a significant moderator, then the survival analysis would have to be restricted to the control group only, otherwise the analysis could be performed on the complete sample. All models were checked for confounding effects of residual depressive symptoms ($HDRS_{17}$) and use of ADM.

Finally, we were interested in the mediating effect of changes in cognitive-, cognitive extremity-, and mood-reactivity on the effect of PCT on relapse in 5.5 years. Since the effectiveness of PCT depended on the number of previous MDEs with the cutoff point at four previous episodes (Bockting et al., 2005, 2009), its impact was examined in a subset of patients with four or more previous MDEs which included more than half the sample. The effect of PCT on the course of cognitive-, cognitive extremity-, and mood-reactivity was determined in three separate linear regression models in which we predicted $Zres_{post}$ with treatment condition and $Zres_{pre}$ as independent variables. The amount of mediation of the effect of PCT on relapse by the course of cognitive-, cognitive extremity-, and mood-reactivity was defined as the change in the magnitude of the effect of PCT on relapse when including the pretreatment to post-treatment change in the Cox model as independent variables. The amount of mediation was scaled as the relative change in the beta coefficient (log hazard ratio) for PCT, and was expressed as a percentage. In randomized trials this is often called the proportion of treatment effect explained (Freedman, Graubard, & Schatzkin, 1992). More than a 5% change in a regression coefficient when a covariate is added is generally considered substantial (Maldonado & Greenland, 1993).

As a previous study only used post-treatment cognitive reactivity as a mediator (Kuyken et al., 2010), we replicated these analyses with a Cox model including PCT, post-treatment cognitive reactivity, and PCT × Post-Treatment Cognitive Reactivity interactions only, with number of previous MDEs, gender, post-treatment $HDRS_{17}$, and mood reactivity as covariates (Kuyken et al., 2010). A significant interaction (PCT × CR) and main effect of cognitive reactivity would have indicated a mediating effect of cognitive reactivity (Kraemer, Wilson, Fairburn, & Agras, 2002).

Results

Patient Flow

In total, 187 formerly depressed patients were randomized. For the ITT analyses we excluded 15 patients (dropouts) in total—nine from TAU + PCT because they did not attend any session and six from TAU because they dropped out from the study immediately. The resulting 172 patients were analyzed on an ITT basis. Dropouts were slightly younger than the ITT group, $t(170) = -2.25$, $p = .03$, but did not differ on any of the other characteristics. For the Completers group ($n = 165$), we excluded an additional seven patients who attended less than five PCT sessions. Non-Completers were younger, $t(170) = -2.85$, $p = .005$, and had a lower score on the DAS, $t(170) = -2.01$, $p = .048$, than Completers. A previous study on this sample demonstrated that PCT, when added to TAU, was effective in reducing cumulative relapse risk over 5.5 years, Wald $\chi^2(1, N = 172) = 8.80$, $p = .003$, hazard ratio = 0.56. With the indicating cutoff being four previous MDEs, dichotomized number of previous MDEs (fewer than four vs. four or more) resulted in a significant interaction between treatment condition and number of previous MDEs, Wald $\chi^2(1, N = 172) = 7.76$, $p = .02$, hazard ratio = 0.379. The median survival time in patients with four or more previous MDEs was 713 weeks (TAU + PCT) compared to 205 weeks (TAU). PCT reduced cumulative relapse over 5.5 years from 95% (TAU) to 75% (TAU + PCT). The results were closely similar within the Completers group (Bockting et al., 2009).

Patient Characteristics

Demographic and clinical characteristics of the ITT group are summarized in Table 1. Patient groups did not differ on any of the demographic variables. Initial baseline DAS-A scores differed between conditions, $F(1, 170) = 4.023$, $p = .046$. The same differences were observed for post-treatment DAS-A and DAS-B scores: DAS-A, $F(1, 170) = 3.993$, $p = .047$; DAS-B, $F(1, 170) = 4.477$, $p = .036$. However, we controlled for initial DAS differences by using standardized residual DAS scores in our analyses. No baseline differences in CR, CER, or MR were revealed and neither did the level of CR, MR, or CER differ between patients who were on ADM versus patients who were not.

Mood Provocation

Mood provocation at both baseline and post-treatment was successful (average change was >10%; Martin, 1990), and increased sad mood according to the VAS with, respectively, 22.9 mm and 20.8 mm in the TAU and 21.3 mm and 17.2 mm in the TAU + PCT group (difference *ns* between groups).

