Vulnerability and emotional processing in depression

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Part 2

Chapter 4

Cognitive vulnerability and implicit emotional processing: imbalance in frontolimbic brain areas?

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Abstract

It has been proposed that the neural basis for cognitive vulnerability to depression involves an imbalance in frontolimbic activity during the processing of cues with a negative affective value. Although the question is central to cognitive theory, whether this association is amplified by diagnosis of an affective disorder or recent life stress has not been investigated. A composite cognitive vulnerability score based on questionnaire assessment was used to predict neural responses to negative emotional stimuli in N = 112 participants. Potential moderating effects of psychiatric diagnosis and negative life events were examined. Main and interaction effects were tested against a threshold of $p < .05$, family-wise error (FWE) corrected at the cluster level, and the results were small-volume corrected in regions of interest. Cognitive vulnerability predicted higher activation of superior parietal areas ($p_{FWE} < .01$) for negative than for positive faces. The association was significantly stronger in healthy participants. For negative versus control stimuli, cognitive vulnerability predicted higher ventrolateral prefrontal and subgenual anterior cingulate activation ($p_{FWE} < .05$) to equal extents in both groups. We found no evidence for an association with amygdala activation. Life events did not moderate the findings. We concluded that cognitive vulnerability was associated with higher activation of frontoparietal areas during an implicit emotional task. These higher levels of activation may potentially reflect increased effort being required to ignore irrelevant negative emotional information in vulnerable populations.

4.1. Introduction

A schema of expectancies that give rise to persistent negative cognitions about oneself, the world and the future is considered to be an important risk factor for depression (Alloy et al., 1999; Beck, 1963; Scher et al., 2005). This form of cognitive vulnerability is generally embedded in a causal diathesis-stress framework (Monroe and Simons, 1991) in which negative cognitions can be stimulated by significant stressors or by a negative mood challenge (Lau et al.,, 2004; Van der Does, 2002). Epidemiological studies have demonstrated that stressful life events (Hammen, 2005) and a current negative mood state (Scher et al., 2005) enhance the predictive power of cognitive vulnerability. The results from a large longitudinal study have confirmed that the self-reported vulnerability factors of cognitive reactivity, negative attribution style, and negative self-evaluations predict future depressive symptom levels over and above current depressive symptom levels, especially when a major negative life event has been faced in the interim (Struijs et al., 2013).

Cognitive vulnerability does not affect mood in isolation, but is thought to fuel the automatic activation of negatively biased information processing (Beck, 2008). By definition, negative thoughts influence the appraisal of stimuli and therefore guide perception (Kircanski et al., 2012). It has been proposed that cognitive vulnerability is also related to difficulties with disengaging attention from negative information. This hypothesis is based upon studies in depressed patients that have reported interference effects from emotional stimuli at relatively late stages of processing, which may be most pertinent for negative self-relevant information, such as facial expressions (De Raedt and Koster, 2010).Therefore, emotional valence is critical to consider when investigating altered information processing in affective disorders (Browning et al., 2010; De Raedt and Koster 2010).

Neural models of depression vulnerability have attributed negatively biased appraisal (bottom-up) to the amygdala, and deficient control over negative information (top-down) to the lateral prefrontal cortex, with the rostral anterior cingulate cortex (Beck, 2008; Disner et al, 2011; Roiser et al., 2012) serving as an intermediary between emotion and cognition. These areas have been consistently implicated in functional neuroimaging studies with emotional tasks in healthy individuals (Lindquist et al., 2012). Furthermore, depressed patients show diametrically opposed activation abnormalities for negative and

positive stimuli, with higher activation in limbic areas and lower activation in lateral prefrontal areas for negative stimuli (Groenewold et al., 2013). A few empirical studies have additionally investigated whether these activation differences are exclusively present in the depressed state, or may also reflect vulnerability for depression.

Specifically, it has been found that patients in remission from depression exhibit higher activation in the left dorsolateral prefrontal cortex (dlPFC) when disengaging from negative stimuli and lower activation in the right dlPFC when disengaging from positive stimuli (Kerestes et al., 2012). Moreover, an association has been reported between trait rumination and higher activation in right dlPFC for disengaging from negative as compared to positive stimuli (Vanderhasselt et al., 2011). Of note, this direction of effects is opposite to what is observed in the depressed state. Trait rumination and cognitive vulnerability have been associated with higher amygdala (AMG), anterior cingulate cortex (ACC) and ventrolateral prefrontal cortex (vlPFC) activation during the perception of negative emotional information in nondepressed participants (Ray et al., 2005; Thomas et al., 2011; Zhong et al., 2011), although one of the studies found associations in participants with a history of depression only. The results from studies investigating vulnerability have shown mixed results for the lateral prefrontal areas, indicating that the alterations found in depressed patients may not be generalizable to vulnerable populations.

