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Cognitive Reactivity Versus Dysfunctional Cognitions and the Prediction of Relapse in Recurrent Major Depressive Disorder

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ABSTRACT

Objective: Major depressive disorder (MDD) is a burdensome disease that has a high risk of relapse/recurrence. Cognitive reactivity appears to be a risk factor for relapse. It remains unclear, however, whether dysfunctional cognitions alone or the *reactivity* of such cognitions to mild states of sadness (ie, cognitive reactivity) is the crucial factor that increases relapse risk. We aimed to assess the long-term predictive value of cognitive reactivity versus dysfunctional cognitions and other risk factors for depressive relapse.

Method: In a prospective cohort of outpatients (N = 116; studied between 2000–2005) who had experienced ≥ 2 previous major depressive episodes (MDEs) and were in remission (*DSM-IV*) at the start of follow-up, we measured cognitive reactivity, with the Leiden Index of Depression Sensitivity (LEIDS), and dysfunctional cognitions, with the Dysfunctional Attitudes Scale, simultaneously. Course of illness (with the primary outcome of MDE assessed by the Structured Clinical Interview for *DSM-IV* Axis I Disorders Patient Edition) and time to relapse were monitored prospectively for 3.5 years.

Results: Cognitive reactivity scores were associated with time to relapse over the 3.5-year follow-up and also when corrected for the number of previous MDEs and concurrent depressive symptoms (hazard ratio for 1 standard deviation [(HR_{SD}); 20 points of the LEIDS, measuring cognitive reactivity] = 1.47; 95% CI, 1.04–2.09; $P = .031$). Rumination appeared to be a particularly strong predictor of relapse ($HR_{SD} = 1.60$; 95% CI, 1.13–2.26; $P = .007$). Dysfunctional cognitions did not predict relapse over 3.5 years ($HR_{SD} = 1.00$; 95% CI, 0.74–1.37; $P = .93$). Every 20-point increase on the cognitive reactivity scale resulted in a 10% to 15% increase in risk of relapse (corrected for previous MDEs and concurrent depressive symptoms).

Conclusions: Cognitive reactivity—and particularly rumination—is a long-term predictor of relapse. Future research should address whether psychological interventions can improve cognitive reactivity scores and thereby prevent depressive relapses.

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In the treatment of major depressive disorder (MDD), the challenge of preventing relapse might be even greater than the challenge of treating acute episodes. In secondary health care settings, the rate of relapse and recurrence over a 5-year period (both referred to as *relapse* hereafter) can be as high as 80%.[1] Cognitive theory states that so-called dysfunctional cognitions are the key factors that cause and maintain depressive episodes,[2] but evidence is equivocal. While some studies report higher levels of dysfunctional cognitions in remitted depressed patients,[3,4] others failed to find differences.[5] The same holds for longitudinal research: Dysfunctional cognitions predicted relapse in some studies[3,4,6–9] but not consistently.[10,11] Additionally, when assessing dysfunctional cognitions, content instead of form should be taken into consideration. In 1 study, the Dysfunctional Attitudes Scale (DAS) scores only predicted relapse when controlling for extreme responding style.[12] Furthermore, prediction may depend on depression history; lower associations with relapse were observed in patients with more previous episodes.[13]

When dysfunctional cognitions are not measurable during remission, they may exist in a latent state, prone to reactivation by life events,[14] daily hassles, or dysphoric mood states.[15,16] This shifts the focus from unprimed dysfunctional cognitions toward the mood-linked activation of these beliefs—cognitive reactivity. Cognitive reactivity is typically assessed by measuring changes in dysfunctional cognitions before and after a sad mood induction. Higher levels of cognitive reactivity are associated with a higher risk of depressive relapses.[17–19] However, nonreplications exist,[5,6] and differential activation of dysfunctional cognitions versus never-depressed controls remains controversial.[11,20–22] Moreover, van Rijsbergen et al[6] recently reported that changes in dysfunctional cognitions after a mood induction could not predict relapse over a 5.5-year follow-up period, while unprimed dysfunctional cognitions directly predicted relapse.

Furthermore, application of a complicated mood induction may not be feasible in clinical settings, and approximately 25% of participants do not respond to the procedure, precluding assessment of cognitive reactivity.[23] The Leiden Index of Depression Sensitivity (LEIDS)[15] provides clinicians with a measure of

Clinical Points

- Relapse of a depressive episode occurs often in major depressive disorder; accurate prediction of relapse risk is clinically needed.
- Cognitive reactivity (mood-linked activation of dysfunctional cognitions) represents a subject's vulnerability to relapse and can be measured by the Leiden Index of Depression Sensitivity (LEIDS).
- We quantify how relapse rates can be predicted by a combination of concurrent depressive symptoms of depression, previous number of depressive episodes, and the LEIDS score.

cognitive reactivity, independent of mood induction. Participants are instructed to imagine feeling somewhat sad and to indicate their agreement on statements describing thoughts and behaviors during sad moods. LEIDS scores correlated highly with cognitive reactivity scores measured by mood induction.[15] The consistency of research using the LEIDS is higher than research investigating (unprimed) dysfunctional cognitions or research using mood inductions, so it may be considered a preferred measure of cognitive reactivity. In at least 6 studies, LEIDS and LEIDS-revised (-R) scores distinguished previously depressed from never-depressed groups.[15,23,24,25,26,27] LEIDS-R scores correlated with biological markers of depression vulnerability[28,29] and predicted first onsets of depression.[30] No study has yet investigated whether LEIDS scores predict relapses in a clinical sample of remitted depressed patients.

