Vulnerability and emotional processing in depression

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Part 3

Chapter 7

Cognitive vulnerability differentially predicts symptom dimensions of depression

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Abstract

We examined the association of cognitive vulnerability to depression with changes in homogeneous measures of depressive symptoms. Baseline and 1-year follow-up data were obtained from 2981 participants of the Netherlands study of depression and anxiety. Multivariate regression analyses were carried out on cognitive reactivity, locus of control and implicit and explicit self-depressive associations in combination with negative life events. The purpose of this analysis was to predict changes on the mood/cognition and anxiety/arousal subscales of the inventory of depressive symptomatology - self report. Cognitive reactivity, locus of control and explicit self-depressive associations were independently associated with changes in depressive symptoms after adjustment for covariates and baseline severity (all $p < 0.01$). Negative life-events interacted with cognitive vulnerability to depression to predict depressive symptoms. Locus of control ($b_1 = 0.16$, $SE = 0.02$, $\eta^2 = 0.01$; $b_2 = 0.10$, $SE = 0.02$, $\eta^2 = 0.004$, $F = 8.69$, $p < 0.01$) and explicit self-depressive associations ($b_1 = 0.10$, $SE = 0.03$, $\eta^2 = 0.02$; $b2 = 0.02$, $SE = 0.04$, $F = 7.50$, $p < 0.01$) were more strongly associated with the cognitive (b_1) than the somatic (b_2) symptom dimension of depression. The study sample is over-inclusive of depressed patients. Therefore it might be problematic generalizing the findings to the general population. Cognitive etiological factors may play a role in a "cognitive" subtype of depression. The findings strengthen the notion that homogeneous measures of depressive symptoms enable a greater degree of discrimination between subtypes than a multidimensional conception of depression.

7.1. Introduction

Major depressive disorder (MDD) causes a major burden for modern society and it is predicted that the burden of MDD will be the largest of all diseases by 2030 (World Health Organization, 2008). In recent years, pharmacological (Kirsch, et al., 2008) and psychotherapeutic (Cuijpers, et al., 2010) interventions have reported disappointing results. The complex and heterogeneous nature of the construct major depression may contribute to these modest results (Kendler and Gardner, 1998; Lichtenberg and Belmaker, 2010; Lux and Kendler, 2010; Parker, 2005). Treatments that work for one specific individual might not work for another individual, resulting in an attenuated treatment effect. Therefore, unaccounted heterogeneity in symptoms of depression may arrest our knowledge about the etiology and the effective treatment of MDD. Heterogeneity in depressive symptoms has particularly gained attention in psychosomatic research (de Jonge, 2011). In the field of general psychology thereis a recent movement to address syndrome heterogeneity by assessing intermediate phenotypes across current diagnostic criteria (Insel and Cuthbert, 2009; Sanislow, et al., 2010).

Heterogeneity in depression leads to decreased clinical specificity and a loss of statistical power. Dichotomizing results in the dismissal of valuable information, which may lead to biased results (Shorter and Tyrer, 2003). A dimensional model of psychopathology resolves both issues by assuming that symptom severity follows a continuum rather than a dichotomy. Furthermore, dimensional models assume that psychopathology consists of several co-existing symptom domains, thereby allowing for multidimensionality (Watson, 2005).

Accordingly, two factors of the IDS-SR have been optimized with Rasch analysis to serve as homogeneous measures of depressive symptom dimensions (Wardenaar, et al., 2010). The mood/cognition subscale of the IDS-SR contains symptoms of depressed mood, affect and cognition, e.g. ‘sad mood’ (referred to in this document as the cognitive symptom dimension of depression). The anxiety/arousal subscale of the IDS-SR contains symptoms of anxiety, somatic arousal and somatic complaints, e.g. sympathetic arousal (referred to in this document as the somatic symptom dimension of depression). These homogeneous measures of depressive symptom dimensions may be useful to identify multiple etiological pathways that lead to depression (Parker, 2005).