In summary, there is empirical evidence that depression is associated with altered activity in limbic areas (AMG and ACC) and in lateral prefrontal areas (vlPFC and dlPFC) for processing negative stimuli. However, the nature of the association between cognitive vulnerability and brain activation is still unclear. Although the question is central to the cognitive theory of depression whether the association between cognitive vulnerability and brain activity is amplified in the context of negative life events or the diagnosis of an affective disorder has not been investigated. Therefore, in the present study we aimed to investigate the effects of cognitive vulnerability on brain activation in interaction with negative life events and a current diagnosis of depression or anxiety. The AMG, ACC, vlPFC, and dlPFC were selected as *a priori* regions-of-interest.

4.2. Method

4.2.1. Sample

To examine the neural correlates of cognitive vulnerability, data were derived from the Netherlands Study of Depression and Anxiety (NESDA). This multicenter, naturalistic, longitudinal cohort study was designed to examine the psychosocial and neurobiological factors associated with depressive and anxiety disorders. NESDA included patients meeting diagnostic criteria for a current or lifetime depressive and/or anxiety disorder (N = 2,329), along with control participants who had never met the diagnostic criteria (N = 652). All participants provided written informed consent in accordance with the declaration of Helsinki before inclusion. The protocol was approved by the ethical review boards of the collaborating institutions (University Medical Center Groningen [UMCG], Leiden University Medical Center [LUMC] and VU Medical Center [VUMC]) and has been described in more detail elsewhere (Penninx et al., 2008).

A subsample of participants (N = 267) performed an emotional faces task during functional magnetic resonance imaging (fMRI) scanning at the baseline measurement. Participants with a lifetime but not a current (6-month) diagnosis were not invited for the scan. Scanning was performed at the three different institutions. For the present study, patients who reported antidepressant medication use at baseline were excluded from the analyses (N = 71). Participants were also excluded due to missing questionnaire data (N = 21), a >13-week interval between baseline interview and scan (N = 39), or technical problems that became evident after visually checking the raw data and preprocessing parameters (N = 24). For seven of these participants the faces task could not be completed during the scanning session. For five participants movement resulted in incomplete coverage of the amygdala. Furthermore, for 12 participants, the data were of insufficient quality to be analyzed (missing logfiles, signal loss in other regions of interest, movement >3 mm, failed normalization). The final sample consisted of N = 112 participants.

4.2.2. Cognitive vulnerability

Three self-report questionnaires were selected to measure cognitive vulnerability, on the basis of good psychometric properties and convergent validity. The questionnaires capture the well-known and often studied domains of cognitive reactivity, negative

attribution style, and negative self-evaluations (Alloy et al., 1999; Beck, 1963; Scher et al., 2005). Moreover, all three measures have been found to interact with negative life events to predict longitudinal changes in depressive symptom levels (Struijs et al., 2013). The Leiden Index of Depression Sensitivity - Revised (LEIDS-R; Van der Does and Williams, 2003) measures cognitive reactivity with 34 items (e.g. When I feel down, I more often feel hopeless about everything). The Mastery Scale (Pearlin and Schooler, 1978) measures attributions about stressful events with five items (e.g. I have little control over the things that happen to me). Attributes from an Implicit Association Task (IAT; Glashouwer and De Jong, 2010) were used to measure explicit self-depressive associations in an Explicit Association Task (EAT). It contained five depressed attributes and five elated attributes that were combined in a total score. All questionnaires used 5-point rating scales with higher scores indicating higher vulnerability. To statistically optimize the multidimensional measurements of cognitive vulnerability, a principal components analysis was performed on total scores of the three questionnaires. The continuous factor score (eigenvalue > 1) was used as the predictor in the analyses.

4.2.3. Moderating variables

The List of Threatening Experiences (LTE; Brugh et al., 1985) instrument was administered by a trained interviewer to record serious negative life events in the past year, such as the death of a loved one. A dichotomous variable (any event in the past year, yes/no) was constructed, because this resulted in evenly distributed groups and facilitated the interpretation of the interaction effect. Lifetime and current (6-months) diagnosis was assessed by a structured clinical interview, the Composite Interview Diagnostic Instrument (CIDI version 2.1; Kessler and Ustun, 2004). The questions corresponded directly to the symptoms of axis-I psychiatric disorders listed in the Diagnostic and Statistical Manual of mental disorders (DSM-IV-TR; APA, 2004). The moderator psychiatric diagnosis was defined as meeting DSM-IV criteria for major depression or any anxiety disorder in the past six months. Affective disorders were combined into one group, because of partial overlap in cognitive biases (Browning et al., 2010) and high comorbidity rates between the disorders. According to the NESDA design, participants with a current anxiety disorder may have experienced depression in the past. Moreover, they are at greater risk of developing depression in the future (Penninx et al., 2008).

