Vulnerability and emotional processing in depression

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Part 3

Chapter 8

Associations between cognitive vulnerability levels and depression course following treatment in primary care

Submitted as:
Groenewold, N.A., Roest, A.M., Wardenaar, K.J., Bos, E.H., Conradi,H.J., & De Jonge, P. (2014). Associations between cognitive vulnerability levels and depression course following treatment in primary care.

Abstract

This study investigates whether depression course predicts follow-up cognitive vulnerability and whether long-term associations between depression course and cognitive vulnerability are modified by enhanced treatment for depression in primary care. Post-hoc analyses were performed on data from 267 depressed primary care patients randomized to care-as-usual or one from three enhanced treatment groups: psycho-education (3 sessions, n=112), cognitive behavioral therapy (10-12 sessions+psycho-education, n=44), or psychiatric consultation (1 session+psycho-education, n=39). Main and interaction effects of treatment group and depression course (based on quarterly depression measurements) on cognitive vulnerability levels at 12- and 24-months follow-up were tested with linear regression models. A favorable depression course predicted greater reductions in cognitive vulnerability after 12 months (β=0.363/β=0.309, $p<0.001$) and 24 months (β=0.360/β=0.314, $p<0.001$). Although treatment did not affect cognitive vulnerability, participants with a favorable depression course after enhanced treatment showed lower vulnerability levels, while participants with an unfavorable course showed higher vulnerability levels in complete cases (group-by-course interaction: β=0.214/β=0.214, p=0.017/p=0.006, largely diminished after imputation: β=0.155/β=0.140, p=0.131/p=0.118). The interaction was absent at 24 months. Our data confirmed a long-term association between depression course and cognitive vulnerability. The effects of enhanced treatment on the association had a limited time window in this primary care sample.

8.1. Introduction

Cognitive vulnerability is a major risk factor for the development of depressive symptoms. Originally the term cognitive vulnerability was coined by Beck (1963) to describe a pervasive negative cognitive style that biases information processing. Accordingly, the hopelessness theory of depression postulated that several cognitive vulnerability factors such as negative self-evaluations, attribution styles, and outcome expectancies can give rise to depression (Abramson et al., 1989). Cognitive vulnerability has been shown to predict the onset of depression in never-depressed individuals (Kruijt et al., 2013; Rude et al., 2010) and recurrence in remitted patients (Alloy et al., 2006). Moreover, cognitive vulnerability levels predict a detrimental course in naturalistic studies and randomized controlled trials of depressed patients (Conradi et al., 2008; Garratt et al.,2007; Iacoviello et al., 2006; Struijs et al., 2013). Establishing a lasting reduction in cognitive vulnerability may improve long-term depression prognosis, and could therefore be viewed as a treatment objective (Beck and Dozois, 2011; Bockting et al., 2005; Hollon et al., 2006; Jarrett et al., 2013).

The modification of dysfunctional cognitions and attitudes is a central hypothesized mechanism of treatment in cognitive behavioral therapy (CBT). These alterations are thought to evoke a reduction of depressive symptom levels, according to the so-called mediation model (DeRubeis et al., 1990; Hollon et al., 1987). The complication model challenges this view by stating that the observed reductions in vulnerability levels after CBT can be fully explained by preceding reductions in depressive symptoms, as observed after other interventions (Hollon et al., 1987; Quilty et al., 2008). There is some evidence for temporal precedence of cognitive vulnerability changes before depressive symptom reductions during CBT (DeRubeis et al., 1990; Strunk et al., 2010; Tang et al., 2005). If CBT does act through the modification of cognitive vulnerability, it could be expected that cognitive vulnerability levels would decrease to a larger extent, and there would be a stronger association between reductions in depressive symptoms and cognitive vulnerability after CBT compared to interventions that do not target cognitive vulnerability.

Indeed, absolute reductions in cognitive vulnerability after CBT, and concomitant change in cognitive vulnerability levels and depressive symptoms after CBT are established findings (see Garratt et al., 2007 for a review). Response to treatment is

associated with a greater reduction in cognitive vulnerability levels than non-response to CBT (e.g. Dingle et al., 2010; Kuyken, 2004), and studies with a pre-post design have established positively correlated reductions in cognitive vulnerability and depression severity (Backenstrass et al., 2006; Christopher et al., 2009; McEvoy et al., 2013). These studies have been presented as supporting the mediation model of CBT. However, most studies have examined these associations within a single treatment group, and with cross-sectional analyses and crude measures of depression course (Garratt et al., 2007). It is also important to study the effects of alternative types of treatment on cognitive vulnerability levels and on the association between reductions in depressive symptom and cognitive vulnerability levels following treatment, to examine the specificity of effects.