Cognitive vulnerability to depression plays an important role in the etiology of MDD (Alloy, et al., 1999). The concept of a negative thinking style regarding oneself, the world and the future was first introduced by Beck (1963) and had a major impact in clinical and research settings. Hereafter, several cognitive themes have been highlighted in influential theories such as experienced control in stressful situations (helplessness theory; Abramson, et al., 1978) and negative predictions about future consequences of one's behavior and a resulting negative self-image (hopelessness theory; Abramson, et al., 1989). The Temple-Wisconsin cognitive vulnerability to depression project (Alloy, et al., 2000) and the Oregon Adolescent Depression Project (Lewinsohn, et al., 1998) have previously examined the effect of cognitive vulnerability in a longitudinal design using multiple measures, demonstrating that cognitive vulnerability is multifaceted. These measures assessed participant's explicit negative self-evaluations, attitudes and inferential style. It was not assessed whether vulnerability measures relating to implicit associations provide incremental risk in developing depressive symptoms. More importantly, it is unknown whether cognitive vulnerability to depression is differentially predictive of more homogeneous symptom dimensions of depression. Recently, Iacoviello and colleagues (2010) argued that prodromal and residual symptoms of depression represent the core of the disorder. These primary symptoms (e.g. sad mood, concentration loss) resemble symptoms from the cognitive symptom dimension. Therefore, cognitive vulnerability to depression is expected to be more predictive of cognitive symptoms. The diathesis-stress model of depression states that vulnerability predisposes individuals to experience psychopathology, particularly when activated by stress (Monroe and Simons, 1991). This is why cognitive vulnerability is expected to put individuals at risk for the development of depressive symptomatology when they are faced with a stressful life event.

The aims of this project are twofold: (1) to examine whether different measures of cognitive vulnerability are independently predictive of depressive symptoms and (2) to examine the impact of cognitive vulnerability on the development of homogeneous symptom dimensions of depression. We expect that: (1) all measures of cognitive vulnerability to depression are independently positively associated with the development of overall symptoms of depression; (2) these associations are moderated by negative life events; (3) the prospective association of cognitive vulnerability with the cognitive

symptom dimension is significantly larger than with the somatic symptom dimension of depression.

7.2. Methods

7.2.1. Study Design

The Netherlands study of depression and anxiety. Data were derived from the baseline and 1-year follow-up assessment of The Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal cohort study designed to study the long term course and consequences of depression and anxiety. Baseline data were used as predictor variables and covariates; the 1-year follow-up data were used as moderators and outcome variables. A detailed description of the NESDA design and sampling procedure is provided elsewhere (Penninx, et al., 2008).

Sample. The baseline assessment was completed by 2981 participants, of which 2455 (82%) completed the 1 year follow-up assessment. Subjects were recruited from three different settings: the community, primary care and mental health care. At the baseline assessment 2329 participants had a lifetime depressive and/or anxiety disorder and 652 participants had no history of any depressive and/or anxiety disorder.

Procedure. Recruitment maintained the following inclusion and exclusion criteria: an age of 18 through 65, proficiency in the Dutch language and no diagnosis of a psychotic disorder, obsessive compulsive disorder, bipolar disorder or severe addiction disorder. The study protocol was approved by the ethical review board of each participating center. All subjects signed an informed consent before participating in the study. The baseline assessment started in September 2004 and ended in February 2007 The lifetime version of the composite international diagnostic interview was used to establish diagnoses of (current) mood and anxiety disorders. The 1-year follow-up assessment started in September 2005 and ended in February 2008.

7.2.2. Measures

Depressive symptom dimensions. The Inventory of Depressive Symptomatology Self Report (IDS-SR; Rush, et al., 1996) was used to assess depressive symptom dimensions at baseline and 1-year follow-up. The 1-year follow-up measures were used as outcome variables and the baseline measure were used as covariates. The IDS-SR

contains all symptoms of depression as defined by the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (American Psychiatric Association, 2000) and symptoms commonly associated with depression. The IDS-SR has demonstrated satisfactory psychometric qualities with good internal consistency ($\alpha = 0.92 - 0.94$), good convergent validity and high sensitivity to change in previous research (Rush, et al., 1996; Trivedi, et al., 2004). Principal component analysis and confirmatory factor analysis of the IDS-SR in the NESDA sample have indicated a three-factor model of which two factors (the mood/cognition factor and the anxiety/arousal factor) have been optimized with Rasch analyses to function as homogeneous measures of depressive symptoms dimensions (Wardenaar, et al., 2010).