We, therefore, tested the predictive properties of the LEIDS (measuring cognitive reactivity), its subscale scores, and unprimed dysfunctional cognitions over a 3.5-year follow-up period against 2 established predictors: number of previous episodes (MDEs)[1,31–33] and concurrent/residual depressive symptoms.[33–35]

We hypothesized that cognitive reactivity, measured by the LEIDS, predicts time to relapse, as it appears to be a consistent measure of cognitive reactivity. We expected dysfunctional cognitions to predict relapse, as found in the same study population, but at a different timepoint; dysfunctional cognitions predicted relapse over 5.5 years.[6]

METHOD

Design

After obtaining approval by the local ethics committee and written informed consent from participants, we assessed cognitive reactivity, dysfunctional cognitions, and MDEs at the 2-year follow-up of a randomized trial that investigated the effectiveness of cognitive therapy in preventing relapse up to 5.5 years (ISRCTN Identifier: 68246470).[36] We measured depressive relapse over the next 3.5 years (see Supplementary eFigure 1 at Psychiatrist.com).

Participants

For inclusion in the original study (conducted between 2000–2005), participants (N = 187) had to be in remission (no MDE according to the Structured Clinical Interview for *DSM-IV* Axis I Disorders Patient Edition [SCID-I/P][37] and have a 17-item Hamilton Depression Rating Scale [HDRS][38] score < 10) and had to have experienced ≥ 2 MDEs during the preceding 5 years. Participants were randomly assigned to 8 weeks of preventive cognitive therapy or treatment-as-usual.[36] Preventive cognitive therapy participants received 8 weekly 2-hour group sessions, as described before.[36] Treatment-as-usual involved naturalistic care, ie, standard treatment (including primary care, specialty care, or no treatment). After 8 weeks, all participants received treatment-as-usual. There was no restriction of antidepressant use. In order to predict relapse, we examined currently remitted participants (SCID-I/P) at 2-year follow-up after preventive cognitive therapy. We assessed cognitive reactivity and the other predictors and examined relapses within a 3.5-year follow-up.

Study Measures

Depression. Primary outcome was the occurrence of an MDE (assessed by the SCID-I/P) in the 3.5-year follow-up period. The number of previous episodes was also assessed with the SCID-I/P by adding the number of self-reported earlier MDEs from the interview before randomization and the number of MDEs assessed over the first 2 years thereafter. Severity of remaining symptoms was assessed with the HDRS.[38]

Cognitive reactivity. Cognitive reactivity was measured with the 34-item, self-reported LEIDS.[15,23] Participants rate the degree to which their thinking changes during an imagined dysphoric mood on a 5-point Likert scale (totally disagree to completely agree). We used the original LEIDS[15] with its 4 subscales (Negative Self-Evaluation, Acceptance/Coping, Indifference, Risk Aversion/Harm Avoidance), plus the Rumination subscale (see Supplementary Method).

Dysfunctional cognitions. The 40-item, self-reported DAS[39] measures dysfunctional cognitions. DAS items are rated on a 7-point Likert scale (totally agree to totally disagree).

Statistical Analysis

The association of cognitive reactivity (LEIDS total and subscale scores) with relapse was investigated with Cox regression models, with time to first relapse as endpoint. Participants lost to follow-up or without relapse during follow-up were considered censored. As half of our sample had received preventive cognitive therapy at study entry, we first determined whether preventive cognitive therapy modified the relation between cognitive reactivity and relapse. If so, all analyses on cognitive reactivity should be restricted to the control group (treatment-as-usual). Effect modification was assessed by testing the treatment condition (preventive cognitive therapy/treatment-as-usual) by LEIDS interaction. Considering that the number of previous MDEs was an independent moderator of the effect of preventive cognitive therapy on relapse,[6,36] the 3-way treatment condition by LEIDS by MDEs interaction was also analyzed.

Table 1. Demographic and Clinical Characteristics of Study Population (N = 116)

Characteristic	TAU Group (n = 54)	PC T Group (n = 62)	Total[a] (N = 116)	Statistical Significance[b]
Female sex, n (%)	46 (85.2)	43 (69.4)	89 (76.7)	< .05
Age, mean ± SD, y[a]	43.4 ± 9.16	45.8 ± 8.56	44.7 ± 8.89	NS
Median number of previous episodes at randomization (IQR)	3.0 (2–5)	4.0 (3–6)	3.5 (3–6)	< .05[c]
Education level (A/B/C), %[d]	28/39/33	32/31/37	30/35/35	NS
HDRS, mean ± SD[a]	4.6 ± 4.13	4.6 ± 4.26	4.6 ± 4.18	NS
BDI, mean ± SD[a]	6.9 ± 6.01	6.4 ± 6.19	6.6 ± 6.10	NS
DAS version A, mean ± SD[a]	112.5 ± 30.05	108.5 ± 24.96	110.3 ± 27.40	NS
LEIDS score, mean ± SD[a]	39.0 ± 19.50	40.9 ± 21.00	40.0 ± 20.25	NS
Patients with LEIDS score ≤ 40, n (%)[e]	28 (51.9)	31 (50.0)	59 (50.9)	NS
Negative self-evaluation, mean ± SD	10.4 ± 6.56	10.9 ± 7.00	10.6 ± 6.78	NS
Acceptance, mean ± SD	1.7 ± 2.59	1.6 ± 2.24	1.7 ± 2.40	NS
Indifference, mean ± SD	9.1 ± 4.50	9.4 ± 5.39	9.3 ± 4.98	NS
Risk aversion, mean ± SD	7.5 ± 5.00	7.9 ± 5.12	7.7 ± 5.05	NS
Rumination, mean ± SD	9.6 ± 6.21	10.6 ± 5.78	10.2 ± 5.98	NS
≥ 1 Relapse in 3.5-year follow-up, n (%)	28 (51.9)	29 (46.8)	57 (49.1)	NS