So far, there is not much evidence to support the specificity of cognitive vulnerability reductions after CBT. Pharmacotherapy appears to result in reductions of similar magnitude as CBT (Garratt et al., 2007). Other psychological treatments such as psycho-education have not been extensively studied. Also, only modest attention has been directed to concomitant change in cognitive vulnerability and depressive symptoms. Modest evidence for stronger associations between changes in cognitive vulnerability and depressive symptoms has been reported for psychological interventions compared to pharmacotherapy (Dozois et al., 2009; Rector et al., 2000) or a waiting list control group (Van der Zanden et al., 2014; Warmerdam et al., 2010). The attribution of control aspect of hopelessness theory has been investigated in intervention studies (Van der Zanden et al., 2014; Warmerdam et al., 2010), however the link between depressive symptoms and self-esteem over the course of treatment has received less research attention. Also, due to short follow-up periods in most intervention studies, long-term associations between changes in depressive symptoms and cognitive vulnerability in response to interventions have hardly been investigated.

In the current study, we aimed to investigate the association between depression course and changes in vulnerability levels over a 12-to-24 months period in depressed primary care patients. In line with the hopelessness theory of depression, locus of control (Rodgers 1991; Struijs et al., 2013) and self-esteem (Orth and Robins, 2013) were used as measures of cognitive vulnerability. A data-driven approach was used to establish depression course trajectories, using multiple measurement points of depression severity. This approach was taken to capture the natural variability in course profiles that were

present in the sample, without pre-specified cut-off scores. Interventions with an active psychological component, i.e. cognitive behavioral therapy followed by psycho-education, psychiatric consultation followed by psycho-education, or psycho-education alone, were compared to care-as-usual.

First, we aimed to replicate findings of an association between changes in cognitive vulnerability and depressive symptoms, with this more advanced measure of depression course in a primary care sample. Next, we investigated whether the association between depression course and changes in cognitive vulnerability was stronger in the enhanced treatment groups compared to care-as-usual. Finally, long-term effects were examined by testing whether the associations still held after 24 months.

8.2. Methods

8.2.1. Sample and design

We conducted a post-hoc analysis of data from a randomized controlled effectiveness trial that was conducted in Dutch primary care practice, which aimed to investigate whether enhanced treatment intensity would improve long-term depression outcomes in primary care. The study protocol was approved by the ethical review board of the leading institution. Patients aged between 18 and 70 years with a current or recent (<3 months) major depressive episode were recruited. Exclusion criteria were psychotic disorder, bipolar disorder, dementia, substance abuse, pregnancy, and treatment for depression in a specialty mental health setting. Diagnosis was confirmed with a structured clinical interview administered by an experienced research assistant (CIDI; WHO 1997). After providing written information about the study protocol and the screening procedure, informed consent was obtained from 267 patients that were randomized to care-as-usual (CAU), a psycho-education prevention program (PEP), psychiatric consultation plus PEP (PC+PEP), or cognitive behavioral therapy plus PEP (CBT+PEP). A ratio of 2:3:1:1 was used for randomization based on a priori power calculations.

CAU consisted of care according to clinical guidelines by the General Practitioner, including brief counseling, antidepressant prescription and referral to specialized mental health care when necessary. PEP (Katon et al., 1996) consisted of three individual contacts of one and a half hour each with an experienced psychiatric nurse or psychologist to establish a prevention plan including symptom registration, coping, and

activation components, followed by quarterly telephone-based contacts discussing the prevention plan through motivational interviewing. PC+PEP consisted of a one-hour session with a psychiatrist, who thereupon advised the GP to optimize antidepressant treatment, followed by PEP. CBT+PEP consisted of 10-12 individual 45-minute sessions of manual-based CBT (Beck, 1979; Boelens et al., 1997) prior to PEP, including behavioral activation and cognitive strategies specifically directed at situation-contingent cognitions and core assumptions. The primary outcomes of the RCT, including a more detailed description of the study design, are available in Conradi et al. (2007).

