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Vulnerability and emotional processing in depression

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Chapter 1

General Introduction

1. GENERAL INTRODUCTION

“Sadness flies away on the wings of time” – Jean de la Fontaine

Transient sadness is a natural part of life. However, for some individuals sad mood is more intense and refuses to dissolve. Numerous individuals suffer from depression and feel that they are ill and in need of treatment. In fact, depression is one of the leading causes of disability worldwide. Despite major research efforts, it remains unknown what the driving force behind depression is.

1.1. Depression: a definition

The Diagnostic and Statistical Manual of Mental Disorders (DSM) provides a solution to the question: what is clinical depression? This solution is used as a working definition for research into depression. According to this international standard, depression consists of a constellation of symptoms related to lowered mood. The DSM-IV Text Revision (American Psychiatric Association, 2000) recognizes sad mood and demotivation or loss of pleasure (anhedonia) as core symptoms of depression. Next to the core symptoms, somatic correlates of a negative mood state are included as symptoms. The somatic symptoms of depression include aberrant levels of energy, sleep, movement and weight or food intake. Cognitive correlates of a negative mood state are also recognized. The cognitive symptoms of depression include subjective impairments in concentration and decision-making as well as thought patterns dominated by ideas of guilt, worthlessness, and suicidal ideation.

These symptoms are used as diagnostic markers for a clinical depression that requires treatment. The DSM-IV diagnosis of major depression is based on the number (i.e., minimum of 1 core symptom and minimum of 5 out of 9 symptoms in total) and the duration of symptoms (i.e., minimum of 2 continuous weeks). In addition, the symptoms should be accompanied by marked distress and suffering, or impairments in role functioning, for instance in the vocational or psychosocial domain. There is debate on the construct validity of depression as a categorical illness that is either present or absent in episodes or as a dimensional phenomenon that can be present in gradations. This debate is currently reflected in DSM definitions, since depression is also recognized in lighter

forms (minor depression: 2-4 symptoms with duration of 2 weeks or dysthymia: 4 symptoms with duration of 2 years).

The assumption that depression is an on-or-off illness that is marked by a clinical cut-off point has the practical advantage of allowing relatively straightforward research into prevalence, onset and history of disease. A number of large population studies have generated these statistics for major depression. In the United States, the National Comorbidity Survey (original: N=8,089 in 1990-1992; Blazer et al., 1994, replication: N=9,090 in 2001-2002; Kessler et al., 2003) gave lifetime prevalence estimates of 15-20% and one-month prevalence estimates of 5% for adults. The Netherlands Mental health Survey and Incidence Study (NEMESIS: N=7,076 in 1996; Bijl et al., 1998) reported comparable figures. The median age at onset for major depression is around 20-25 (Andrade et al., 2003). Estimates of recurrence range from 50-90%, with increasing odds of recurrence and chronicity with each new episode (Judd et al., 1998; Solomon et al., 2000). These findings substantiate that major depression has a very large burden of disease (i.e. is very expensive for society), mainly due to healthcare costs and loss of productivity (WHO, 2008).

1.2. Depression: advancing the definition

The definition of depression provided by the DSM-IV serves as an instrument for clinicians and a working definition for researchers, and is particularly useful for standardized sample selection for clinical studies. In healthcare, it consequently serves as foundation for evidence-based treatment for depression. However, the DSM definition of depression gives a false sense of scientific objectivity regarding the classification of who is ill and who is not. Population studies show that up to half of DSM-IV depressed individuals do not seek treatment (Kessler et al., 2003). Mild depression is more likely to remit spontaneously (Kirsch et al., 2008), and therefore a concern for overdiagnosis has been voiced (Dowrick & Frances, 2013). In clinical practice, diagnostic classification often requires clinical judgment and thus still has a subjective element. Finally, it is important to note that the definition of depression is evolving over time.

The first manuals, DSM-I and DSM-II, took a prototypical approach to classifying mental illness by matching disease presentation to the most similar prototype. This

system was deemed unreliable, because similar patients were frequently classified as having different disorders (Spitzer et al., 1978). The symptom-based or checklist approach was adopted in DSM-III and greatly increased reliability. However, symptom selection was subject to debate and decisions on which symptoms to include for depression diagnoses were acknowledged to be somewhat arbitrary. For instance, there was a debate on whether to include anhedonia (loss of motivation/pleasure) and anxious (fearful/worried) mood as core symptoms of depression (Feighner et al., 1972; Spitzer et al., 1978). A case classified as anxious in the current system might have been classified as depressed in an alternative system. It appears that the validity of diagnosis is still under construction as we enter the DSM-V era today.