[a]At 2 years after randomization (N = 116), consisting of the TAU and PCT groups.
[b]Independent samples *t* tests unless indicated otherwise.
[c]Based on log-transformed values.
[d]Education level (completed at high school): A = pre-university education, B = higher general secondary education, C = lower general secondary education.
[e]Median LEIDS score = 40.
Abbreviations: BDI = Beck Depression Inventory, DAS = Dysfunctional Attitudes Scale, HDRS = Hamilton Depression Rating Scale (17 items), IQR = interquartile range, LEIDS = Leiden Index of Depression Sensitivity, NS = nonsignificant, PCT = preventive cognitive therapy, TAU = treatment-as-usual.

If neither was significant, the total sample could be used.

To assess the predictive value of the LEIDS total (and to conduct an exploratory analysis of its subscale scores) for depressive relapse over a 3.5-year follow-up period, we used a 2-step procedure: (1) a Cox regression analysis with only the LEIDS as predictor adjusted for gender and treatment condition and (2) a Cox regression with concurrent depressive symptoms (HDRS) and previous episodes of MDD as additional predictors plus the treatment condition by LEIDS and previous episodes by LEIDS interactions. In case an interaction was not significant, this interaction was removed from step 2. We used a similar approach for the DAS and LEIDS subscales.

To develop a clinical tool to determine the risk of future relapse based on the LEIDS scores, we used logistic regression and assessed the change in risk of relapse by every 20-point (approximately 1 standard deviation [SD]) increase on the LEIDS score (see Supplementary Method). Although Cox regression provides a more valid analysis for longitudinal follow-up, logistic regression analysis is expected to be a reasonable alternative if (1) the number of patients lost to follow-up is small and (2) the focus is whether patients relapse (yes/no) within the 3.5-year follow-up period.

Because the number of previous MDEs was not normally distributed, we used the natural logarithm transformed value. We used IBM-SPSS v19.0. Threshold for significance was < .05. Hazard ratios (HRs) are reported for 1 SD change (HR_{SD} = 20 points in LEIDS); 95% confidence intervals are reported, unless indicated otherwise.

RESULTS

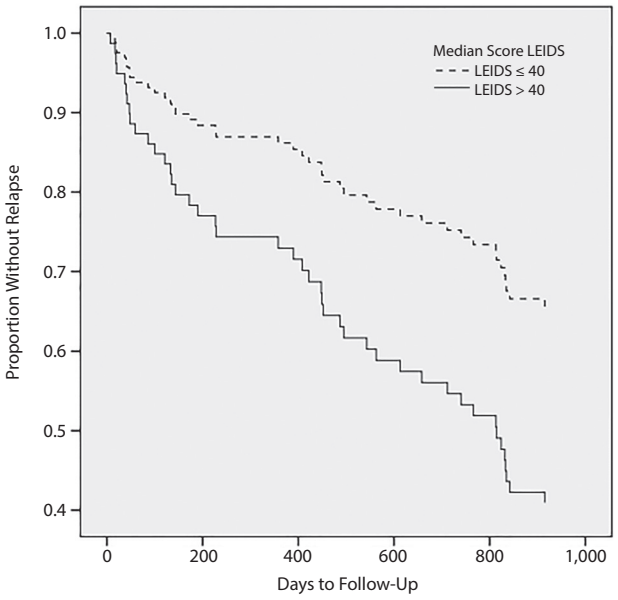
Of the 187 participants originally included,[36] 153 were not depressed at the 2-year follow-up. Of these, 25 participants did not complete the LEIDS and 12 were lost during the 3.5-year follow-up, leaving 116 nondepressed participants for analyses (Table 1). Fifty-nine of these 116 participants (50.9%) did not have a relapse in the previous 2 years. Demographic and clinical characteristics of excluded participants (n = 37) did not statistically differ from those of participants included in the present analyses (N = 116). Of these 116 participants, 62 were previously treated with preventive cognitive therapy and 54 with treatment-as-usual. These participants from the original randomization groups were comparable on demographic and illness characteristics, except that former preventive cognitive therapy participants experienced more MDEs (median = 4.0 vs 3.0, respectively; $P = .043$) and consisted of fewer women (85.2% vs 69.4%, respectively; $P = .041$) than did treatment-as-usual participants. The mean LEIDS score of the pooled sample was 40.0 ± 20.3 (range, 2–93). The groups did not differ on LEIDS total ($P = .61$), LEIDS subscales (all P values > .39), and DAS scores ($P = .41$). Thus, almost 2 years after having received either treatment-as-usual or preventive cognitive therapy, the groups were comparable in terms of cognitive reactivity.

Cognitive Measures and Time to Relapse

Of the 116 nondepressed participants, 57 (49.1%) experienced at least 1 MDE during the 3.5-year follow-up. Earlier treatment condition did not modify the relation between LEIDS and relapse. Neither the treatment condition × predictor interaction nor the 3-way treatment condition × predictor × MDEs interaction was significant (all P values > .82; Cox regression). Therefore, all analyses were performed on the total sample (N = 116).