8.2.2. Outcome measures

The *Mastery Scale* (Pearlin and Schooler, 1978) measures locus of control orientation with 7 items (e.g. "*I have little control over the things that happen to me*") scored on a 5-point Likert response scale, ranging from "strongly disagree" (1) to "strongly agree" (5). The mean score of the Mastery Scale items was used as a measure of locus of control, with higher scores indicating lower control and therefore higher vulnerability. Internal consistency was sufficient, with α=0.73 at baseline, α=0.82 at 12-months and α=0.86 at 24-months follow-up.

The *Rosenberg Self-Esteem Scale* (Rosenberg, 1965) measures self-esteem with 10 items (e.g. "*At times I think I am no good at all*") scored on a 4-point Likert response scale, ranging from "strongly disagree" (1) to "strongly agree" (4). The mean score of the items was used as a measure of self-esteem, with higher scores indicating lower self-esteem and therefore higher vulnerability. Internal consistency was very good, α=0.86 at baseline, α=0.91 at 12-months and α=0.92 at 24-months follow-up.

The correlation between locus of control and self-esteem was r=0.49 at baseline. This supported the idea that locus of control and self-esteem can be viewed as two different aspects of cognitive vulnerability, as was suggested previously (Metalsky et al., 1993). Follow-up measurements of both cognitive vulnerability factors were used as dependent variables in separate analyses.

8.2.3. Predictors

Depression severity was assessed quarterly with the Beck Depression Inventory (BDI; Beck et al., 1961). Two participants had no BDI scores and were therefore excluded from

the analysis, leaving 265 participants. The internal consistency of the BDI was very good (α=0.86-0.91 for the different measurements). Previous analyses of the data showed the largest decline in depressive symptoms early in the first year, as may be expected due to the interventions (Conradi et al., 2007; Wardenaar et al., 2014). To fully capture treatment effects, the first five BDI measurements (0-12 months) were selected to evaluate the course of depression.

A growth mixture model with class-specific random intercepts and fixed slopes was used as a data-driven approach to identify latent classes with different growth trajectories. Missing data were handled with robust maximum likelihood estimation as implemented in the Mplus software package version 6 (Muthén and Muthén, 2010). The number of classes was increased sequentially and the best solution was chosen based upon model fit parameters (smallest Bayesian Information Criterion [BIC] / Akaike Information Criterion [AIC] with a significant Bootstrap Likelihood Ratio Test [BLRT]). Individual posterior class probabilities, indicating the probabilities of belonging to each of the identified classes, were used as main predictors in the primary analyses. This approach was preferred to a pre-post design for being more informative. Difference scores between 12-months follow-up and baseline depression severity were also calculated and used as predictors in post-hoc analyses, for comparability with previous studies.

Consistent with the study design and to retain power, the enhanced treatment groups that each included PEP (low-intensity treatment with CBT elements) were compared against CAU. A dummy variable was created for enhanced treatment (PEP, PC+PEP, and CBT+PEP, coded as 1) versus CAU (reference). Another variable was created for per-protocol analysis, excluding participants that did not complete the intervention as prescribed in the protocol. For the enhanced treatment groups, protocol adherence was defined as receiving at least the 3 psycho-education face to face sessions (PEP, PC+PEP, and CBT+PEP), or at least 10 CBT sessions (CBT+PEP). The CAU group was by definition protocol adherent.

8.2.4. Statistical analysis

As a preparation for intention-to-treat analysis, missing values on key variables (self-esteem, locus of control, and depression) were imputed with multiple imputation (Rubin,

1987) as implemented in SPSS 20. Multiple imputation is recommended in CONSORT guidelines for analyzing data from randomized clinical trials to preserve randomization (Moher et al., 2010). There were 89 cases (33.6%) with at least one missing value to be imputed. The imputation model included variables used in the analysis (including the probability scores derived from the growth mixture model), together with auxiliary variables (Rubin, 1996) that either predicted values of the key variables or predicted missingness (CIDI sum scores, BDI at 24 months, age, years of education, comorbid anxiety, >2 previous depressive episodes, protocol adherence). The resulting imputed datasets were standardized to report comparable regression coefficients (β) over regression models. Statistical analyses were performed on the imputed data, in addition to the original dataset (complete cases analysis).

For the primary analysis, a linear regression model was constructed with locus of control at 12-months follow-up as dependent variable and locus of control at baseline as covariate. The class probability score reflecting depression course was used as predictor, next to treatment group. To test the potential moderating role of enhanced treatment, a dummy variable coding for the main effect of enhanced treatment and an interaction variable multiplying the dummy variable with class probability score were entered into the model. The analyses were repeated for self-esteem at 12 months as dependent variable, with self-esteem at baseline as covariate. To investigate long-term effects, vulnerability levels at 24 months were used as dependent variable in secondary analyses.