4.2.4. Covariates

Education level at baseline was used as a continuous covariate, measured in years of education. The Inventory of Depressive Symptomatology Self Report (IDS-SR; Rush et al., 1996) was used to measure depression severity at the time of scanning. The IDS-SR has demonstrated satisfactory psychometric qualities and high sensitivity to change in previous research (Rush et al., 1996). Both current psychiatric diagnosis and depression severity were used as covariates when assessing the main effect of cognitive vulnerability, in order to examine potential confounding effects of the depressed state. Finally, since negative life events may predict both psychiatric diagnosis and cognitive vulnerability levels, this variable was included as a covariate in analysis of the main effects of cognitive vulnerability and the interaction effect between cognitive vulnerability and psychiatric diagnosis.

4.2.5. Emotional faces task

The event-related task paradigm took approximately 12 min. The stimuli consisted of color photographs from the Karolinska Directed Emotional Faces System (Lundqvist et al., 1998) depicting 12 male and 12 female faces with angry, fearful, sad, happy, and neutral facial expressions. Furthermore, a scrambled face was presented 80 times as control condition. The stimuli were presented in E-prime (Psychological Software Tools, USA) for 2.5 s in pseudorandomized order, interspersed with a black screen that was displayed over a variable interstimulus interval of 0.5 to 1.5 seconds. The participants were instructed to make a gender judgment for the emotional faces or to indicate the direction of an arrow for the scrambled faces.

4.2.6. MRI data acquisition

Scanning was performed on a Philips Intera 3 T MR scanner in all three institutions. A T1-weighted anatomical image (TR = 9 ms, TE = 3.5 ms, matrix size 256 × 256, voxel size 1 × 1 × 1 mm) was acquired for spatial reference. During the task, 310 T2*-weighted echo planar imaging volumes (TR=2,300 ms, UMCG: TE = 28 ms, AMC and LUMC: TE = 30 ms, flip angle 90°) were obtained. At the UMCG 39 slices and at the AMC and LUMC 35 slices were acquired in interleaved order with no gap and a 3-mm thickness. All images were acquired parallel to the anterior commissure – posterior commissure

plane. The heads of the participants were fixated with cushions to prevent movement during scanning. The procedure was described in further detail in a previous report (Demenescu et al., 2011).

4.2.7. Statistical analysis

The fMRI data analysis was performed with SPM5, implemented in Matlab 7.1.0 (The MathWorks Inc., USA). Preprocessing consisted of slice-timing to correct for interleaved acquisition, realignment of functional images, and coregistration of the anatomical image to the functional images, followed by spatial normalization to the Montreal Neurological Institute (MNI) space, resampling into a 3 × 3 × 3 mm voxel grid. Coregistration and normalization were visually checked and manually corrected, if necessary. The data were spatially smoothed with an 8 mm full-width at half-maximum Gaussian kernel. At first level, a canonical hemodynamic response function was applied in a general linear model. The onset and total duration of stimulus presentation were modeled at the voxel level for all experimental conditions. Next, contrast maps were created for the comparisons of negative (angry, fearful, sad) to happy faces, negative to scrambled faces, and positive to scrambled faces. Negative facial expressions were combined, because previous studies that combined multiple categories of negative facial expressions had reported comparable results across categories (Stuhrmann et al., 2011). Since the contrast negative > positive faces was deemed most powerful to examine negativity bias, these contrast images were entered as dependent variable into a general linear model for the primary analysis. Finally, to increase comparability with previous studies two *post-hoc* analyses were performed with the contrast values for negative>scrambled faces and positive > scrambled faces as dependent variables.

Cognitive vulnerability was entered as a continuous regressor to examine linear associations with brain activation. The interactions between cognitive vulnerability and the moderators were statistically modeled by entering two entering two separate continuous regressors stratified by level of the moderator. So, we created two cognitive vulnerability regressors in a first general linear model for participants with and without psychiatric diagnosis, and in a next model for participants with and without negative life events (NLE). Cognitive vulnerability was centered for each group, to statistically separate the effects of vulnerability from differences between diagnostic groups and

between stress groups. The main effect of the moderator was also included. Interaction effects were examined by testing whether the regression coefficients for cognitive vulnerability were significantly different between the groups. Main and interaction effects were tested with t-contrasts and initially thresholded at $p < .001$ uncorrected $k > 5$ and evaluated against a predefined threshold of $p_{FWE} < .05$ cluster-level family-wise error (FWE) correction for multiple comparisons. Relevant interaction effects were followed up by visualization of the main effects in each group separately.

One composite mask was created combining the following *a priori* regions of interest (ROIs) in the Wake Forest University Pickatlas: bilateral amygdala, rostral ACC Brodmann's Area (BA)25, bilateral vlPFC BA45, bilateral dlPFC BA46. These anatomical ROIs were selected on the basis of task activations from a previous study (Wolfensberger et al., 2008) using the same task to avoid circular analysis (Kriegeskorte et al., 2009). Small-volume correction was applied in SPM5 to results that fell within the composite ROI mask. In all models, covariates associated with cognitive vulnerability levels were entered to examine potential confounding effects.