The LEIDS predicted time to relapse of depression in 3.5 years, correcting for gender and treatment condition

Figure 1. Relapse Within 1,000 Days Over 3.5 Years of Follow-Up for Low/High LEIDS Scores[a]



[a]Survival curves for time to relapse of participants with LEIDS score ≤ 40 (n = 59; upper dashed line) vs LEIDS score > 40 (n = 57; lower solid line), while controlling for gender, treatment condition, number of previous depressive episodes, and HDRS score (hazard ratio = 2.119 (95% CI, 1.111–4.032; Wald = 5.20; $P = .023$).
Abbreviations: HDRS = Hamilton Depression Rating Scale (17 items), LEIDS = Leiden Index of Depression Sensitivity.

($HR_{SD} = 1.35$ [CI, 1.04–1.79]; Wald = 4.88; $P = .027$). Despite a correlation of the LEIDS with concurrent depressive symptom severity ($r = 0.27$; $P = .007$), this effect remained after controlling for previous MDEs and concurrent depressive symptoms ($HR_{SD} = 1.47$ [CI, 1.04–2.09]; Wald = 4.63; $P = .031$; entered together or separately); confounders were not significant (all P values > .24). Interactions of LEIDS by number of previous episodes or treatment were nonsignificant (all P values > .95; see Supplementary eTable 1).

Although LEIDS scores (measuring cognitive reactivity) were moderately correlated with DAS scores (measuring dysfunctional cognition) assessed at the same visit ($r = 0.45$; $P < .001$), Cox regression analysis showed that DAS scores did not significantly predict relapse ($HR_{SD} = 1.12$ [CI, 0.85–1.50], corrected for condition and gender). Results did not change after additional correction for concurrent depressive symptoms and previous MDEs ($HR_{SD} = 1.000$ [CI, 0.74–1.37]; entered together or separately). DAS scores by number of previous episodes or by treatment interactions were nonsignificant (all P values > .26; see Supplementary eTable 1).

We compared participants with relatively low cognitive reactivity (LEIDS ≤ 40 points; 50.9%; median split) to those with relatively high scores. Cox regression showed that participants with high cognitive reactivity scores had a more than 2-fold increased risk of relapse within 1,000 days in the next 3.5 years (HR = 2.12 [CI, 1.111–4.032]; Wald = 5.20; $P = .023$; Figure 1). The effects of treatment condition, previous MDEs, concurrent depressive symptoms, and gender were controlled for in this analysis.

Cox regression, controlling for treatment condition, gender, concurrent depressive symptoms, and previous MDEs, revealed that the LEIDS subscales Negative Self-Evaluation ($HR_{SD} = 1.21$ [CI, 0.86–1.71]), Acceptance ($HR_{SD} = 0.80$ [CI, 0.57–1.14]), and Harm Avoidance ($HR_{SD} = 1.32$ [CI, 0.97–1.80]; Wald = 3.12; $P = .077$) did not predict depressive relapse. However, the Indifference ($HR_{SD} = 1.48$ [CI, 1.10–1.99]; Wald = 6.62; $P = .010$) and the Rumination ($HR_{SD} = 1.60$ [CI, 1.13–2.26]; Wald = 7.21; $P = .007$) subscales in exploratory analysis appeared to be somewhat stronger predictors than the total LEIDS score. For both of these subscales, we found no interaction with previous episodes (all P values > .63).

Effect of Increases in Cognitive Reactivity on the Risk of Relapse

In the logistic regression model, only the LEIDS score was a significant predictor of depressive relapse in this model (odds ratio [OR] = 1.031 [CI, 1.005–1.058]; Wald = 5.57; $P = .018$). We determined the goodness of fit of models with fewer variables by using the log-likelihood ratios. The most parsimonious model included the LEIDS score (OR = 1.032 [CI, 1.006–1.058]; Wald = 5.99; $P = .014$), concurrent depressive symptoms (OR = 1.061 [CI, 0.995–1.180]; Wald = 1.22; $P = .270$), and previous MDEs (OR = 1.049 [CI, 0.972–1.133]; Wald = 1.51; $P = .220$).

According to this model, we determined the increase in risk of relapse by increasing the LEIDS score, while keeping other conditions (previous MDEs or concurrent depressive symptoms) constant. A 20-point increase on the LEIDS score (≈ 1 SD) resulted in a 10% to 15% increase in predicted relapse rate, being dependent on concurrent depressive symptoms and previous MDEs (Table 2).

DISCUSSION

Our findings show that cognitive reactivity predicts relapse over a 3.5-year follow-up period, after controlling for established predictors (previous depressive episodes and concurrent/residual depressive symptoms). Although assessed exploratorily, the Rumination subscale of cognitive reactivity appears particularly relevant in the prediction of future relapses. Contrary to previous analyses, unprimed dysfunctional cognitions did not predict relapses at this timepoint.

Cognitive Reactivity as a Predictor of Relapse

Our findings corroborate evidence for cognitive reactivity as a stable risk factor for future relapse.[17–19] Although we convincingly report that high LEIDS scores are significantly predictive of future relapse above concurrent depressive symptoms and previous MDEs (the most robust clinical predictors of relapse[18]), 2 previous reports (using a mood induction) proposed that cognitive reactivity does not represent a vulnerability factor. In a community

Table 2. Prediction of Risk of Relapse of a Major Depressive Episode for Different Levels of LEIDS Scores, Number of Previous Depressive Episodes, and Concurrent Depressive Symptoms[a]