A significant group-by-course interaction effect was visualized with MODPROBE (SPSS macro to probe interactions by Hayes and Mattes, 2009). Analyses were reported for the different treatment groups (PEP, PC+PEP, and CBT+PEP) separately to take differences in intensity between treatments into account. Hereafter, linear association between depression and cognitive vulnerability reductions was tested by replacing the class probability score with the difference score between depression severity at 12 months and baseline as main predictor. Baseline depression severity was added as a covariate. A significance level of $\alpha=0.05$ was used throughout the analyses. These analyses were performed with SPSS package version 20.

8.3. Results

8.3.1. Sample characteristics

There were no baseline differences in demographic or clinical characteristics at baseline between the enhanced treatment and care-as-usual groups after randomization (Table 1). Data looked very similar after imputation. The majority of participants in both groups used antidepressant medication. Cognitive vulnerability decreased over time in both groups, with the strongest decline from 0-12 months and a smaller decline from 12-24 months. On average, the groups reported depressive symptom levels in the moderate range (19-29) at baseline and in the mild range (10-18; Beck et al., 1988) after 12 months.

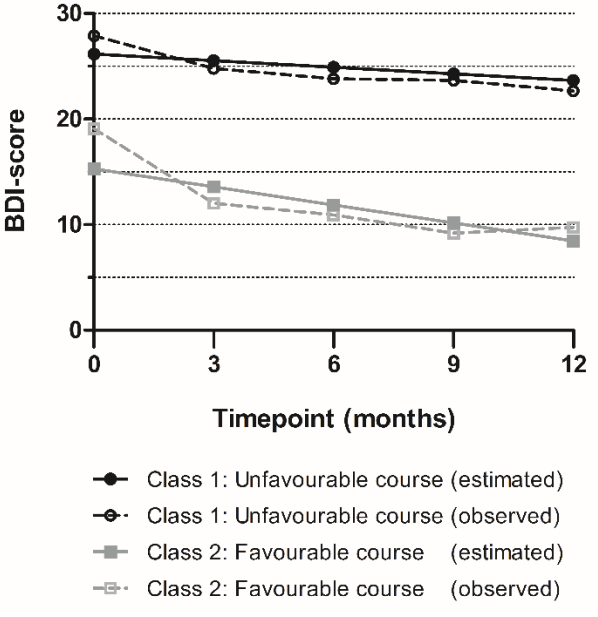
Table 1: Sample descriptives for the care-as-usual and enhanced treatment groups, before and after imputation

Characteristic	Original data		Imputed data	
	Care as usual (*N*=72)	Enhanced treatment (*N*=193)	Care as usual (*N*=72)	Enhanced treatment (*N*=193)
Demographic				
Age (sd)	44.2 (11.3)	42.4 (11.3)	44.2 (11.3)	42.4 (11.3)
Female sex (%)	47 (65.3)	124 (64.2)	47 (65.3)	124 (64.2)
Years of education (sd)	12.3 (3.87)	12.7 (3.64)	12.3 (3.90)	12.7 (3.65)
Clinical				
Age at onset (sd)	32.4 (14.3)	31.0 (12.8)	32.4 (14.3)	31.0 (12.8)
>2 Previous episodes (%)	30 (41.7)	68 (35.4)	30 (41.7)	68 (35.4)
Antidepressant use (%)	55 (76.4)	142 (73.6)	55 (76.4)	142 (73.6)
Comorbid anxiety (%)	25 (34.7)	63 (32.6)	25 (34.7)	63 (32.6)
Per protocol (%)	-	173 (89.6)	-	173 (89.6)
Depression (BDI)				
Baseline (sd)	18.8 (9.45)	20.5 (9.36)	19.1 (9.93)	20.6 (9.38)
12 months (sd)	11.4 (8.98)	10.9 (7.75)	11.3 (10.1)	11.6 (8.97)
Locus of control				
Baseline (sd)	3.07 (0.66)	3.02 (0.56)	3.08 (0.69)	3.03 (0.60)
12 months (sd)	2.79 (0.77)	2.68 (0.76)	2.78 (0.79)	2.70 (0.87)
24 months (sd)	2.64 (0.91)	2.56 (0.76)	2.64 (0.87)	2.56 (0.83)
Self-esteem				
Baseline (sd)	2.46 (0.42)	2.48 (0.45)	2.46 (0.43)	2.48 (0.45)
12 months (sd)	2.19 (0.53)	2.16 (0.55)	2.17 (0.66)	2.20 (0.59)
24 months (sd)	2.08 (0.61)	2.06 (0.58)	2.06 (0.66)	2.07 (0.60)