4.3. Results

4.3.1. Sample characteristics

A principal components analysis was performed to generate a composite cognitive vulnerability score from the LEIDS-R, Mastery, and EAT total scores. A one-factor solution with an eigenvalue of 2.390 explaining 79.7 % of variance was considered optimal. The Kaiser-Meyer-Olkin (0.74) and Bartlett's tests ($\chi^2 =$ 164.3, $df = 3$, $p < .001$) confirmed a good fit. Next, continuous factor scores were extracted for each participant. A median split was performed on the cognitive vulnerability scores to summarize the sample characteristics for participants with high and low cognitive vulnerability (Table 1).

Participants with high cognitive vulnerability had received less education ($t = 2.05$, $p = .04$), reported more negative life events ($\chi^2 = 8.02$, $p = .005$), and more often met diagnostic criteria for an affective disorder ($\chi^2 = 74.3$, $p < .001$). We found no differences in age, sex, handedness or scanning center. The mean reaction times for negative, positive, and scrambled stimuli indicated that cognitive vulnerability levels did not predict task performance. However, responses were generally faster for scrambled faces than for emotional faces. Cognitive vulnerability was used as a continuous predictor in the subsequent analyses.

4.3.2. Task effects

Previous analyses of the data demonstrated consistent activation of bilateral fusiform areas and bilateral amygdala for emotional versus scrambled faces (Demenescu et al., 2011). All emotional conditions were associated with this activation pattern. The contrast of negative versus positive faces showed more activation in the bilateral middle temporal gyrus (left: x=-54, y=57, z=9, T=4.44, cluster-level p_{FWE}=.05); right: x = 63, y = -39, z = 6, $t = 4.95$, cluster-level $p_{FWE} < .001$). Furthermore, the ROI mask showed that the left ventrolateral prefrontal cortex (BA45) was more active for negative than for positive faces (x =

-48, y = 24, z = 9, $t = 4.67$, cluster-level $p_{FWE} = .032$). In contrast, visual areas (BA17: x = -18, y = -96, z = 12, $t = 6.62$, cluster-level $p_{FWE} = .002$), orbitofrontal cortex (BA10: x = -9, y = 60, z = 0, $t = 4.58$, cluster-level $p_{FWE} = .006$), and dorsomedial prefrontal cortex (BA32: x = -3, y = 21, z = 48, $t = 3.97$, cluster-level $p_{FWE} = .001$) were more active for positive than for negative faces.

Table 1. Sample characteristics presented separately for participants with low and high cognitive vulnerability.

Variable	Low vulnerable (N=56)	High vulnerable (N=56)	Test statistics
Education, M (sd)	13.89 (2.85)	12.75 (3.04)	T=2.05, p=0.04
Age, M (sd)	37.63 (10.19)	35.34 (10.40)	T=1.18, p=0.24
Female sex	62.5 %	67.9 %	χ^2=0.35, p=0.55
Handedness, left	10.9 %	8.9 %	χ^2=0.12, p=0.73
UMCG	17.9 %	21.4 %	χ^2=0.37, p=0.83
AMC	26.8 %	28.6 %	
LUMC	55.4 %	50.0 %	
NLE past year	42.9 %	67.9 %	χ^2=*7.08*, p<0.01
Diagnosis DEP (6 month)	14.3 %	39.3 %	χ^2=*67.2*, p<0.01
Diagnosis ANX (6	10.8 %	23.2 %	
month)	0.0 %	37.4 %	
Diagnosis CAD (6 month)	830.9 (142.1)	820.6 (116.0)	T=0.416, p=0.68
RT negative, M (sd)	859.8 (134.4)	855.2 (126.1)	T=0.187, p=0.85
RT positive, M (sd)	751.2 (147.9)	739.4 (144.4)	T=0.424, p=0.67
RT scrambled, M (sd)			

Note. Group differences are tested with χ^2 and two-sample *T*-tests as appropriate. Education and age are measured in years, reaction time in milliseconds. Abbreviations: UMCG = University Medical Center Groningen, AMC = Amsterdam Medical Center, LUMC = Leiden University Medical Center, NLE = negative life event, DEP = depression, ANX = anxiety, CAD = combined anxiety and depression, RT = reaction time.