LEIDS Score	Depressive Symptoms[b]	No. of Previous Major Depressive Episodes		
		2	5	10
10	2	**17.8** (8.9–32.5)	**20.0** (10.6–34.6)	**24.1** (12.8–40.8)
	5	**20.5** (10.4–36.5)	**23.0** (12.3–38.9)	**27.5** (14.8–45.6)
	10	**25.8** (11.6–48.1)	**28.7** (13.5–51.0)	**33.7** (15.9–58.1)
30	2	**28.8** (18.8–41.3)	**31.8** (22.5–42.9)	**37.2** (26.2–49.7)
	5	**32.6** (22.4–44.6)	**35.8** (26.4–46.4)	**41.5** (30.2–53.8)
	10	**39.4** (24.2–57.0)	**42.9** (27.7–59.6)	**48.9** (31.5–66.5)
50	2	**43.0** (29.9–57.2)	**46.6** (34.7–58.8)	**52.6** (39.6–65.2)
	5	**47.4** (35.6–59.6)	**51.0** (40.7–61.1)	**57.0** (45.4–67.8)
	10	**54.9** (39.0–69.8)	**58.4** (43.6–71.9)	**64.1** (48.0–77.5)
70	2	**58.5** (37.9–76.5)	**61.9** (42.6–78.1)	**67.4** (48.2–82.2)
	5	**62.8** (44.2–78.2)	**66.1** (49.0–79.8)	**71.2** (54.3–83.8)
	10	**69.4** (50.0–83.7)	**72.4** (54.5–85.2)	**76.9** (59.3–88.4)
90	2	**72.5** (44.4–89.7)	**75.3** (48.9–90.6)	**79.5** (54.6–92.6)
	5	**75.9** (50.7–90.6)	**78.4** (55.1–91.5)	**82.2** (60.6–93.3)
	10	**80.9** (57.8–92.9)	**83.1** (61.9–93.7)	**86.2** (66.7–95.1)

[a]Table shows chances (%) and 90% confidence intervals for a relapse, based on an optimized logistic regression model including baseline LEIDS score (OR = 1.03 [CI, 1.01–1.06]), concurrent depressive symptoms (OR = 1.06 [CI, 0.96–1.18]), and number of previous episodes (OR = 1.05 [CI, 0.97–1.13]). Estimations from a sample of patients (N = 116) with recurrent MDD with at least 2 previous episodes at baseline with a prospective follow-up of 3.5 years. Colors indicate risk of relapse (yellow: 33.3%–50%; orange: 50%–75%; red > 75%).
[b]Score on Hamilton Depression Rating Scale (17 items).[35]
Abbreviations: LEIDS = Leiden Index of Depression Sensitivity, MDD = major depressive disorder, OR = odds ratio.

sample with a 12-month follow-up, Lethbridge and Allen[5] were unable to demonstrate that cognitive reactivity predicted relapse. Furthermore, in approximately the same study population as ours but with a 5.5-year follow-up, van Rijsbergen et al[6] previously reported that cognitive reactivity measured by a *change* in DAS score by sad mood induction was not predictive for depressive relapse over 5.5 years, while *unprimed* dysfunctional cognitions (DAS scores) predicted relapse. Possible explanations for these apparently contradictory results in approximately the same study sample could be as follows: (1) Cognitive reactivity was assessed at baseline in individuals who volunteered for a relapse-prevention trial and who could have been, by their own recognition of their risk for relapse, already primed with a sad mood, reflected by high DAS scores, before the mood induction, thus reducing its sensitivity and resulting in an association of unprimed DAS scores with relapse. At 2-year follow-up, this priming might have been lower, reducing the predictive effect of DAS scores on relapse; (2) by exclusion of participants with a concurrent relapse (n = 34) and dropouts partly due to online administration problems of the LEIDS (n = 25), there might be differences in vulnerability profiles of our sample at 2-year follow-up and the sample of van Rijsbergen et al[6] at baseline, which might have impacted the current outcomes; or (3) the LEIDS measures cognitive reactivity more reliably than a mood induction procedure with DAS assessments.

Cognitive Reactivity and Sad Mood Induction Procedures

A mood induction may not be a very stable measure to examine cognitive reactivity. Various methods exist to induce sad mood, among which are procedures that require subjects to read emotionally charged sentences,[40,41] listen to emotionally charged music,[42–44] or recall a time in their lives in which they experienced a specific emotion.[43,45] Little research addressed the validity of these methods to optimize sad mood induction.[46] As some studies found no evidence for cognitive reactivity or even reported a decrease in dysfunctional cognitions after sad mood induction,[3,47] future studies should compare (different) mood induction procedures with the LEIDS as predictors of relapse. Because the mood induction and the LEIDS were administered at different timepoints, we were unable to conduct this comparison. Nevertheless, the LEIDS appears to measure cognitive reactivity more reliably than a mood induction procedure,[15,23,24] and if the LEIDS in replication proves a stable predictor of relapse, complicated mood provocations become unnecessary.

Specificity of Cognitive Reactivity Subscales

The Rumination and the Indifference subscales appeared better predictors of relapse than the total LEIDS scale. Therefore, if our results are replicated, a reduction of the LEIDS to only these subscales may be more efficient to assess patients' risk of relapse.