Table 1
*Demographic and Clinical Characteristics (*N = *172)*

Variable	TAU (n = 84)	TAU + PCT (n = 88)
Characteristic[a]		
Female % (n)	73.8 (62)	72.7 (64)
Age	43.4 (9.8)	45.9 (9.1)
Previous episodes (median; IQR, No.[b])	3.0; 3.8, 2.8	4.0; 3.8, 2.9
Age of first onset	28.1 (12.5)	28.8 (12.6)
Patients on antidepressants % (n)	50.0 (42)	52.2 (46)
Cumulative relapse over 5.5 years[c] %	95 (79)	75 (82)
Median survival time over 5.5 years[d]	205.0 (502.0)	713.0 (502.0)
Pretreatment		
$HDRS_{17}$	3.7 (2.9)	3.8 (2.8)
DAS-A	129.4 (36.6)*	119.2 (29.4)*
DAS-B	122.4 (32.8)	114.4 (30.2)
CE	7.1 (9.0)	6.9 (6.6)
CR_{DAS}	−7.0 (14.8)	−4.8 (18.5)
CER_{DAS}	−1.4 (5.2)	−1.1 (4.4)
MR_{VAS}	2.3 (2.4)	2.1 (2.3)
Post-treatment		
$HDRS_{17}$	6.5 (6.1)**	4.0 (4.4)**
DAS-A	122.4 (32.2)*	113.4 (26.8)*
DAS-B	118.6 (29.8)*	109.8 (25.0)*
CR_{DAS}	−3.8 (16.2)	−3.6 (16.2)
CER_{DAS}	−1.4 (4.3)	−0.9 (4.8)
MR_{VAS}	2.1 (2.1)	1.7 (1.9)

Note. TAU = treatment as usual; PCT = preventive cognitive therapy; IQR = interquartile range; $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale; DAS-A = Dysfunctional Attitude Scale Form A; DAS-B = Dysfunctional Attitude Scale Form B; CE = cognitive extremity on the baseline DAS; CR = cognitive reactivity (post–pre induction DAS); CER = cognitive extremity responding reactivity (post–pre induction extremity DAS); MR = mood reactivity (post–pre induction Visual Analogue Scale [VAS]).
[a] All values represent M (SD) unless stated otherwise. [b] Average number of dichotomized previous episodes (two or three and more). [c] Cumulative relapse over 66 months in patients with four or more and, in parentheses, with less than four previous major depressive episodes (MDEs). [d] Median survival time in weeks for patients with four or more previous and, in parentheses, with less than four previous MDEs.
* $p < .05$. ** $p < .01$.

Interaction With Condition and Number of Previous MDEs

For each predictor, separate Cox models were fitted including the three-way interaction (Predictor × Condition × Previous MDEs) and, second, including the two-way interaction (Predictor × Condition). Since none of the interaction terms were significant and neither depressive residual symptoms, use of ADM, nor condition confounded the predictor of interest, interaction terms were subsequently dropped from the model, and Cox regression was fitted on the ITT sample (N = 172) for each predictor. Results on completers were not different from ITT and were therefore omitted from the results (in the online supplemental materials, see Tables I and II for interaction coefficients, and see Table III for completers).

Baseline Risk of Relapse: Unprimed Dysfunctional Beliefs and Cognitive Extremity

Cox regression revealed that dysfunctional beliefs but not cognitive extremity were predictive of time to relapse in 5.5 years: DAS-A, Wald $\chi^2(1, N = 172) = 12.294$, $p \leq .001$, hazard ratio = 1.01; CE, Wald $\chi^2(1, N = 172) = 1.663$, $p = .197$, hazard ratio = 0.99 (see Table 2). Increases in DAS-A by one unit increased prospective risk of relapse by 1%, and DAS-A remained a significant predictor when the number of previous MDEs and depressive symptoms were added to the model. Moreover, with cognitive reactivity already in the model, the DAS-A also remained a significant predictor of time to relapse.

Prediction of 5.5-Year Relapse by Cognitive Reactivity and Cognitive Extremity Reactivity

Including all 172 patients in the Cox regression, neither baseline cognitive reactivity nor cognitive extremity reactivity predicted time to relapse within 5.5 years: CR, Wald $\chi^2(1, N = 172) = 1.143$, $p = .285$, hazard ratio = 0.90; CER, Wald $\chi^2(1, N = 172) = 0.751$, $p = .386$, hazard ratio = 1.08. Moreover, baseline residuals for the DAS change score did not differ significantly between patients who relapsed within 5.5 years and patients who did not, $F(1, 170) = 2.292$, $p = .132$.