8.3.2. Depression course profiles

A growth mixture model with random intercept and fixed linear slope was applied to the BDI-scores at 0, 3, 6, 9, and 12 months follow-up. A two-class solution outperformed a one-class solution (BLRT: $p<0.001$). Next, the two-class solution ($df=12$) with an AIC-value of 7661.08 and a BIC-value of 7704.04 was compared to a three-class solution ($df=16$) with an AIC-value of 7646.58 and a BIC-value of 7703.85. Although the three-class solution yielded the smallest BIC-value, the BLRT showed that the three-class solution did not fit significantly better than the two-class solution ($p=0.08$). Therefore, the two-class solution was selected.

Figure 1. The 2-class solution of latent growth trajectory classes based upon depression severity scores from 5 assessments in the first year after baseline.



The first and also largest class (proportion sample = 0.89 based on estimated model, favorable course) had a relatively low severity of symptoms at baseline and showed a gradual decline over time (slope = -1.7, $p<0.01$). The second class (proportion sample = 0.11 based on estimated model, unfavorable course) had a higher initial severity, with no significant change over time (slope = -0.6, $p=0.57$). The depression course profiles are depicted in Figure 1. Entropy was rather low (0.695) indicating that the model showed

uncertainty in hard-classifying individuals. Thus, posterior class probabilities for the unfavorable depression course were saved for subsequent analysis. There were no differences in class probabilities for an unfavorable course between the CAU (median=0.037, interquartile range=0.066) and enhanced treatment group (median= 0.032, interquartile range=0.068), Mann-Whitney U-test p=0.730.

8.3.3. Baseline predictors of cognitive vulnerability levels at 12 months: vulnerability, course and treatment

Univariate analysis showed no differences in cognitive vulnerability levels between enhanced treatment and the CAU group ($p>0.05$). Higher baseline cognitive vulnerability predicted higher follow-up vulnerability levels (locus of control: β=0.438, $p<0.001$, self-esteem: β=0.579, $p<0.001$). The posterior class probability of having an unfavorable depression course predicted higher baseline-adjusted follow-up cognitive vulnerability levels (locus of control: β=0.475, $p<0.001$, self-esteem: β= 0.464, $p<0.001$). Multivariate models were also constructed predicting cognitive vulnerability levels at 12 months follow-up (Table 2). Both univariate and multivariate results were very similar for the original and imputed datasets.

Table 2. Linear Regression Analysis Predicting Locus of Control and Self-esteem at 12-Months Follow-up By Baseline Cognitive Vulnerability and Probability of Unfavorable Depression Course

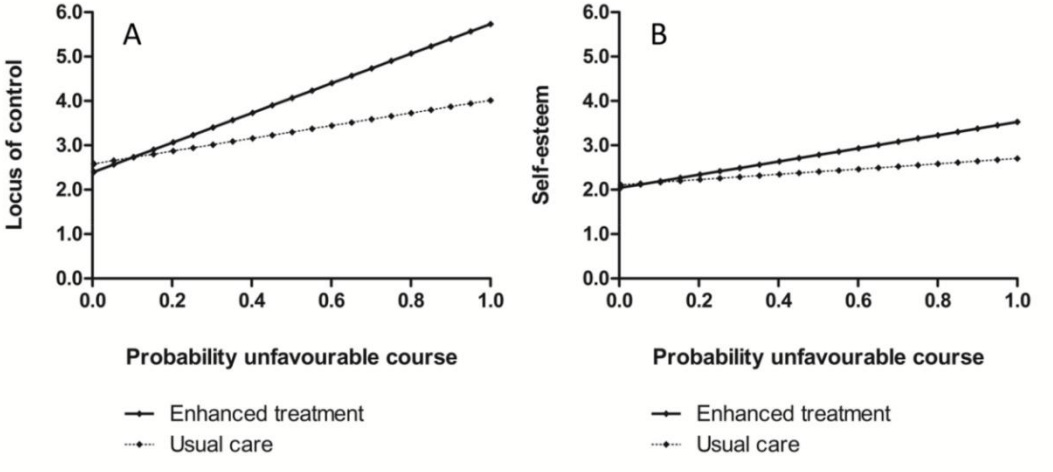
	Complete cases (*n*=197)			Intention-to-treat (*n*=265)		
Variables in model						
Locus of control (12m)	β	95% CI	*p*	β	95% CI	*p*
Locus of control (0m)	0.30	0.18-0.43	**<0.01**	0.30	0.17-0.44	**<0.01**
Unfavorable course	0.40	0.28-0.53	**<0.01**	0.36	0.24-0.48	**<0.01**
Enhanced treatment	-0.02	-0.13-0.10	0.78	-0.02	-0.13-0.10	0.77
Variables in model		Complete cases (*n*=195)			Intention-to-treat (*n*=265)	
Self-esteem (12m)	β	95% CI	*p*	β	95% CI	*p*
Self-esteem (0m)	0.48	0.36-0.59	**<0.01**	0.48	0.36-0.59	**<0.01**
Unfavorable course	0.34	0.23-0.46	**<0.01**	0.31	0.19-0.43	**<0.01**
Enhanced treatment	0.03	-0.08-0.13	0.64	0.03	-0.10-0.16	0.64