Rumination is an established vulnerability factor for relapse in MDD.[2] Rumination (especially brooding[48]) prospectively predicted onset, severity, and duration of MDD[2] and was associated with relapses.[49,50] Cognitive reactivity assessed by the LEIDS-R was correlated with depressive rumination by the Ruminative Response Scale in a nonclinical sample.[24] Importantly, cognitive reactivity by the LEIDS-R made a unique contribution to the prediction of depression over and above rumination. This suggests that how one responds to a low mood is more important than solely the process of ruminative thoughts. In addition, there is evidence that rumination and cognitive reactivity are both linked to activity of the default mode network,[51] a neural circuit that is active when someone is awake but not actively involved in attentionally demanding tasks.[52] The default mode network comprises 2 subcomponents, the task-negative component, which processes internally focused attention, and the task-positive component, which is involved in task performance, both of which are highly linked but negatively correlated.[51] Rumination has been related to enhanced connectivity within the task-negative component and dominance of the task-negative component over the task-positive component of the default mode network.[51,53,54] Marchetti et al[51] proposed that the tendency toward task-negative dominance over task-positive persists in remitted MDD patients. The task-negative–task-positive imbalance might represent a habitual mode of trait-like ruminative thinking, still present in remitted MDD patients, which can be easily accelerated during stressful times and might initiate an acute phase of depression, all in association with cognitive reactivity and vulnerability

for relapse.[50,51] Taking these findings together, we hypothesize that the LEIDS and its Rumination scale might be highly correlated with this task-negative–task-positive imbalance, which might be a crucial biomarker for relapse.

Indifference (a lack of interest in others, negligence, and cynicism[15]) has not yet been studied as a vulnerability factor for relapse. Since our findings indicate that indifference could also be an important aspect of cognitive reactivity in the prediction of relapse, future studies should address this risk factor. Indifference might represent maladaptive avoidant coping, which was reported as a predictor of relapse.[13]

Limitations

This study has inevitable limitations. First, we included only nondepressed participants, yielding a smaller sample than that directly after the intervention,[6,36] potentially resulting in selection (participants at different risk for relapse) and decreased statistical power. Second, due to this modest sample size, testing the interaction term with the original preventive cognitive therapy intervention might have had limited power. Nevertheless, because estimates were small, we concluded that there are no effects of preventive cognitive therapy on the present predictors of relapse. This also suggests that preventive cognitive therapy does not change cognitive reactivity. This seems likely because, in the full study population, no differences in cognitive reactivity (measured by mood induction after the intervention phase) existed after preventive cognitive therapy versus treatment-as-usual.[6] Third, we included well-known but nonsignificant confounders in our analyses. Some might argue that these confounders are abundant, but we can now conclude that cognitive reactivity (measured by the LEIDS) might even outperform clinical risk factors (previous MDEs and residual symptoms). Fourth, by inclusion of only nondepressed participants in this assessment of cognitive reactivity, we excluded the possibility of bias (worse prediction when measured in depressed patients). Although this might be a strength, we do not yet know how cognitive reactivity can be measured in a depressed state in order to subsequently predict relapse. Fifth, due to measurements at different timepoints, we were unable to compare results of the LEIDS with changes in dysfunctional cognitions by mood induction or a visual analog mood scale as reported by van Rijsbergen and colleagues.[6,55] This needs further examination. Sixth, we could not reliably monitor treatments during follow-up, which might have impacted course of predictors. Seventh, we did not examine personality disorders, which predicted relapse in remitted MDD patients in a 6-year prospective study.[56] Finally, for clinical utility, we constructed a model that showed a 10% to 15% increased risk of relapse for every 20-point increase of the LEIDS. One should realize that this prediction, which is based on our patient sample and might not be generalizable to other populations or different time frames, requiring replication.

CONCLUSION AND IMPLICATIONS

We show that cognitive reactivity significantly predicted future relapse, in addition to the known clinical variables, MDEs and residual depressive symptoms, in euthymic participants with recurrent MDD. This association corroborates cognitive reactivity as a cognitive vulnerability factor in recurrent MDD.[17–19] Our results have 3 important clinical implications: (1) cognitive reactivity can be assessed easily by the LEIDS and predicts relapse risk of depression over 3.5 years, (2) individualized care for recurrent MDD can be improved by application of this measure, and (3) prediction by the use of more specific aspects of cognitive reactivity (rumination and indifference) needs further investigation.

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Potential conflicts of interest: **Dr Van der Does** is the developer of the LEIDS and LEIDS-R. No other author reports conflicts of interest.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Cognitive Reactivity Versus Dysfunctional Cognitions and the Prediction of Relapse in Recurrent Major Depressive Disorder

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List of Supplementary Material for the article

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Supplemental information belonging to

Cognitive reactivity versus dysfunctional cognitions and the prediction of relapse in recurrent major depressive disorder

Caroline A. Figueroa, Henricus G. Ruhé, Maarten W. Koeter, Philip Spinhoven, Willem Van der Does, Claudi L Bockting and Aart H. Schene

Supplementary Method

Psychometrics of the Structured Clinical Interview for DSM-IV (SCID),[34] the Leiden Index of Depression Sensitivity (LEIDS)[15;23] and Dysfunctional Attitude Scale (DAS)[36]

The SCID assessments of relapse showed excellent interrater agreement between the interviewers and an independent psychiatrist (Kappa (κ) ranged from .94 to .96).

The Leiden Index of Depression Sensitivity has good psychometric properties and is a validated measure of CR.[15] The version of the LEIDS used in this paper is the original LEIDS plus an additional subscale, the rumination scale. Therefore, to justify the use of this structure with its 4+1 subscales, we conducted additional analyses to examine the structure of the questionnaire and the reliability of the subscales.