Cognitive symptom dimension of depression. The mood/cognition subscale of the IDS-SR comprises 11 equally-weighted items rated on a three-point scale, containing symptoms of depressed mood, affect and cognition. The sum score (range 0 - 22) of this subscale was used as a measure of cognitive symptoms of depression. Internal consistency was $\alpha = 0.86$ at baseline and $\alpha = 0.88$ at follow-up.

Somatic symptom dimension of depression. The anxiety/arousal subscale of the IDS-SR comprises 8 equally-weighted items rated on a three-point scale, containing symptoms of anxiety, somatic arousal and somatic complaints. The sum score (range 0 - 16) of this subscale was used as a measure of somatic symptoms of depression. Internal consistency was $\alpha = 0.78$ at baseline and follow-up.

Cognitive reactivity. Cognitive reactivity is the activation of depressive cognitions during periods of low moods (Scher, et al., 2005). The Leiden Index of Depression Sensitivity-Revised (LEIDS-R) is a questionnaire that intents to measure such dysfunctional attitudes during low mood without a mood-induction procedure (van der Does and Williams, 2003; Van der Does, 2002). The LEIDS-R is a self-report questionnaire that contains 34 equally weighted items rated on a five-point scale. Results from previous studies support the notion that the LEIDS-R measures cognitive reactivity (Antypa, et al., 2010; Booij and Van der Does, 2007; Moulds, et al., 2008). The items are divided among 6 different subscales: Hopelessness/Suicidality; Acceptance/Coping; Aggression; Control/Perfectionism; Harm Avoidance and Rumination. The sum score (range 0 - 136) of the LEIDS-R was used as measure of cognitive reactivity with higher scores indicating stronger cognitive reactivity. Internal consistency was $\alpha = 0.93$.

Locus of control. The Mastery Scale was used to measure locus of control, the degree in which the individual experience that s/he has control over his or her life (Pearlin and Schooler, 1978). An external locus of control is a negative thinking style that is related to an increased incidence of MDD (de Graaf, et al., 2002). The Mastery Scale is a self-report questionnaire containing 5 equally weighted items rated on a five-point rating scale. The sum score (range 5 - 25) of the Mastery Scale was used a measure of locus of control, with lower scores indicating stronger personal control. Internal consistency was $\alpha = 0.87$.

Implicit self-depressive associations. The Implicit Associations Test (IAT) was used to measure implicit self-depressive associations. The IAT is a computerized reaction time task (Greenwald, et al., 1998). The strength of association between concepts and attributes is measured by reaction times (with faster reaction times indicating a stronger association between attribute and concept). Implicit self-depressive associations are derived from the relative strength of associations between the concept 'self' and attribute 'depressed' versus the concept 'self' and attribute 'elated'. A more detailed description of how the IAT was operated in the NESDA is provided elsewhere (Glashouwer, et al., 2010). The algorithm developed by Greenwald and colleagues was used to calculate the IAT-effect, with higher scores indicating stronger self-depressive associations (Greenwald, et al., 2009).

Explicit self-depressive associations. The attributes from the IAT were used to measure explicit depressive associations in the form of a self-report questionnaire. The explicit association questionnaire contained 5 equally weighted depressed attributes and 5 equally weighted elated attributes from the IAT rated on a five-point scale. To compute explicit self-depressive associations, the scores of the elated attributes were reversed and the scores on all items were summed (range 0 - 40). Therefore, a higher score indicates stronger explicit self-depressive associations. Internal consistency was $\alpha = 0.95$.

Negative life events. The List of Threatening Experiences (LTE) was assessed at the 1-year follow-up measurement. The LTE was used to measure negative life events in the past year. The LTE is a self-report questionnaire that assesses the exposure to one or more serious negative life events such as the death of a loved one or the loss of a job (Brugha, et al., 1985). For ease of interpretation, we transformed negative life events into a dichotomous variable.

Demographic characteristics and confounders. Sociodemographic characteristics included age, sex, years of education, partner status and smoking status. Drinking behavior was measured with the alcohol use disorders identification test (Babor, et al., 1989). Drinking behavior and smoking status are associated with depression (Grant, et al., 2004; Hasin, et al., 2005) and were therefore used as covariates in the analyses. Since it can reasonably be argued that somatic illness is more strongly associated with somatic than cognitive symptoms of depression, the presence of sixteen self-reported somatic conditions were summed and used as a covariate in the analyses.