In medical science there often is a biological substrate for the observed symptoms (nosology on the basis of etiology). The classification of psychiatric conditions does not yet rely on a clear biological or psychological substrate. Antidepressant medication is advertised to solve a chemical imbalance in the depressed brain, however the evidence for a clear-cut chemical imbalance is rather weak (Lacasse & Leo, 2005). The mechanisms of action of psychological therapies are debated as well (Garratt et al., 2008). Although results from family studies suggest that depression is partly heritable (35-40%; Fava & Kendler, 2000; higher in early-onset and clinical groups), genetic association studies have not found any loci consistently implicated in depression (Bosker et al., 2011). Thus, the diagnostic entity is subjected to clinical, psychological and biological validators with at best varying degrees of success. This raises the question whether depression truly is a unitary construct.

There is an increasing recognition that multiple etiological pathways play a role in depression (Lichtenberg and Belmaker, 2010; Kendler, 2012). It is less clear whether etiological factors are uniformly or randomly distributed across depressed individuals (providing validity for depression as multifactorial disorder), or whether subgroups exist that show dominance of particular pathways. For example, neural and clinical alterations might be more prominent for groups that show particular risk factors for depression. This thesis therefore takes the approach to relate several risk factors for depression to the neural and clinical expressions of depression. This approach could further elucidate the functional significance of neuroimaging findings, testing validity for different conceptualizations of depression, and by this means develop our understanding of the

multiple pathways to depression. Vascular and cognitive vulnerability are selected as the main risk factors of interest, because there are indications that they are associated with a detrimental course of depression, and well-developed theories exist regarding pathophysiological mechanisms that allow hypothesis-driven research (e.g., Alexopoulos et al., 1997; Abramson et al., 1989).

1.3. Risk factors for depression

“A *risk factor* is any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury” – World Health Organization

Stress is perhaps the most studied risk factor for depression. Exposure to early life stress is a distal risk factor that is mainly predictive of depression with an onset in adolescence or early adulthood. Major life events such as job loss, divorce, or widowhood often precede depressive episodes later in life (Kessler, 1997). This concerns up to 80% of the episodes observed in the general population (Hammen, 2005). Virtually anyone will experience major negative life events, yet only 20% of the population suffers from depression at some point in their lives. Predisposing factors that render an individual more vulnerable for the effects of these events presumably play a significant role (Monroe & Simons, 1991), and even further sensitization to stress may occur as the disorder progresses (Post, 1992; Kendler et al., 2000; Monroe & Harkness, 2005).

Cognitive vulnerability or a persistent negative thinking style regarding oneself, the world and the future is a well-established risk factor for depression (Alloy et al., 1999). After initial conceptualizations of cognitive distortions by Beck in 1963, additional facets have been highlighted such as appraisals of low experienced control in stressful situations (helplessness theory; Abramson et al., 1978), and feelings of hopelessness for the future and a resulting negative self-image (hopelessness theory; Abramson et al., 1989). Cognitive vulnerability is thought to explain individual differences in stress sensitivity, because stress experience results in activation of negative schemas that facilitate appraisal and processing of incoming information in accordance with the schema. Accordingly, cognitive vulnerability is considered to enhance the odds of developing depression after experiencing a negative life event (Scher et al., 2005).

Cardiovascular disease (CVD) is another risk factor for depression, although the relationship between CVD and depression is clearly bidirectional. Depression predicts the onset and accelerates the progression of CVD (Nemeroff & Goldschmidt-Clermont, 2012). Conversely, CVD and CVD risk factors such as hypertension, diabetes, and myocardial infarction (Meng et al., 2012; Valkanova & Ebmeier, 2013) also predict onset of depression. Responsivity of the cardiovascular system is a relevant factor for individual differences in stress reactivity that may be associated with depression in individuals with CVD or CVD risk factors (McEwen, 2012). Alternatively, cardiovascular disease in itself could be such a severe stressor that individuals with a low pre-existing vulnerability for depression become depressed (Ormel & De Jonge, 2011).