4.3.3. Primary analysis: cognitive vulnerability and brain activation for negative as compared to positive faces

For negative versus positive faces, we found no interaction between negative life events and cognitive vulnerability. However, the interaction between vulnerability and psychiatric diagnosis was significant. Therefore, results are presented for a model including this interaction (Table 2). The whole-brain analysis showed a trend towards an overall association of cognitive vulnerability with higher activation in the right dlPFC (cluster-level $p_{FWE} < .10$ small-volume corrected) and left dlPFC ($p < .001$ uncorrected). No association was apparent between vulnerability and activation levels in the

hypothesized limbic areas. Cognitive vulnerability was positively associated with a cluster of activation in superior parietal areas and precuneus (t = 4.08, cluster-level p_{FWE} = .011). This association was weaker for participants with a psychiatric diagnosis than for healthy controls (negative interaction superior parietal areas t = 4.56, p_{FWE} = .001). Post-hoc separation of the groups revealed that the association was only present in participants without a psychiatric diagnosis (t = 4.83, cluster-level p_{FWE} = .003), and did not reach significance in participants with a psychiatric diagnosis (no peak voxels in the area at p < .001 uncorrected). The correlations between activation and vulnerability are depicted separately for the diagnostic groups in Figure 1. These findings did not change substantially after adding relevant covariates (education and negative life events) to the model.

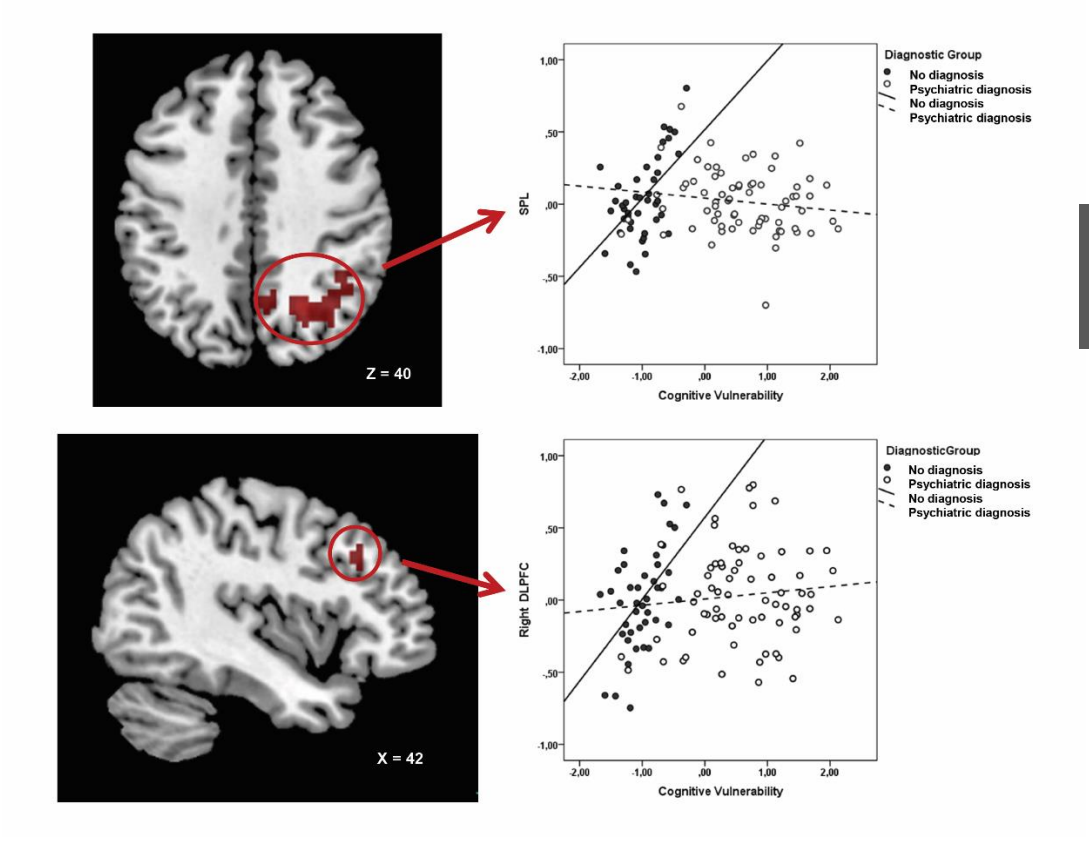
Table 2. Peak Coordinates of Activation Differences between Negative>Positive Faces for the Main Effect of Cognitive Vulnerability and the Cognitive Vulnerability x Diagnosis Interaction.

Cluster label	**BA**	**Volume** (# voxels)	**X.max**	**Y.max**	**Z.max**	**T-value**	**P-value** (FWE-cluster)
Main effect cognitive vulnerability							
Parietal	7	71	21	-60	42	4.08	.011
Precuneus	7		6	-60	42	3.88	
Right DLPFC	46	12	48	36	24	3.66	.095
Left DLPFC	46	11	-42	27	33	3.64	n.s.
Interaction cognitive vulnerability x diagnosis							
Parietal	7	114	21	-60	42	4.56	.001
	7		33	-63	39	4.11	
	40		42	-51	42	3.47	
Precuneus	7	10	6	-60	42	3.66	n.s.