7.2.3. Data Analysis

The baseline and follow-up sum scores of the cognitive and somatic symptom dimension of the IDS-SR were calculated using the description provided by Wardenaar and colleagues (2010). The scores on the cognitive and somatic symptom dimensions of the IDS-SR at the baseline and 1-year follow up assessments, and the scores on all cognitive vulnerability to depression measures, were standardized because of different units of measurement and scale length. Missing data were multiply imputed by chained equations using Stata's user-written package ICE (Royston, 2005). All variables and interaction terms that were used in the analyses were also included in the imputation model. Neuroticism and conscientiousness at baseline and depressive symptoms at the two-year follow-up assessment were added to the imputation model as auxiliary variables (these variables are not used in the main analyses). From this model 10 imputed datasets were created in 1000 cycles while bootstrapping all variables. Analyses on the imputed datasets were conducted taking in to account the within and between imputation variance (Rubin, 1987).

To determine the association between cognitive vulnerability to depression and changes in overall depressive symptoms, a multivariate regression model was built. This utilized both the cognitive and somatic symptom dimensions of the 1-year follow-up assessment as outcome measures and the same measures at baseline as covariates. The adjusted follow-up score was preferred to the difference score as outcome measure for several reasons: (1) with the baseline score included as predictor variable, it is possible to examine the influence and stability of the measure over time; (2) the error term of the adjusted model is smaller than when the difference score is analyzed and (3) the

reliability of the difference score becomes compromised when the correlation between the two measures approaches the average reliability of the two measures (Stevens, 2009).

Measures of cognitive vulnerability and stress were added to the model as predictor variables. Demographics, somatic diseases, smoking status and drinking behavior were added as covariates. Measures of cognitive vulnerability multiplied with stress were added as interaction variables. The first model contained all main effects of the predictor variables and covariates, as well as all interaction effects. Because non-significant interaction effects indicate that the main effect parameters for different groups are similar, the weakest interaction effects were sequentially eliminated until only significant interaction effects remained. Although the analyses are based upon a dimensional framework, it is possible that the associations are dependent on a depressive or anxious state. Furthermore, the use of antidepressant medication can influence cognitive biases (Harmer, et al., 2004). Therefore, interaction terms of diagnostic status and antidepressant use were also added as covariates to the model.

Wald tests were used in the final model to determine the association of cognitive vulnerability to depression with cognitive and somatic depressive symptoms combined. Next, Wald tests were used to determine the association of cognitive vulnerability to depression with homogeneous symptom dimensions of depression separately. We report *F*-ratios with corresponding *p*-values of all Wald tests. As a measure of effect size η^2 was calculated. Variance inflation factors were calculated for every variable to examine potential multicollinearity. All analyses were carried out by Stata (version 11.2, special edition) and the significance level was set at $p < 0.05$.

Table 1: Demographic and clinical characteristics of participants

Characteristic	Complete cases (n=2180)		Complete cases after imputation (n=2981)	
	Mean	*Sd*	Mean	*Sd*
Age	42.6	(13)	41.9	(13)
Female (%)	67.6		66.4	
Years of education	12.4	(3.3)	12.2	(3.3)
Partner (%)	70.7		69.3	
Smoking (%)				
- Current	32.8		38.5	
- Past	37.1		33.4	
- Never	30.1		28.0	
Drinking behavior	4.69	(4.5)	4.81	(4.8)
Number of somatic diseases	0.89	(1.1)	0.89	(1.1)
Mood disorder at baseline (%)	24.5		26.9	
Cognitive symptoms at baseline	6.01	(4.5)	6.38	(4.5)
Somatic symptoms at baseline	4.57	(2.7)	4.78	(2.8)
Cognitive reactivity	33.2	(19.6)	34.4	(19)
Locus of control	7.60	(4.6)	7.90	(4.6)
Implicit self-depressive associations	−0.243	(0.39)	−0.227	(0.39)
Explicit self-depressive associations	2.60	(1.7)	2.67	(1.7)
Negative life event experienced (%)	61.5		62.1	
Cognitive symptoms at follow-up	4.96	(4.1)	5.20	(4.1)
Somatic symptoms at follow-up	3.82	(2.6)	3.97	(2.7)

Note: Sd = Standard deviation.