8.3.4. Group differences in association between depression course and vulnerability levels after 12 months

The group-by-course interaction was significant in complete cases analysis: locus of control: β= 0.214, p=0.017, self-esteem: β= 0.214, p=0.006). For both cognitive vulnerability factors, a favorable course predicted lower follow-up vulnerability and an unfavorable course predicted higher follow-up vulnerability levels in the enhanced treatment group compared to CAU (Figure 2). However, in intention-to-treat analyses on imputed data the group-by-course interaction was largely diminished (locus of control: β= 0.155, p=0.13, self-esteem: β= 0.140, p=0.12). A highly similar pattern was found in a per-protocol analysis on the imputed dataset.

Post-hoc analyses were conducted to further explore the significant interaction effects at 12 months in complete cases. As a first step, the enhanced treatment groups were separately compared against the CAU group. The separate interventions gave similar results (locus of control: CBT+PEP versus CAU: β=0.205, PC+PEP versus CAU: β=0.206, PEP versus CAU: β=0.190, and self-esteem: CBT+PEP versus CAU: β=0.169, PC+PEP versus CAU: β=0.232, PEP versus CAU: β=0.191).

Figure 2. Differential association between class probability and 12-month cognitive vulnerability scores stratified by treatment group (panel A: locus of control, panel B: self-esteem). Data from complete cases analysis are presented. Note that the majority of participants had a favorable course.



For comparability with previous studies, the interaction between treatment group and 12-months changes in depression severity was tested as well. Baseline depression severity was included as a covariate. The group-by-change interaction was attenuated for locus of control (β=-0.196, p=0.124), and completely absent for self-esteem (p=0.917) in the complete cases analysis. In contrast with the course trajectories, the interaction was now completely driven by the CBT group (β=-0.340, p=0.023). There were no interactions for the PC+PEP or PEP alone groups (p>0.25). After imputation the interaction was diminished for the combined groups (p=0.351), although there was still a strong trend in the CBT group (β=-0.234, p=0.094).

8.3.5. Baseline predictors of cognitive vulnerability levels at 24 months: vulnerability, course and treatment

Finally, the long-term associations between depression course and follow-up vulnerability levels were examined. In univariate analysis, there were no differences between the treatment groups in cognitive vulnerability levels at 24 months (p>0.05). Baseline cognitive vulnerability predicted vulnerability at 24 months (locus of control: β= 0.410, p<0.001 and self-esteem: β= 0.591, p<0.001). Moreover, probability of an unfavorable depression course in the first year was predictive of higher cognitive vulnerability at 24 months (locus of control: β= 0.463, p<0.001 and self-esteem: β= 0.473, p<0.001). These associations were also significant in multivariate linear regression models, and the results were very similar for the original and imputed datasets (Table 3).