Abbreviations: BA = Brodmann's Area, FWE = family wise error, DLPFC = dorsolateral prefrontal cortex. For completeness, results are presented at p < .001 k > 10. The p-values for regions of interest are small-volume corrected.

Figure 1. The Association between Cognitive Vulnerability and Brain Activation in the Negative > Positive Contrast Presented Separately for Participants without and with Psychiatric Diagnosis.

Top row: Activation in superior parietal lobule (Y-axis: eigenvariate 114 voxels with FWE-significant vulnerability x diagnosis interaction). Bottom row: Activation in right dorsolateral prefrontal cortex (Y-axis: eigenvariate 12 voxels with main effect of vulnerability at $p < .001$ uncorrected in BA46).



4.3.4. Post-hoc analysis: Cognitive vulnerability and brain activation for negative as compared to scrambled faces

Previous studies had generally compared negative stimuli to neutral control stimuli, with negative faces eliciting robust amygdala activation relative to scrambled faces. Therefore, a post-hoc analysis was performed to test whether this contrast would show associations between cognitive vulnerability and activation in limbic areas. For the contrast of negative versus scrambled faces, we observed no interactions between cognitive

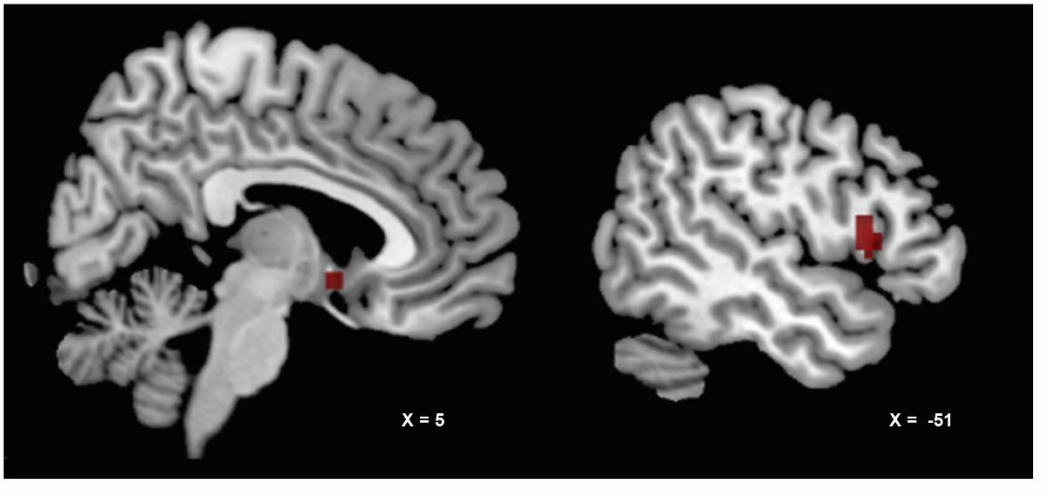
vulnerability and negative life events or psychiatric diagnosis. However, cognitive vulnerability was associated with higher activation in the left vlPFC (t = 4.71, cluster-level p_{FWE} = .043 after small-volume correction) and ventral ACC (t = 4.19, cluster-level p_{FWE} = .047 after small-volume correction). The foci of activation are depicted in Table 3 and Figure 2. The findings did not change after adding relevant covariates to the model.

Table 3. Peak Coordinates of Activation Differences between Negative>Scrambled Faces for the Main Effect of Cognitive Vulnerability within the Regions of Interest.

Cluster label	**BA**	**Volume** (# voxels)	**X.max**	**Y.max**	**Z.max**	**T-value**	**P-value SVC** (FWE-cluster)
Left VLPFC	45	19	-51	15	9	4.71	0.043
ACC	25	18	-3	6	-6	4.19	0.047

Abbreviations: BA Brodmann Area, SVC small volume correction, FWE family wise error, VLPFC ventrolateral prefrontal cortex, ACC anterior cingulate cortex. Note: For completeness, results are presented at p<0.001 k>10. P-values are small-volume corrected.

Figure 2. Association Between Cognitive Vulnerability and Brain Activation in the Negative > Scrambled Contrast in Anterior Cingulate Cortex (left panel: BA25) and Left Ventrolateral Prefrontal Cortex (right panel: BA45).



To examine whether the results could be explained by the current depressed state, psychiatric diagnosis was added to the model. A minor reduction in effect size was observed (vlPFC: t = 4.20, p_{FWE} = .052 and ACC: t = 3.57, p_{FWE} = .23). Next, cognitive

vulnerability was replaced by IDS score to avoid multicollinearity, in the model with covariates and without psychiatric diagnosis. Severity of depression as measured by the IDS-score predicted brain activation in the same area of the ventral ACC as cognitive vulnerability. However, cognitive vulnerability was a better predictor of brain activation in the ACC (t = 4.19, cluster-level p_{FWE} = .047) than was psychiatric diagnosis (p_{unc} > .005) or IDS-score (t = 3.95, p_{FWE} > .05). Finally, there was no association between cognitive vulnerability and amygdala activation.