First, we conducted a Principle Components Analysis (PCA). PCA estimates the regression weights that best describe the inter-item correlations within the different factors. However, other regression weights may also explain a comparable proportion of variance, although less than the PCA regression weights. When we define factors that resemble the theoretical subscales (by using binary weights (i.e. weight of 1 for items that pertain to the subscale and 0 for all items that do not pertain to this factor) we can compare the explained variance of

these factors to the maximal possible explained variance (of the PCA solution). This method is comparable to conducting a Confirmatory Factor Analysis (CFA).
For the LEIDS, the subscales explained 48% of the variance of the factors, whereas PCA explained 53% of the variance. Although PCA performs better (which is by definition the case), our subscales performed in an almost comparable matter, indicating that the factor structure measures what it is supposed to measure, i.e. is a good reflection of the data. For this reason we feel that the factor structure of this version of the LEIDS, including the rumination scale can be used in our population.

In addition, we examined the reliability of the different subscales. The internal consistencies (Cronbach's alpha) of our the original 4 subscales was: 0.85 (Negative Self Evaluation), 0.64 (Acceptance), 0.72 (Indifference), 0.78 (Harm Avoidance). These reliabilities are all satisfactory and comparable with those reported by Van der Does et al. 2002, except the ACC subscale. In our population, ACC scores were less reflective of total LEIDS scores. This might be due to the differences between study populations of this study (with remitted patients in the present study) and the study by Van der Does (a population of healthy undergraduate students).[15] In addition and importantly, the reliability of the additional rumination subscale was high, with a Cronbach's alpha of 0.81. The internal consistency (Cronbach's alpha) of the total LEIDS questionnaire was 0.92, which is excellent.
The DAS also demonstrated excellent internal consistency (Cronbach's $\alpha = .94$).

Primary outcome and follow-up

The main outcome measure, time to relapse, was assessed with the SCID only. We decided to designate 'relapse' only when a subject fulfilled SCID-criteria for a depressive episode, regardless the HDRS score at that timepoint. A SCID negative interview but with a HDRS-

score >10 was considered as residual symptoms and not as relapse, as basic criteria for a depressive episode were not fulfilled.

In the full study, after the baseline assessment five follow-up assessments occurred: at 3, 12, 24, 36 and 66 months after study entry, outlined in the eFigure 1. At those timepoints current and MDEs preceding the follow-up point were checked for all patients by applying the SCID interview. To keep the assessors blind to treatment condition, we instructed participants not to reveal this information to the interviewers throughout the follow-up. As stated above, the Kappa (κ) for interrater agreement on relapse between interviewers and an independent psychiatrist indicated excellent agreement.

Logistic model to develop a clinical tool to determine the risk of future relapse

Logistic regression has the advantage that given the parameter estimates of the logistic regression model and the assumption that the sample is representative for the target population, the risk of relapse for an individual patient given the covariates can be determined relatively easy by the following formula:

$$p(relapse) = (1 + e^{-z})^{-1}$$

in which $z = b_0 + b_1$*LEIDS + b_2*HDRS + b_3*Prev.Episodes + b_4*etc and b_0, b_1, b_2, b_3 and b_4 are the parameter estimates of the logistic regression analysis.

Supplementary Results

Supplementary eTable 1**.** Estimations of Hazard Ratios in different Cox-models to predict time to relapse.

	Cognitve reactivity (LEIDS)				Dysfunctional Cognitions (DAS)			
Model	HR	95%-CI	Wald	p	HR	95%-CI	Wald	p
1. LEIDS[a]	1.35	1.04-1.79	4.88	0.027	-			
DAS[a]	-				1.15	0.87-1.50	0.81	0.367
Gender	1.96	0.90-4.28	2.87	0.090	2.13	0.98-4.64	3.63	0.057
Condition	1.25	0.72-2.18	0.62	0.430	1.29	0.74-2.56	0.82	0.364
2. LEIDS[a]	1.44	0.61-3.26	0.68	0.411	-			
DAS[a]	-				0.90	0.63-1.24	0.49	0.484
Symptoms[b]	1.04	0.97-1.12	1.21	0.271	1.054	0.98-1.13	1.84	0.175
MDEs[c]	1.19	0.42-3.38	0.11	0.745	0.87	0.39-1.94	0.12	0.735
Gender	1.70	0.72-4.01	1.49	0.222	1.72	0.73-4.03	1.55	0.213
Condition	1.15	0.19-6.88	0.02	0.879	0.84	0.16-4.29	0.05	0.829
LEIDS*Condition	1.00	0.97-1.04	0.04	0.950	1.01	0.98-1.04	0.21	0.648
LEIDS*MDEs	1.00	0.98-1.03	0.02	0.964	1.01	0.99-1.03	1.25	0.264
Final model[d]								
2.1. LEIDS[a]	1.47	1.04-2.09	4.63	0.031	-			
DAS[a]	-				1.00	0.74-1.39	0.00	0.961
Symptoms[b]	1.04	0.97-1.11	1.34	0.246	1.06	0.99-1.14	3.21	0.073
MDEs[c]	1.21	0.81-1.82	0.88	0.349	1.30	0.89-1.90	1.85	0.173
Gender	1.70	0.73-4.00	1.50	0.220	1.74	0.75-4.07	1.64	0.200
Condition	1.21	0.63-2.33	0.33	0.565	1.16	0.60-2.24	0.20	0.658
2.1a.[e] LEIDS[a]	1.52	1.08-2.13	5.61	0.018	-			
DAS[a]	-				1.03	0.76-1.39	0.27	0.869
Symptoms[b]	1.03	0.97-1.10	1.02	0.313	1.06	0.99-1.13	2.64	0.104
Gender	1.81	0.78-4.21	1.90	0.168	1.89	0.81-4.39	2.19	0.139
Condition	1.33	0.71-2.48	0.79	0.374	1.35	0.72-2.50	0.88	0.349
2.1b.[e] LEIDS[a]	1.56	1.13-2.17	6.86	0.009	-			
DAS[a]	-				1.12	0.82-1.50	0.58	0.446
MDEs[c]	1. 61	0.78-1.73	0.56	0.453	1.25	0.86-1.81	1.33	0.249
Gender	1.83	0.79-4.24	2.01	0.156	1.92	0.83-4.42	2.33	0.127
Condition	1.32	0.70-2.48	0.73	0.394	1.28	0.68-2.43	0.57	0.449