Table 3. Linear Regression Analysis Predicting Locus of Control and Self-esteem at 24-Months Follow-up By Baseline Cognitive Vulnerability and Probability of Unfavorable Depression Course

Variables in model	Complete cases (*n*=195)			Intention-to-treat (*n*=265)		
Locus of control (24m)	β	95% CI	*p*	β	95% CI	*p*
Locus of control (0m)	0.26	0.13-0.38	<**0.01**	0.28	0.13-0.43	<**0.01**
Unfavorable course	0.40	0.27-0.53	<**0.01**	0.36	0.23-0.49	<**0.01**
Enhanced treatment	0.00	-0.12-0.12	0.98	-0.01	-0.12-0.10	0.86
Variables in model	Complete cases (*n*=193)			Intention-to-treat (*n*=265)		
Self-esteem (24m)	β	95% CI	*p*	β	95% CI	*p*
Self-esteem (0m)	0.48	0.36-0.59	<**0.01**	0.49	0.38-0.59	<**0.01**
Unfavorable course	0.34	0.23-0.46	<**0.01**	0.31	0.21-0.42	<**0.01**
Enhanced treatment	0.02	-0.09-0.13	0.71	0.02	-0.09-0.12	0.78

8.3.6. Group differences in association between depression course and vulnerability levels after 24 months

Next, the group-by-course interaction was added to the models. There were no interaction effects between treatment and depression course in the prediction of cognitive vulnerability levels at 24 months, both for the original and imputed datasets (complete cases: locus of control: β= 0.067, *p*=0.469 and self-esteem: β= 0.054, *p*=0.508).

8.4. Discussion

This post-hoc analysis of a randomized controlled trial was undertaken to examine the long-term association between depression course and cognitive vulnerability levels. A favorable depression course in the first year predicted greater reductions in vulnerability levels at 12 months and 24 months. Enhanced treatment did not result in a larger reduction in cognitive vulnerability than care-as-usual. The interaction between treatment group and depression course was significant in participants with complete cognitive vulnerability data, indicating that the effects of treatment on cognitive vulnerability were contingent on the course of depressive symptom levels. Notably, the effects of enhanced treatment were detrimental in case of an unfavorable course. Nonetheless, this moderating effect of enhanced treatment may not generalize to depressed patients that do not finish their treatment or refuse follow-up contact, and it did not persist at the 24-months follow-up.

The study findings should be interpreted in the light of several strengths and limitations. A major strength of the study is that it is a large trial with random treatment allocation. Also, the follow-up time of 24 months allowed for investigation of long-term associations, and both predictors and outcome measures were assessed repeatedly. Limitations included the small size of the CBT+PEP and PC+PEP groups, providing limited statistical power for group comparisons. The identified growth trajectories reflected little qualitative between-subject variation in depression course. However, this is in line with previous studies using the same approach (Gueorguieva et al., 2011; Uher et al., 2010). Of note, post-hoc exploration of group-by-severity interactions showed that the moderation effects of enhanced treatment were not attributable to severity differences at baseline (data not shown). Cognitive vulnerability was not measured during active treatment, and therefore it was impossible to investigate temporal mechanisms of change. The cognitive vulnerability measures were fairly specific and may not have captured the full range of relevant cognitive vulnerability dimensions. Antidepressants were frequently prescribed in CAU, which may have resulted in an underestimation of the effect of the studied interventions.

8.4.1. The associations between depression course and cognitive vulnerability after treatment

The hypothesized association between depression course and changes in cognitive vulnerability levels was confirmed, as previously reported for the treatment phase of CBT trials (e.g. Backenstrass et al., 2006; McEvoy et al., 2013). Our findings show that the association is probably not specific for CBT, but can also be observed after PEP or CAU in depressed primary care patients. The association between depression course and change in cognitive vulnerability appeared to be stronger for interventions with a psychological component than for CAU. This is in line with previous findings (Dozois et al., 2009; Warmerdam et al., 2010) and suggests that the observed changes in cognitive vulnerability do not merely reflect depressive symptom improvement. The comparison with the CAU group generated an interesting finding: the effects of enhanced treatment on cognitive vulnerability levels were positive for a favorable course, but negative for an unfavorable course. Our results suggest that a small group of non-responding participants could experience deleterious effects of treatment continuation. The absence of

improvement despite the invested efforts and expectations may decrease experienced control and self-esteem, and increase hopelessness. These participants might have benefited from a switch in therapeutic strategy (Rush et al., 2006; Owen and Hilsenroth, 2014).