Table 2
Predictors of Time to Relapse Within 5.5 Years (ITT, N = *172)*

Variable	Predictor (β_1)
Pretreatment	
$DAS_{Form\ A}$	
β	0.008
SE (β)	0.002
p	0.000
CE	
β	−0.015
SE (β)	0.012
p	0.197
CR_{DAS}	
β	−0.101
SE (β)	0.094
p	0.285
CER_{DAS}	
β	0.073
SE (β)	0.084
p	0.386
MR_{VAS}	
β	0.021
SE (β)	0.084
p	0.807
Post-treatment	
CR_{DAS}	
β	0.134
SE (β)	0.092
p	0.147
CER_{DAS}	
β	0.015
SE (β)	0.083
p	0.854
MR_{VAS}	
β	0.241
SE (β)	0.084
p	0.004

Note. All predictors remain significant after applying a Bonferroni correction of α/8 = .006. ITT = intention to treat; $DAS_{Form\ A}$ = Dysfunctional Attitude Scale Form A; CE = cognitive extremity on the DAS before mood provocation; CR_{DAS} = cognitive reactivity on the DAS; CER_{DAS} = changes in cognitive extremity on the DAS following mood provocation; MR_{VAS} = mood reactivity on the Visual Analogue Scale.

Until now, only post-treatment cognitive reactivity had been examined (Kuyken et al., 2010; Segal et al., 1999, 2006). We therefore repeated previous analyses for post-treatment cognitive reactivity and cognitive extremity reactivity. Still, both were not predictive for time to relapse: CR, Wald $\chi^2(1, N = 172) = 2.103$, $p = .147$, hazard ratio = 1.14; CER, Wald $\chi^2(1, N = 172) = 0.034$, $p = .854$, hazard ratio = 1.02, and the residuals of the DAS change scores did not differ between patients who relapsed within 5.5 years and patients who did not, $F(1, 170) = 0.088$, $p = .767$.

Although the mood provocation was successful overall, sadness on the VAS did not increase with ≥10% in all patients. We therefore repeated the cognitive reactivity analyses while selecting patients on their level of increase in sadness on the VAS. The results did not change when we selected patients with an increase in sadness on the pretreatment VAS of at least 10% ($n = 121$, $p = .335$), and similarly of at least 20% ($n = 95$, $p = .709$), 30% ($n = 62$, $p = .825$), 40% ($n = 36$, $p = .975$), and 50% ($n = 20$, $p = .781$), respectively. Similar results were obtained for post-treatment cognitive reactivity, although we could only select patients with a mood change up to 40%, since the number of events (i.e., relapses) in the survival analysis was below 10 for patients with a mood change of 50% or more ($n = 9$; 4.8% of the sample).

Prediction of 5.5-Year Relapse by Mood Reactivity

Cox regression for change in negative mood following mood provocation revealed that baseline mood reactivity did not predict time to relapse within 5.5 years: MR, Wald $\chi^2(1, N = 172) = 0.059$, $p = .807$, hazard ratio = 1.02. Furthermore, no difference in relapse emerged between patients unresponsive to the mood provocation (i.e., no mood response or positive mood increase; $n = 26$; 77% relapse) and patients experiencing a negative mood ($n = 109$; 79% relapse) ($p = .455$, Fisher exact test).

At post-treatment, however, higher mood reactivity was predictive of time to relapse, Wald $\chi^2(1, N = 172) = 8.285$, $p = .004$, hazard ratio = 1.27.

Effect of PCT on Cognitive Reactivity and Mood Reactivity

In order to examine mediation by change in cognitive reactivity, cognitive extremity reactivity, and mood reactivity on the effect of PCT on relapse, we first examined whether the course (change over 3 months) of reactivity measurements was predictive of relapse. Patients who became increasingly mood reactive and cognitive reactive (but not cognitive extremity reactive) were at increased risk of relapse: CR, Wald $\chi^2(1, N = 172) = 6.765$, $p = .009$, hazard ratio = 1.25; MR, Wald $\chi^2(1, N = 172) = 6.853$, $p = .009$, hazard ratio = 1.25; CER, Wald $\chi^2(1, N = 172) = 0.348$, $p = .555$, hazard ratio = 0.96. However, after we selected patients with four or more previous MDEs (for mediation purposes), the course of reactivity measurements was no longer predictive of time to relapse.

Second, PCT was not related to changes in cognitive reactivity, cognitive extremity reactivity, or mood reactivity over time as putative mediators on the effect of PCT on relapse (see Figure 1), although PCT did prolong time to relapse in 5.5 years.