1.4. Depression and the brain

At present, the origins of disordered mood are not fully understood. However, it is likely that alterations in emotional brain circuits are involved (Sheline, 2003). Emotional responses are orchestrated in the brain after the integration of sensory input from perceived stimuli in the external (e.g. sounds) and the internal milieu (e.g. heart rate). There is also a central cognitive component to emotion (e.g. expectancies and interpretation). Emotional brain circuits receive sensory input and give output to the stress axes, which generate the bodily emotional response. These functions are all integrated to produce motivated behavior. Convergent results from lesion studies in animals and humans established a critical role for frontolimbic brain areas in motivated behavior (Feinstein, 2013; Cardinal et al., 2013). The important role of these circuits was confirmed by meta-analysis of studies examining brain activation in response to emotional cues (Lindquist et al., 2012).

Depressed individuals show fundamental abnormalities in the processing of emotional cues, surpassing the mere correlates of emotional experience. The clinical picture tells that it is difficult to look at the bright side for someone in a depressed state. In a figurative manner, this can be attributed to dysfunction in appraisal and interpretation (e.g. increase in negative over positive interpretations, increase in self-relevance and self-blame appraisals; Beck, 1963; Scher et al., 2005). In addition, the negative outlook might be more literally true than one would initially expect. Visual attention is directed towards

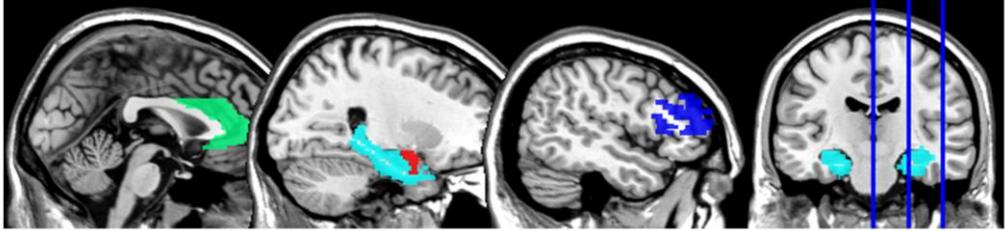
negative information in a prolonged and involuntary manner, because it is more difficult to disengage from negative information for someone who is depressed. In addition, negative information appears to be preferentially recalled from memory. These processes could contribute to the development and maintenance of low mood (De Raedt & Koster, 2010).

Research has therefore been directed at identifying the neural correlates of abnormalities in emotional processing in depressed patients. The main areas of interest are part of the frontolimbic system [box 1]. The amygdala is an important component that receives direct sensory input and is involved in emotional learning and memory. It is thought of as a relevance detector (Sander et al., 2003), and therefore is involved in appraisal. The amygdala is closely connected to the anterior cingulate cortex (ACC). These areas together are involved in generating the bodily response to emotion and stress. The lateral prefrontal cortex is involved in affective state monitoring and cognitive control processes. It does not have direct connections with the amygdala, but the ACC acts as an intermediary station to connect emotional and cognitive processes. The frontolimbic network has been implicated in depression by dysfunctions at the appraisal, monitoring and response levels (Mayberg, 1997; Phillips et al., 2003).

1.5. Neural correlates of cognitive and vascular vulnerability

Many studies investigating the neural correlates of depression – such as activation abnormalities during the processing of emotional information, network organization and volumetric brain alterations - confirm the involvement of frontolimbic brain areas. However, results from these studies are difficult to interpret, because there is a large heterogeneity of findings and it is uncertain what the functional significance of the findings is. Experimental design is one potential explanatory factor for differential results. For instance, the activation abnormalities might be more pronounced for or restricted to particular experimental characteristics, such as negative valence and self-relatedness of emotional cues. Moreover, an individual differences approach could identify sources of heterogeneity within groups of depressed individuals, by investigating whether distinct risk factors are associated with more pronounced brain alterations. Combining data from multiple sources in such a fashion would achieve an integration of different levels of explanation (i.e. psychological/physiological and neural explanation levels).

Box 1: Frontolimbic brain areas *Ochsner & Gross, 2005; Phillips et al., 2008*



The frontolimbic system is a collection of brain areas that give rise to emotional responses. The exact definition in terms of brain areas is variable in the literature, however the main areas as described in this thesis are depicted from left (medial/central) to right (lateral):

The **anterior cingulate cortex** (green) has been related to emotional experience and response, particularly sadness. The location in the brain is very central and it is highly connected to other areas, most prominently to the amygdala, with which it works in concert to generate emotional responses. It is also thought to be involved in automatic emotion regulation.

The **hippocampus** (light blue) is a subcortical brain structure named after a seahorse, due to the distinct curly shape that follows the wall of the ventricle. Functionally the hippocampus and adjacent parahippocampal areas are related to memory and inhibition of one of the stress axes.