7.3. Results

The analyses were performed twice, using the complete data after listwise deletion of missing cases and the complete data after imputation. No differences in patterns of significance emerged. The results of the imputed data analyses are reported, because they give a less biased estimate of the effects in the original sample.

7.3.1. Sample Description

Of the total 2981 participants from the baseline assessment of the NESDA, 2445 participated in the 1 year follow-up assessment. Complete data were available from 2180 (89%) participants. The mean age of participants was 42.6 years (*Sd* = 13.1) and 67.6% were female. 24.5% of the participants were diagnosed with a current (within the last month) mood disorder at baseline. Demographic and clinical characteristics of the sample

with complete data and of the sample with complete data after imputation are provided in table 1.

7.3.2. Combined outcomes

The final multivariate regression model contained all main effects of the predictor variables, covariates and the interaction effect of NLE*explicit self-depressive assumptions. It must be noted that the interaction effects of NLE*locus of control did achieve significance when the interaction effects were allowed to enter the model separately. Results from multivariate multiple regression analysis examining the associations of predictor variables with both the cognitive and somatic symptom dimensions are presented in table 2. Cognitive reactivity, $F(2, 160.9) = 19.20$, $p < 0.001$, locus of control, $F(2, 239.8) = 28.25$, $p < 0.001$, explicit self-depressive associations, $F(2, 130.8) = 5.79$, $p < 0.01$, and NLE*explicit self-depressive associations, $F(2, 257.1) = 4.76$, $p < 0.01$, were all predictive of overall depressive symptoms at follow-up after adjustment for baseline severity of depressive symptoms and covariates. Implicit self-depressive associations were not predictive, of depressive symptoms at follow-up $F(2, 184.1) = 0.98$, $p = 0.38$, even after removing the other measures of cognitive vulnerability from the model. The strongest predictors of depressive symptoms at follow-up were depressive symptoms at baseline: cognitive symptoms, $F(2, 193.7) = 101.58$, $p < 0.0001$ and somatic symptoms, $F(2, 209.5) = 359.55$, $p < 0.0001$.

We checked whether there were significant interaction effects between diagnostic status at baseline with cognitive vulnerability and the use of antidepressants with cognitive vulnerability. After sequential discarding of insignificant interaction effects from the model, none remained significant (all $p < 0.05$). The effect of cognitive vulnerability on the development of depressive symptoms is therefore not dependent on a depressive state, an anxious state nor the use of antidepressants.

Table 2. Results from Wald tests assessing the overall association of predictor variables with both the cognitive and somatic symptom dimensions of depression after multivariate multiple regression analysis (n=2981).

Variable	F-ratio	Probability
Sex	1.07	0.34
Age	1.03	0.36
Education	3.18	<0.05
Partner	4.69	<0.01
Smoking	0.81	0.44
Drinking behavior	0.37	0.69
Somatic diseases	7.36	<0.001
Cognitive symptoms at baseline	101.58	<0.001
Somatic symptoms at baseline	359.55	<0.001
Negative life event experienced	2.21	0.11
Cognitive reactivity	19.20	<0.001
Locus of control	28.25	<0.001
Implicit self-depressive associations	0.98	0.38
Explicit self-depressive associations	5.79	<0.01
Explicit self-depressive associations times negative life events experienced	4.76	<0.01

7.3.3. Separate outcomes

The multivariate regression model was used to examine the effects of cognitive vulnerability on the symptom dimensions separately. No variable showed problematic multicollinearity (VIF < 6 for all variables). Wald tests were performed to assess the differential association of the predictor variables with the outcome measures. The coefficients from the multivariate regression analysis and their corresponding F-ratio's assessing the differential association with the cognitive and somatic symptom dimensions for all predictor variables and depressive symptoms at baseline are presented in table 3.

Table 3. Tests of equality between standardized regression coefficients of the multivariate multiple regression model (n=2981), regressing cognitive and somatic symptom dimensions of depression on measures of cognitive vulnerability adjusted for baseline severity and covariates.