4.3.5. Post-hoc analysis: Cognitive vulnerability and brain activation for positive compared to scrambled faces

We found no interactions between cognitive vulnerability and negative life events or psychiatric diagnosis. Moreover, cognitive vulnerability was not associated with brain activation in this contrast (no clusters present in any region of interest at the initial threshold of p < .001 and k > 5).

4.4. Discussion

In this study, we aimed to identify the neural correlates of cognitive vulnerability for the processing of negative emotional stimuli. In addition, we examined whether these associations were amplified by recent life stress or diagnosis of an affective disorder. Cognitive vulnerability was associated with higher activation of superior parietal areas and precuneus, as well as a positive trend in dlPFC, for negative as compared to positive faces. The association with parietal activation was present in healthy participants, yet not in participants with a psychiatric diagnosis. In addition, overall cognitive vulnerability was associated with higher vlPFC and subgenual ACC activation for negative as compared to scrambled faces. No associations with amygdala activation were apparent. The experience of recent life stress did not moderate the associations between cognitive vulnerability and brain activation.

For the negative versus positive emotion contrast, vulnerability was associated with increased activation in parietal areas, with a trend in the dorsolateral prefrontal cortex. Unaffected first-degree relatives of depressed patients have demonstrated higher activation in parietal and frontal areas when shifting attention away from negative stimuli

relative to controls (Lisiecka et al., 2013). Similar findings were reported for remitted patients in the dlPFC (Kerestes et al., 2012; Norbury et al., 2010, however see also Mannie et al., 2011). These studies all included an emotional valence component, indicating that the reported association may be most prominent for negative relative to positive stimuli. It is interesting that frontoparietal areas have been found to be functionally connected in the dorsal frontoparietal attention network (Banich et al., 2009; Greenberg et al., 2010). Therefore, one could speculate that cognitive vulnerability may be associated with difficulties in top-down control. The findings suggest that if blocking task-irrelevant information is more difficult for negative than for positive stimuli, this may constitute a vulnerability for depression.

Cognitive vulnerability was associated with higher activation in left vlPFC and subgenual ACC (BA25) for negative relative to scrambled faces. VlPFC activation has been related to the inhibition of responses to emotional information (Schulz et al., 2009). Deficits in the inhibition of negative stimuli may lead to a higher exposure to negative information in daily life. This is particularly relevant for negative facial expressions, being important social cues that signal potential conflicts. The VlPFC also plays a role in voluntary emotion regulation (Rive et al., 2013), presumably in concert with the ACC (Phillips et al., 2008). Higher activation in these areas may reflect an increased representation of negative stimuli in regulatory circuits. The previously reported association with higher rumination levels (Ray et al., 2005, Thomas et al., 2011) further supports a linear association with vulnerability.

The subgenual ACC is thought to play a central role in depression (Drevets and Savitz, 2008; Hamani et al., 2011). This area projects to the amygdala and hypothalamus and is associated with autonomic and glucocorticoid stress responses. Therefore, it has been proposed that abnormal functioning of this brain area contributes to emotional reactivity in depression (Drevets and Savitz, 2008). Subgenual ACC activation has previously been related to depression severity (Matthews et al., 2009). In the present study, cognitive vulnerability was a stronger predictor than depression severity, even though the latter was assessed more proximal to the scanning session. Depressed patients show higher activation in this area for the processing of emotional faces irrespective of valence (Groenewold et al., 2013). In contrast, in the present study we found that cognitive vulnerability was specifically associated with activation to negative expressions.

Of note, both subgenual ACC and vlPFC activation were related to vulnerability in all participants, indicating a general susceptibility to interference from negative stimuli.

The hypothesis that stress and diagnosis would amplify the associations between cognitive vulnerability and brain activity was not confirmed by our data. Rather, frontoparietal areas were only activated by participants with high vulnerability levels without an affective disorder. Considering the intact task performance, this surplus recruitment may be functional, allowing these participants to effectively ignore irrelevant negative information. It has been proposed that compensatory frontal activation in remitted depression may contribute to maintaining a healthy status (Thomas et al., 2011), whereas in depressed patients, compensation may break down. However, the findings for lateral frontal areas are mixed, with both decreased and increased activation in depressed individuals. The direction of effects may be modulated by the extent to which regulatory capacity is challenged (Groenewold et al., 2013; Rive et al., 2013), which is an interesting avenue for further research.