The **amygdala** (red) is almond-shaped and located at the utmost tip of the hippocampus in the medial temporal lobe, subserving emotional memory and learning, amongst others. Traditionally, the amygdala was viewed as a fear circuit, but it is now known to be involved in a variety of socio-emotional processes.

The **lateral prefrontal cortex** (dark blue) is mainly involved in higher cognitive functions such as inhibition, attention, and executive control. Regarding emotional processing, it is implicated in voluntary and strategic emotion regulation. The ventral/lower part is thought to have an inhibitory role whereas the dorsal/higher part is thought to be more strongly involved in reappraisal.

There is some overlap in the conceptualization of cognitive vulnerability and the theoretical models of neural abnormalities in depression. A persistent negative thinking style and interpretation imply deviances in appraisal and impaired affective state monitoring. An association between self-reported cognitive vulnerability and a frontolimbic imbalance in activation (higher amygdala/anterior cingulate and less lateral prefrontal) would support this line of reasoning (Beck, 2008; Disner et al., 2011). Still,

the first level of explanation focuses on trait-like content of thought as recollected by the individual, whereas the second level focuses on information processing from incoming emotional stimuli to ultimate emotional response in real-time. It is unknown whether cognitive vulnerability is associated with brain activation patterns in a continuous fashion, and whether associations can be found in individuals with and without a current diagnosis of depression.

Vascular depression has been proposed to be a subtype that constitutes a substantial part of late-onset depression (onset > 65 years), and earlier-onset depression of which the course is affected by the consequences of incident vascular disease such as hypertension, myocardial infarction, and stroke (Alexopoulos et al., 1997). In the original conceptualization, emphasis was placed on white matter lesions that contributed in a singular or cumulative way to disconnection and dysregulation of frontolimbic circuits. However, other structural and perfusion abnormalities as a consequence of vascular disease might also play a role. Vascular disease is associated with volumetric reductions in frontolimbic gray matter areas, already in an early stage of disease (Beauchet et al., 2013). Since the brain regulates somatic stress reactivity (e.g. changes in blood pressure and heart rate after stress) and emotional reactivity, alterations in shared brain circuits may also predispose to both cardiovascular disease and depression (Thayer & Lane, 2009; Jennings & Zanstra, 2009). Most research into vascular depression has focused on separate vascular and late-life depression subgroups. It is still unknown whether comorbidity of vascular disease and depression shows specific structural brain alterations.

1.6. Clinical correlates of vascular and cognitive vulnerability

Further investigation of the associations between predisposing risk factors and the phenomenology, course and treatment responsiveness of depression may improve our understanding of the pathways towards depression and may help to identify clinically relevant depression subtypes. For instance, there is accumulating evidence that risk factors have different weights for early-onset and late-onset depression, as predicted by the vascular depression hypothesis (Alexopoulos, 2005). The definition of depression as listed in the DSM allows for many possible combinations of symptoms and in this way

may contribute to the heterogeneity in research findings. If subgroups of depressed patients could be distinguished on the basis of depression symptomatology, this could improve diagnostic validity.

A well-established questionnaire for measuring depression introduced cognitive and somatic symptom dimensions of depression (Beck et al., 1996). Both theory-driven and data-driven analyses confirm this distinction, although there are conceptual differences between samples and measures (e.g. compare Wardenaar et al., 2010 and Hegeman et al., 2012). Clinically it has been observed that vascular patients report less cognitive symptoms (e.g. less feelings of guilt; Alexopoulos et al., 1997). It has further been suggested that illness-related factors such as inflammatory processes contribute to the development of somatic symptoms in patients with vascular disease. Excessive fatigue is a good example of a somatic symptom that can arise from a number of processes, including lack of sleep, job stress, or an inflammatory process. Research in cardiac patients showed that particularly somatic symptoms of depression are associated with illness severity and cardiovascular prognosis (Azavedo et al., 2014). However, there have been few systematic comparisons of symptom profiles between depressed patients with and without cardiovascular disease.

Clinical validators have demonstrated stronger associations with the cognitive than somatic symptom dimension of depression, amongst others for psychiatric comorbidities, duration of illness, personality characteristics, and childhood trauma (Lux & Kendler, 2010). Although cognitive vulnerability has been related to these clinical validators, it has not been studied whether cognitive vulnerability is more strongly related to the cognitive dimension of depression (either cross-sectionally or prospectively). Cognitive vulnerability increases after depression onset and decreases after a depressive episode remits. Thus, self-reported cognitive vulnerability levels presumably to a certain extent reflect schema activation by negative mood state or stress rather than the intended vulnerability trait. Cognitive reactivity (i.e. the increase in negative thinking style after schema activation) is likely to be more trait-like and a better predictor of depressive symptom levels than cognitive vulnerability (Scher et al., 2005). It is uncertain whether cognitive vulnerability predicts depressive symptom levels when the schema is not activated (e.g., in non-depressed individuals that do not experience significant stress).