Variable	*Cognitive*		*Somatic*		*Difference*	
	b	*Sd*	*b*	*Sd*	*F*	*p*
Cognitive symptoms at baseline	0.33	0.03	0.00	0.03	178	<0.001
Somatic symptoms at baseline	0.08	0.02	0.54	0.02	483	<0.001
Cognitive reactivity	0.12	0.02	0.11	0.02	0.54	0.46
Locus of control	0.16	0.02	0.10	0.02	8.69	<0.01
Explicit self-depressive associations	0.10	0.03	0.02	0.04	7.50	<0.01
Explicit self-depressive associations times negative life events experienced	0.09	0.03	0.02	0.03	5.92	<0.05

Note: Sd = Standard deviation.

Locus of control (b_1 = 0.16, *SE* = 0.02, η^2 = 0.01; b_2 = 0.10, *SE* = 0.02, η^2 = 0.004), explicit self-depressive associations (b_1 = 0.10, *SE* = 0.03, η^2 = 0.002; b_2 = 0.02, *SE* = 0.04) and explicit self-depressive associations*NLE (b_1 = 0.09, *SE* = 0.03, η^2 = 0.001; b_2 = 0.02, *SE* = 0.03) were significantly more strongly associated with the cognitive symptom dimension (b_1) than the somatic symptom dimension (b_2) of depression, $F(1, 210.6) = 8.69$, $p < 0.01$, $F(1, 198.9) = 7.50$, $p < 0.01$ and $F(1, 321.6) = 5.92$, $p < 0.05$ respectively.

Cognitive reactivity (b_1 = 0.12, *SE* = 0.02, η^2 = 0.007; b_2 = 0.11, *SE* = 0.02, η^2 = 0.005) and implicit self-depressive assumptions (b_1 = 0.00, *SE* = 0.01; b_2 = 0.01, *SE* = 0.01) were not differentially associated with the cognitive (b_1) versus the somatic symptom dimension (b_2) $F(1, 160.5) = 0.54$, $p = 0.46$ and $F(1, 94.3) = 1.81$, $p = 0.18$, respectively.

The baseline cognitive (b_1 = 0.33, *SE* = 0.03, η^2 = 0.02; b_2 = 0.00, *SE* = 0.03) and somatic symptom dimensions (b_1 = 0.08, *SE* = 0.02, η^2 = 0.002; b_2 = 0.54, *SE* = 0.02, η^2 = 0.11) were significant differently associated with the cognitive (b_1) versus the somatic symptom dimension (b_2) of depression at the 1 year follow-up assessment $F(1, 380.8) = 178.83$, $p < 0.0001$, $F(1, 122.8) = 483.23$, $p < 0.0001$.

7.3.4. Post-hoc analysis of the LEIDS-R-subscales

Cognitive reactivity was associated with overall symptoms of depression at the follow-up assessment, yet it did not differentiate between the cognitive and somatic symptom

dimensions. The subscales of the Leiden Depression Sensitivity Index-Revised (LEIDS-R) might have opposing effects and therefore level out the effects of differentiation. A post-hoc analysis was performed to test this hypothesis.

Table 4. Tests of equality between standardized regression coefficients of the post-hoc multivariate multiple regression model (n=2981), regressing cognitive and somatic symptom dimensions of depression on subscale scores of the LEIDS-R, adjusted for baseline severity of depressive symptoms, covariates and measures of cognitive vulnerability to depression.

Subscale	*Cognitive*		*Somatic*		*Difference*	
	b	*Sd*	*b*	*Sd*	*F*	*p*
Hopelessness/suicidality	0.05	0.02	−0.01	0.02	10.5	<0.001
Acceptance/coping	0.01	0.02	0.02	0.02	0.75	0.39
Aggression	0.03	0.02	0.01	0.02	1.83	0.18
Control/perfectionism	−0.01	0.02	−0.03	0.02	1.31	0.26
Risk aversion	−0.01	0.03	0.06	0.03	8.77	<0.01
Rumination	0.08	0.03	0.08	0.03	0.00	0.98

Note: LEIDS-R=Leiden Index of Depression Sensitivity-Revised. Sd=standard deviation.