After multiple imputation, the interaction between treatment group and depression course was attenuated, indicating that the complete cases analysis possibly overestimated the interaction effect. The conflicting findings could not be attributed to lower protocol adherence in drop-outs. Furthermore, there were no baseline differences in cognitive vulnerability levels between study completers and drop-outs (data not shown). Selective attrition might explain the difference in results, since participants retaining experienced control and self-esteem may be more likely to refuse follow-up measurements after experiencing no benefit from the intervention. An alternative explanation is that the missing-at-random assumption underlying the imputation technique was violated because not all relevant factors predicting missingness (for example: strength of the therapeutic alliance) could be included in the imputation model (Graham, 2009). In that case, the imputation results may also not give a reliable estimate of the true effect. Considering that power to detect an interaction effect was somewhat low (Durand, 2013), the results suggest that moderating effects of enhanced treatment on the association between depression course and cognitive vulnerability in primary care are relatively small.

8.4.2. Interpreting the results from the perspective of cognitive mechanisms of change

The absence of a group-by-course interaction effect in the second year is consistent with the complication model, suggesting that long-term reductions in vulnerability levels are the direct consequence of depressive symptom alleviation (Quilty et al., 2008). However, the more prominent interaction in the first year is consistent with the mediation model, suggesting that in line with previous findings treatment initially does have additional effects in participants with a favorable course. Certainly, the mediation and complication models are not mutually exclusive. Thus, the association between depression and cognitive vulnerability in the psychological intervention groups may as well be the sum of regression to the mean, symptom reductions, and additional treatment effects (Quilty et al., 2008; Warmerdam et al., 2010). The findings are therefore in line with the concept of

consequential non-specificity (Hollon et al., 1997), which underscores that similar outcomes can arise from different processes.

8.4.3. Absolute change and relative stability of cognitive vulnerability over a long period of time

Both an unfavorable depression course and baseline cognitive vulnerability levels predicted higher long-term vulnerability levels. These findings corroborate the state-trait vulnerability model, which states that cognitive vulnerability levels show absolute changes but relative stability over time (Beevers and Miller, 2004; Zuroff et al., 1999). Dysfunctional attitudes and maladaptive schemas have demonstrated relative stability up to 9 years in depressed and non-depressed participants (Wang et al., 2010). Our study shows that a state-trait vulnerability model is applicable to measures of self-esteem and locus of control as well. Of note, negative effects of depression on self-esteem have been interpreted as scar effects (Shahar and Davidson, 2003). In the present study, it was not possible to assess true scar effects because pre-morbid cognitive vulnerability was unknown. A vulnerability model does receive stronger support than a scar model in the self-esteem literature (Orth and Robbins, 2013).

8.4.4. Clinical relevance of the findings

High cognitive vulnerability levels have been previously related to a chronic course of depression (Barnhofer et al., 2014; Wiersma et al., 2011). Our results could be indicative of a clinically relevant feedback loop between depression and vulnerability (also see Van der Zanden et al., 2014). It would be of major importance to intervene early in this process. However, in the current study, no long-term effects of enhanced treatment on cognitive vulnerability were observed – although short-term treatment effects may have been overlooked. Future studies should focus on identifying the time window of treatment effects by investigating changes in cognitions during and after treatment, with adequate control groups to take non-specific factors into account. The negative findings suggest that prophylactic effects of CBT may be due to another mechanism than reductions in cognitive vulnerability, such as increasing strengths (Cheavens et al., 2012), or this mechanism may only apply to relevant subgroups such as recurrent depression or depression in specialized mental health care. Moreover, cognitive reactivity after an

emotional challenge is another relevant factor to investigate, as it may have better prognostic value than absolute cognitive vulnerability levels (Segal et al., 2006).

8.4.5. Conclusion

This study demonstrated a long-term association between depression course and follow-up cognitive vulnerability levels in depressed primary care patients. Enhanced treatment for depression with a psychological component was associated with a stronger association between depression course and cognitive vulnerability reductions in complete cases analysis. The increase in strength of the association was restricted to the initial 12 months. Cognitive vulnerability was not lower after enhanced treatment compared to usual care at any of the measurement points. Therefore, any beneficial effects of enhanced treatment for depression on cognitive vulnerability may expire and have limited prognostic significance after treatment has finished. Instead, in this sample of primary care patients, a favorable depression course prospectively predicted lower cognitive vulnerability irrespective of how this improvement was accomplished.

Acknowledgments

The trial from which the data were sourced was supported by grants from the Netherlands organization for Scientific research (NWO), Medical Sciences Program and Chronic Diseases Program, Research Foundations of Health Insurance Company "Het Groene Land," Regional Health Insurance Company (RZG), National Fund Mental Health (NFGV), and the University Medical Center Groningen. The authors have no conflict of interest to disclose.