Although depressive symptoms and cognitive vulnerability show prospective associations, stronger evidence for causal relations would result from experimental manipulation of a risk factor in a randomized clinical trial. Psychological treatments for depression with a cognitive component are centered on challenging dysfunctional cognitions and depressogenic schemas. Many studies have confirmed associations between improvements in depression and cognitive vulnerability after therapy with a cognitive component. However, reductions in depression and cognitive vulnerability appear not to be at all specific for treatments that explicitly target cognitive processes and therefore inferences regarding causality are inconclusive (Garratt et al., 2007). It remains uncertain whether different treatment types impact the association between depression course and vulnerability reductions, whether associations are different for treatment-responsive and treatment-unresponsive patients, and what the time window of the effects is.

Box 2: Aims and outline of the thesis

In summary, this thesis seeks to explore whether cognitive and vascular risk factors for depression are associated with the neural and clinical expression of depression. The individual studies test pathophysiological pathways from cognitive and vascular risk factors for depression to the brain (activation imbalance and volumetric reductions in frontolimbic circuits) and to symptom profiles (the cognitive and somatic dimensions). By this means, the individual studies examine whether studying depression subgroups may hold more promise than studying depression as a unitary construct.

The first part of the thesis focuses on task-related modulation of the neural correlates of depression. The second part of the thesis concerns the neural correlates of cognitive and vascular risk factors for depression. The third part of the thesis examines whether subgroups based on cognitive and vascular risk factors are associated with differences in the clinical expression of and recovery from depression.

Part 1: Task-related modulation of the neural correlates of depression

Chapter two examines emotional valence as a modulator of brain functional abnormalities during emotion processing in depressed patients. Most models have focused on the processing of negative emotional stimuli, but it is still unclear how the processing of positive emotional stimuli is altered. A meta-analysis was conducted on 44 imaging studies with a total of 795 depressed and 792 control participants.

Chapter three examines self-related processing as a modulator of brain functional abnormalities in depressed patients. Moreover, this paper takes a network approach to test whether the alterations are more pronounced at a network level than at a regional level. Data were derived from a self-reflection task in 24 depressed and 24 matched non-depressed participants from the Depression In the Picture (DIP) study.

Part 2: Neural correlates of cognitive and vascular risk factors for depression

The functional significance of a frontolimbic imbalance in activation in depression is unclear. The *fourth chapter* examines whether alterations in brain activation during emotional processing are associated with the cognitive vulnerability and life stress risk factors for depression, separately for negative and positive emotional cues. Functional imaging data from an emotional faces task in 112 participants were derived from the Netherlands Study of Depression and Anxiety (NESDA).

The *fifth chapter* tests the prediction that structural brain abnormalities are involved in the comorbidity of hypertension and depression. Specifically, the hypothesis is tested that regional volumetric differences are most pronounced for a vascular depression subgroup. Data from the T1-weighted anatomical scans of 301 NESDA participants were analyzed.

Part 3: Clinical correlates of cognitive and vascular risk factors for depression

In *chapter six* it was examined whether depression in myocardial infarction patients has a different phenomenology than depression in primary and secondary mental health care, with a focus on the cognitive and somatic symptom dimensions of depression. Data were combined from 194 depressed myocardial infarction patients from the Myocardial Infarction and Depression – Intervention Trial (MIND-IT), 214 primary care patients and 326 secondary mental health care patients from NESDA.

Chapter seven concerns putative associations between the cognitive vulnerability and life stress risk factors and the cognitive and somatic symptom dimensions of depression, testing the hypothesis that cognitive vulnerability differentially predicts higher cognitive symptom levels over time. Baseline and 12-months follow-up data were derived from 2981 NESDA participants.

Chapter eight examines whether the long-term associations between cognitive vulnerability levels and depression course are modified by enhanced treatment for depression in primary care. The associations are tested at 12-months and 24-months follow-up, to investigate the duration of effects. Data were derived from 265 depressed primary care patients from a randomized controlled trial.

**Part 1: task-related modulation
of the neural correlates of
depression**