The same statistical model was used as before, with the sum-score of the LEIDS-R replaced by the scores on the 6 subscales of the LEIDS-R. Because multiple testing without previously defined hypothesis inflates the overall type-I error rate we applied a Bonferroni-correction to the significance level ($\beta = \alpha/n = 0.05/6 = 0.008$). The results of the post-hoc analysis are presented in table 4. The hopelessness/suicidality subscale (b_1 = 0.05, SE = 0.02; b_2 = -0.01, SE = 0.02) was significantly more strongly associated with the cognitive (b_1) than the somatic (b_2) symptom dimension $F(1, 1046.9) = 10.48$, $p < 0.002$). The risk aversion subscale (b_1 = -0.01, SE = 0.03; b_2 = 0.06, SE = 0.03) was significantly more strongly associated with the somatic (b_2) than the cognitive (b_1) symptom dimension $F(1, 85) = 8.77$, $p < 0.004$). All other subscales had similar associations with both symptom dimensions (all $p < 0.008$).

7.4. Discussion

This study is the first to prospectively examine the differential association of multiple measures of cognitive vulnerability to depression with cognitive and somatic symptom dimensions of depression. We found that cognitive reactivity, external locus of control

and explicit self-depressive associations were independently associated with an increase in depressive symptoms over a one year period. The association of explicit self-depressive associations with depressive symptoms was strengthened by the effect of negative life events. All measures of cognitive vulnerability to depression that were associated with depressive symptoms were more strongly associated with the cognitive than with the somatic symptom dimension of depression. Our hypotheses that (I) cognitive vulnerability is associated with depressive symptoms, (II) negative life events moderate these associations and (III) cognitive vulnerability is more associated with the cognitive than the somatic symptom dimension of depression, were largely supported by the findings.

7.4.1. Cognitive vulnerability is more strongly associated with the cognitive than the somatic symptom dimension of depression

Cognitive vulnerability to depression differentially predicts cognitive and somatic symptom dimensions of depression. This differentiating effect is reflected by the finding that hopeless reactions to sad moods, external locus of control and explicit self-depressive associations were significantly more strongly associated with the cognitive versus the somatic symptom dimension of the Inventory of Depressive Symptomatology-Self Report (Wardenaar, et al., 2010). It has been shown that the measures of cognitive vulnerability to depression that were used in this study are predictive of general depressive symptoms (Scher, et al., 2005; Taylor and Stanton, 2007; Wisco, 2009). However, the longitudinal relationship between multiple measures of cognitive vulnerability to depression and different homogeneous symptom dimensions of depression has not been studied before. Still, it is important to do so because the heterogeneity in symptoms of depression may obscure research into the etiology and the effective treatment of depression. Our results support the notion that the concept of major depression as maintained by the *DSM-IV* might not be sustainable (Lux and Kendler, 2010; Parker, 2005; Zimmerman, et al., 2006). They support the notion that a dimensional approach is preferred to a categorical approach when studying the etiology of depression (Hyman, 2007; Kendler and Gardner, 1998). Our findings indicate that cognitive vulnerability to depression plays a role in the etiology of a more "cognitive subtype" of depression in a continuous linear fashion. This is especially relevant since cognitive symptoms of depression are consistently stronger

predictors of clinical validators than somatic symptoms of depression (Lux and Kendler, 2010).

Cognitive reactivity was associated with overall depressive symptoms at the follow-up assessment. Contrary to our expectation it did not discern between symptom dimensions of depression. The Leiden index of depression sensitivity consists of six different subscales. The post-hoc analysis showed that the association of the subscales with symptom dimensions of depression leveled out the differentiating effect. The hopelessness/suicidality subscale was more associated with the cognitive symptom dimension of depression, while the risk aversion subscale was more associated with the somatic symptom dimension of depression. Although not directly comparable, our results resemble results in studies on the hopelessness theory of depression, showing that a negative inferential style in interaction with negative life events, will predict the occurrence of the hopelessness cluster of symptoms (Abramson et al., 1989 and Hankin et al., 2001). Avoidance may be more typical for both depressed and anxious individuals who display symptoms of anxiety and arousal (Trew, 2011).

7.4.2. Cognitive vulnerability is predictive of depressive symptoms

Cognitive reactivity, external locus of control and explicit self-depressive associations were predictive of depressive symptoms over a one year period. These measures predicted depressive symptoms over and above the other effects of cognitive vulnerability to depression. This indicates that the vulnerability traits independently predict the development of depressive symptoms over time. Baseline depressive symptoms had the largest effect on depressive symptoms at follow-up, underlining the stability of depressive symptoms over time.