Although all findings can be linked to attentional processes and cognition-emotion interactions (Cromheeke and Mueller, 2013), results differed between the primary and post-hoc analysis. Several possible explanations can be raised. Emotional valence was the main contrasting factor in the primary analysis, while task demands were equal across conditions. Instead, the post-hoc analyses maximized power for detecting emotional face processing and interference effects. The emotional conditions included an inhibition and interference component due to the more complex stimulus set and task instructions (focus on gender instead of emotion vs. direct focus on an arrow), which is also supported by the greater reaction times for the emotional conditions. However, the post-hoc analyses demonstrated that the associations between brain activation and cognitive vulnerability were specific for negative stimuli. The results from the primary analysis are most relevant and compelling in demonstrating a relationship between cognitive vulnerability and supplementary recruitment of frontoparietal areas in an implicit emotional task.

When comparing the results to neurobiological models of cognitive vulnerability, our findings mainly support the involvement of top-down processes. Although it was hypothesized that cognitive vulnerability would predict increased stimulus-driven processing in the amygdala, this was not supported by our data. Of note, in our sample

depression and anxiety diagnoses were not associated with increased amygdala activation either (Demenescu et al., 2011). A previous study did report an association between amygdala activation and vulnerability levels (Zhong et al., 2011), yet it employed an explicit emotional task. This discrepancy in results may be explained by the lack of regulatory challenge (Costafreda et al., 2008; Rive et al., 2013) in the task used in the previous study. In at-risk groups diverging amygdala findings have been reported (Barch, 2014), for which the direction of effects may depend on the nature of the emotional task. Integration of results could be established by taking the perspective of frontolimbic imbalance during emotional challenge, rather than by solely focusing on higher amygdala activation. Frontal hyperactivation accompanied by normal amygdala activation could be considered a frontolimbic imbalance in tasks that subtly challenge regulatory capacity (Beevers et al., 2010).

The present study was characterized by several strengths. It is, as of yet, the largest study to investigate the association between vulnerability for depression and brain activations, providing sufficient power to examine linear associations. The sample was highly variable in cognitive vulnerability and included never-depressed participants, allowing for testing of relevant interaction effects. Never-depressed individuals are particularly interesting, since findings cannot be attributed to scar effects from previous depressive episodes, as in remitted depressives. The study used a multifaceted and statistically optimized measure of cognitive vulnerability. Patients reporting antidepressant use at baseline were excluded, reducing possible medication effects (Harmeret al., 2009). However, the study also had several limitations. Because diagnostic status and life events in the past months could have influenced the vulnerability score, potential interactions might be (mis)attributed to the main effect of cognitive vulnerability. Although a maximum interval between interview and scan was set, life events or changes in diagnostic status during this interval were not taken into account. The analyses were not adjusted for scanning center, however, differences in image acquisition between the locations were unrelated to activation levels in the contrasts of interest (see supplement 1). Finally, we did not include neuroticism as a covariate. Neuroticism overlaps with cognitive vulnerability conceptually, yet is a more distal risk factor for depression. Previous findings in the healthy participants from NESDA suggest that neuroticism is

more closely related to amygdala-ACC connectivity than to activity in frontoparietal areas (Cremers et al., 2010).

In conclusion, this study has demonstrated that cognitive vulnerability predicts higher frontoparietal activation during an implicit emotional task, particularly in nondepressed participants. The surplus activation may reflect increased effort being required to ignore irrelevant negative information and an increased representation of negative stimuli in regulatory circuits. Moreover, higher activation in subgenual ACC may be indicative of a general depression vulnerability that surpasses current levels of symptomatology. Neurobiological models of depression vulnerability cannot simply extend findings in depressed patients, because vulnerability may be associated with additional compensatory activation. However, it can be concluded that cognitive vulnerability for depression predicts altered activation patterns in frontolimbic brain areas where cognitive control impacts emotional perception.

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Supplements

Supplement 1. Differences across scan sites

There were no notable differences between sites in characteristics of the recruited participants, except for a smaller number of life events reported by participants from the LUMC (Table 1). The UMCG differed from the other sites in terms of scanning parameters, and contributed the smallest number of participants. Of note, there were no activation differences between scan sites for the contrasts of interest, negative > positive, negative > scrambled and positive > scrambled faces (no significant results at pFWE <0.05 or in regions of interest at punc < 0.001 and k>5). Therefore the differences across scan sites did not influence the findings in the current study.

Supplementary Table 1. Differences in key variables across scan sites

Variable	**UMCG (N=22)**	**AMC (N=31)**	**LUMC (N=59)**	**Test statistics**
Descriptives				
Age, M (sd)	33.41 (11.16)	37.03 (9.13)	37.34 (10.53)	F=1.23, p=0.30
Female sex	63.6 %	64.5 %	66.1 %	χ^2=0.05, p=0.98
Moderators				
NLE past year	68.2 %	67.7 %	44.1 %	χ^2=6.43, p=0.04
Diagnosis	81.8 %	58.1 %	57.6 %	χ^2=67.2, p=0.11
EPI acquisition				
TR (ms)	2300	2300	2300	
TE (ms)	28	30	30	
# slices	39	35	35	