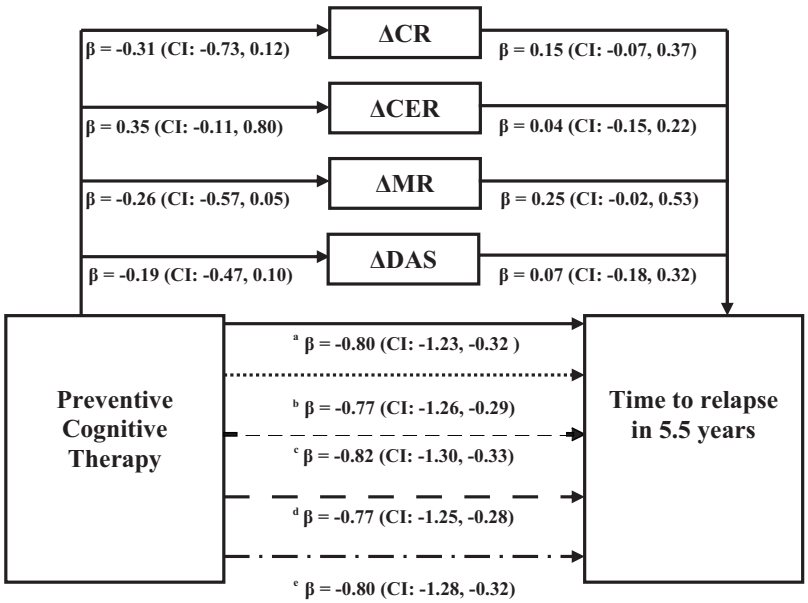

Figure 1. Four multiple regression mediation models in patients with four or more previous major depressive episodes. Change in cognitive reactivity (CR), cognitive extremity responding reactivity (CER), mood reactivity (MR), and Dysfunctional Attitude Scale (DAS) were entered separately. [a] Represents the direct effect. [b] Represents the β after ΔCR was added to the model (effects of preventive cognitive therapy [PCT] mediated by ΔCR = 3.1%). [c] Represents the β after ΔCER was added to the model (effects of PCT mediated by ΔCER = –2.3%). [d] Represents the β after ΔMR was added to the model (effects of PCT mediated by ΔMR = 3.9%). [e] Represents the β after ΔDAS was added to the model (effects of PCT mediated by ΔDAS = −0.3%).

Relative changes in beta's when adding ΔCR, ΔCER, and ΔMR separately to the model with PCT alone were small and ranged between 3.1 and 3.9%, indicating that the relation between PCT and time to relapse was not mediated by change in cognitive reactivity, cognitive extremity reactivity, or mood reactivity. Additionally, we examined whether change in unprimed (latent) dysfunctional beliefs possibly mediated the preventive effect of PCT. Mediation by unprimed dysfunctional beliefs was also not supported by our analyses (change in beta PCT = −0.3%). Similar results were obtained for completers. Finally, we also replicated previous mediation analysis with post-treatment cognitive reactivity only (Kuyken et al., 2010). Again, no indications for mediation were found (see Table IV in the online supplemental materials).

Discussion

To our knowledge, this was the first study that prospectively examined the combination of primed and unprimed cognitive and emotional vulnerability as risk factors for relapse over 5.5 years. Moreover, we are unaware of any studies that examined whether changes in cognitive and emotional vulnerability mediated the effect of PCT in preventing relapse over 5.5 years.

Our findings show that mood reactivity instead of cognitive reactivity and cognitive extremity reactivity predicted relapse over 5.5 years. Further, unprimed dysfunctional beliefs predicted relapse directly, whereas unprimed cognitive extremity did not. We found no indication that cognitive reactivity mediated the effect of PCT, which is in line with findings of Kuyken et al. (2010) using MBCT. Finally, neither cognitive extremity reactivity, nor mood reactivity or unprimed dysfunctional beliefs mediated the preventive effect of PCT on relapse. Explorative analyses revealed that the course of both cognitive reactivity and mood reactivity (i.e., increases in reactivity) was predictive of time to relapse.

Our finding that mood reactivity predicted relapse over 5.5 years supports findings of several other studies, although their follow up was restricted to a maximum of 12 months (Lethbridge & Allen, 2008; Rucci et al., 2011). Especially an increase in negative mood (i.e., self-rated sadness) was predictive of relapse. Lethbridge and Allen (2008) found that the absence of positive mood decrease following mood provocation was predictive of 12-month relapse. Recent studies on mood reactivity in depression highlight the role of daily stress as a provoking factor for mood reactivity and relapse in depressive symptomatology and highlight the role of measuring mood reactivity in daily life (Bockting et al., 2006; Britton et al., 2012; Bylsma, Taylor-Clift, & Rottenberg, 2011; Peeters et al., 2010; ten Doesschate et al., 2009). We speculate that patients who are highly reactive when confronted with a sad or very stressful event might be more susceptible to experiencing negative affect, in turn making them more vulnerable for relapse. This is in line with previous studies that reported evidence for the role of daily hassles and for the ability of lower severity life-events to predict relapse and recurrence (Bockting et al., 2006; Cohen et al., 2005; Monroe & Harkness, 2005; Stroud, Davila, Hammen, & Vrshek-Schallhorn, 2011). Future studies should attempt to unravel the link between mood reactivity and daily stress further.