This study provides the first evidence that cognitive reactivity as assessed by the LEIDS-R is also associated with depressive symptoms over a 1 year period. The findings of the current study are in line with previous studies that show an association between external locus of control and explicit negative self-associations with increased MDD incidence (de Graaf, et al., 2002; Ernst, et al., 1992; Wisco, 2009). The measure we used to assess explicit self-depressive associations was internally consistent and it appears to be valid. However, it is not validated yet, so results need to be interpreted with caution.

Implicit self-depressive associations were not associated with depressive symptoms at the follow-up assessment. When we removed all other measures of cognitive vulnerability from the model, implicit self-depressive associations were still not significantly associated with depressive symptoms. An average effect size of $r = 0.15$ was found in a meta-analysis examining the association between implicit depressed cognitions and depression in sixteen studies (Phillips, et al., 2010). However, fifteen of those studies were cross-sectional. It is possible that depression increases implicit depressive cognitions and not the other way around, i.e. reversed causality. To our knowledge, there is only one study that prospectively examined the effects of implicit self-depressive associations on the development of depressive symptoms. In this study with a follow-up time of five weeks, implicit self-worth cognitions were predictive of depressive symptoms after adjustment for baseline depressive symptoms and explicit self-depressive associations (Haeffel, et al., 2007).

7.4.3. Negative life events moderate the associations between cognitive vulnerability and depressive symptoms

The presence of a negative life event strengthened the association between explicit depressive self-associations and depressive symptoms. The interaction effect of locus of control was significant when it was entered in the model separately, but not when the interaction effect of explicit self-depressive associations was added. This implies that the effect of stress on the association between cognitive vulnerability and depression is non-specific for explicit self-depressive associations and locus of control, but may reflect common explained variance. Cognitive reactivity did not interact with stress. Most support for the interaction of cognitive reactivity with stress to predict depression is derived from priming studies. When this interaction was studied in longitudinal study designs, results were mixed (Scher, et al., 2005). It is possible that some forms of stress that are more acute than negative life events per se are more useful for evaluating the diathesis-stress model of depression (Hammen, 2005).

7.4.4. Strengths and limitations

Our findings have to be viewed in light of some limitations. Although the sensitivity analysis we performed showed that our findings are similar for depressed and not

depressed individuals at baseline, there might still be a problem regarding the generalizability of the findings to the general population. The list of threatening experiences may not provide enough information to capture the complex diatheses-stress interaction, although recent research underlines the sufficient validity and stability of this measure (Rosmalen, et al., 2012). It was beyond the scope of this study to examine the association of biological risk factors for depression with the symptom dimensions. This could be of interest for future research.

Our study has some important strengths. The sample used in this study is over-inclusive of depressed and anxious patients. The large number of participants that were included in the study provides the analysis on which the results are based with substantial statistical power. The model that was used to analyze the data allowed a direct comparison of the effects of predictor variables on different outcome variables. The longitudinal design of the study allowed inferences about the impact of cognitive vulnerability on depressive symptoms over time. Multiple risk factors for depression were analyzed simultaneously, which confirmed that different measures of cognitive vulnerability to depression each show unique predictive validity.

7.4.5. Conclusion

As epidemiologic research shows that depression is a complex and heterogeneous disorder, concerns about the validity of the depression concept as it is defined today are deserved and warranted. The results of this study indeed strengthen the notion of depression as a heterogeneous disorder. More importantly, homogeneous measures of depressive symptoms provide more information about the patient then a heterogeneous measure of depression. This information can be used to more specifically monitor a patient's progress or prognosis, allowing for possible treatment adjustment. As the results of our study indicate, they can also be more informative regarding the risk factors that underlie such complaints. These risk factors (feeling helpless, a negative self-image and unhelpful thoughts during sad mood) can indeed be targeted specifically to cater to the needs of the individual patient. When cognitive symptoms are prominent or do not diminish in a patient, classical cognitive therapy could be indicated. Patients with more somatic symptoms could benefit from more biological treatment strategies such as medication or light therapy. With the use of empirically validated homogeneous subscales,

depression treatment can hopefully become more tailored to the specific nature and origins of complaints.

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