Abbreviations: DAS= dysfunctional attitudes scale; HDRS= Hamilton depression rating scale; HR= hazard ratio; LEIDS= Leiden index of depression sensitivity; MDE= major depressive episode

[a] HRs for 1 SD change

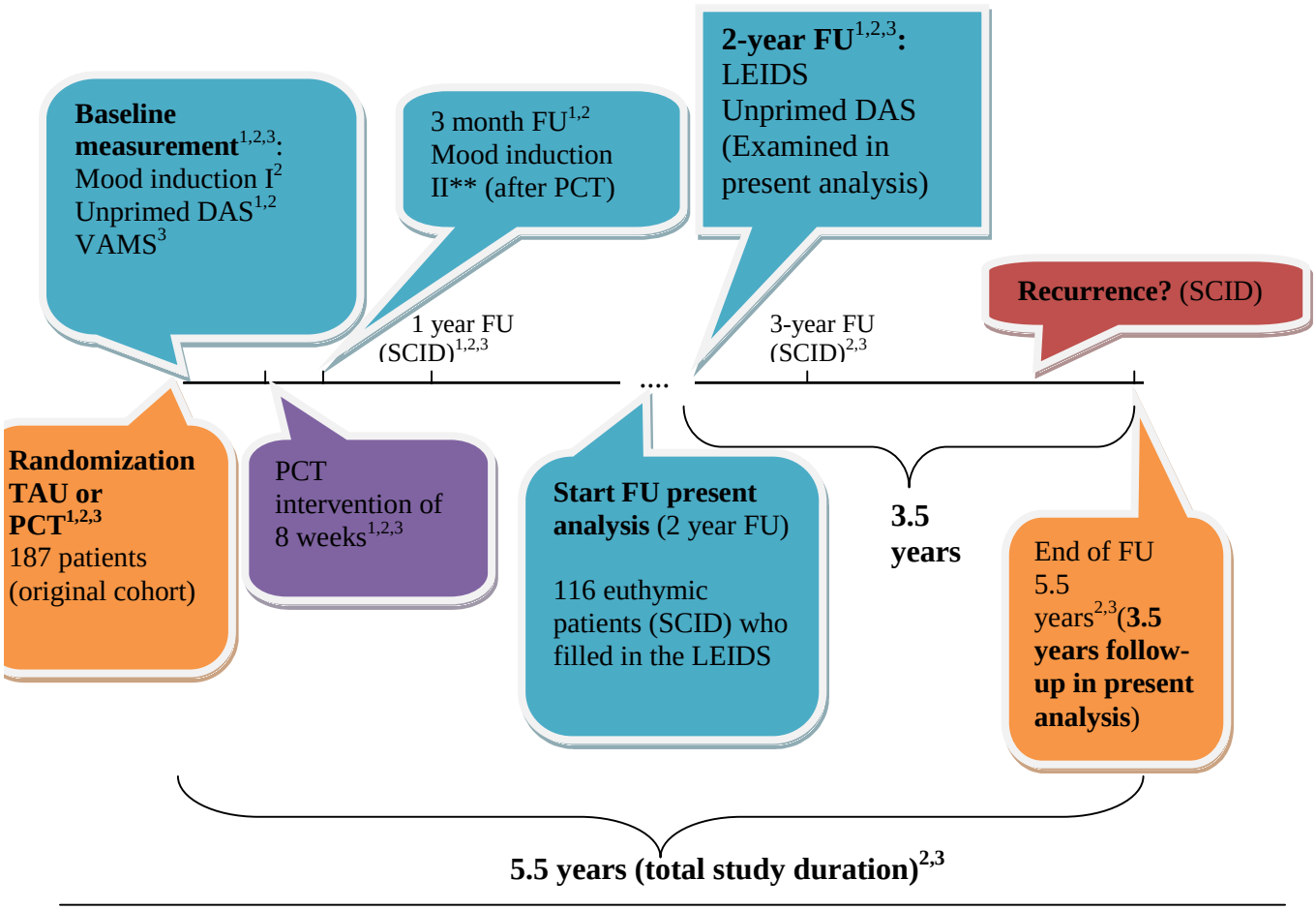
[b] residual/concurrent depressive symptoms measured by $HDRS_{17}$ [35]

[c] number of previous MDEs measured by structural clinical interview for DSM-IV (SCID)[34]

[d] Final, most parsimonious model after exclusion of non-significant interaction terms

[e] Models with symptoms or MDEs separately are shown for comparability with a previous publication.[6]

Supplementary eFigure 1. Overview of present study in relation to previous reports of a Randomized Clinical Trial with PCT intervention and subsequent 5.5 years follow-up.



1) Described in Bockting et al. (2005)[33] 2) Described in van Rijsbergen et al. 2013[6], 3) Described in van Rijsbergen et al. (2012)[52]
Abbreviations: FU= follow up, DAS=Dysfunctional Attitudes Scale, VAMS= Visual Analogue Mood Scale, LEIDS= Leiden Index Depression Sensitivity, PCT= Preventive Cognitive Therapy, SCID=Structural Clinical Interview for DSM disorders.