The finding that cognitive reactivity does not play a role as risk factor for relapse is in line with a previous study that was unable to demonstrate that cognitive reactivity predicted relapse over 12 months in a community sample (Lethbridge & Allen, 2008). Nevertheless, there is also supportive evidence for cognitive reactivity as a vulnerability factor for relapse (Kuyken et al., 2010; Segal et al., 1999, 2006). Explorative analyses revealed that the course of cognitive reactivity over time was also predictive of relapse (i.e., patients with increases in cognitive reactivity over time were more at risk). Cognitive reactivity might have to be assessed repeatedly to detect its impact on relapse. Since no other study reported on the course of cognitive reactivity, no firm conclusions can be drawn and replication is required. Moreover, since the current study and many previous studies found support for the prediction of relapse by unprimed dysfunctional beliefs directly (Jarrett et al., 2012; Rush, Weissenburger, & Eaves, 1986; Simons, Murphy, Levine, & Wetzel, 1986; Thase et al., 1992), the practical question is raised why one would use a complicated repeated mood provocation instead of a single questionnaire (the DAS) in order to determine vulnerability for relapse.

Our findings question the assumption that dysfunctional beliefs have to be activated in the remitted phase to act as a vulnerability factor (Miranda & Persons, 1988; Teasdale, 1988). Although we found significant average change in dysfunctional beliefs following both mood provocations (pretreatment: 5.9 points decrease, post-treatment: 3.7 points decrease; *ns* between conditions), in line with previous studies (Kuyken et al., 2010; Lethbridge & Allen, 2008; Miranda, Gross, Persons, & Hahn, 1998; Segal et al., 1999; Van der Does, 2002, 2005), other studies did not (Jarrett et al., 2012; Miranda & Persons, 1988). Moreover, differential dysfunctional belief activation between remitted patients and never depressed controls remains controversial (Brosse & Craighead, 1999; Dykman, 1997; Fresco et al., 2006; Miranda et al., 1998; Otto et al., 2007; Silverman, Silverman, & Eardley, 1984).

Finally, we found no indications for a modifying effect of PCT on changes in dysfunctional beliefs (i.e., cognitive reactivity and extremity reactivity) or mood reactivity, and moreover, no evidence that changes in these reactivity measures mediated the effect of PCT on reducing the risk of relapse. Yet, the preventive CT used in this study was found to be effective in increasing survival time and reducing cumulative relapse risk up to 5.5 years (Bockting et al., 2005, 2009). Studies on potential mediators of CT after remission have so far provided mixed results (Bieling et al., 2012; Britton et al., 2012; Kuyken et al., 2010; Shahar et al., 2010). Unfortunately, like the before mentioned studies, we were also unable to pinpoint a mediator of the effect of CT after remission. It is therefore currently still unknown how CT after remission exerts its effects on relapse and recurrence.

The current study has several limitations. Differences in cognitive reactivity between the current study and previous studies could relate to differences in patient samples. Our sample consisted of highly recurrent depressed patients currently in remission (M = 6.5 previous MDEs, compared to Ms = 4.8, 1.9, and 6.1 in Segal et al., 1999; Lethbridge & Allen, 2008; and Kuyken et al., 2010, respectively). Particularly the sample of Segal et al. (2006) differed in number of previous MDEs (average of dichotomized 1 vs. 2 or more previous MDEs was 1.69, compared to 2.81 in our sample). For highly recurrent patients, vulnerability factors might be different than for patients with fewer episodes (Bockting et al., 2006; Daley, Hammen, & Rao, 2000; Lewinsohn, Allen, Seeley, & Gotlib, 1999). Finally, the question remains whether laboratory-induced sadness is generalizable to elicited sad mood in daily life,

and what this contributes to our knowledge about vulnerability factors for relapse.

In sum, the current study indicated that mood reactivity after mood provocation predicted relapse in depression while cognitive reactivity did not. Since unprimed dysfunctional beliefs did predict time to relapse directly, the clinical usefulness of a repeated mood provocation over a single DAS questionnaire is questioned. Future studies in this area should focus not only on the experience of daily sad mood and on the role of stress as a provoking factor of mood reactivity, but also on the meaning of the course of cognitive reactivity (i.e., changes in reactivity over time).

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