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Mood related insights : functional and structural MRI studies in depression and anxiety disorders

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Citation

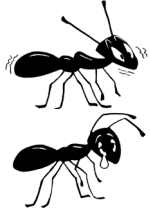
Tol, M. J. van. (2011, May 26). *Mood related insights : functional and structural MRI studies in depression and anxiety disorders*. Retrieved from <https://hdl.handle.net/1887/17672>

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CHAPTER 1

GENERAL INTRODUCTION

In this thesis, the focus is on the brain. More specifically, the focus is on abnormalities in brain function and brain volume in patients with major depressive disorder (MDD) and anxiety disorders as measured using Magnetic Resonance Imaging (MRI). The main questions of this thesis are: 1) do MDD and anxiety disorders share brain abnormalities that can explain the shared symptoms and high comorbidity (i.e., concurrent manifestation)?; 2) should MDD with comorbid anxiety disorder be considered a different diagnostic category than MDD without comorbid anxiety and anxiety disorders without comorbid MDD when considering abnormalities in structure and function of regions associated with emotion perception and regulation? Furthermore, we will explore whether shared risk factors of both MDD and prevalent anxiety disorders are associated with brain abnormalities, abnormalities that may give insight in the aetiology of the disorders.

CLINICAL CHARACTERISTICS

MDD is among the most prevalent and disabling psychiatric disorders in adult age and is in the top-10 of diseases with the largest global disease burden (Blair et al., 2008; Lopez, Mathers, Ezzati, Jamison, & Murray, 2006). Symptoms of MDD include a persistent low or sad mood, a diminished capacity to experience pleasure, difficulties in eating and sleeping, and concentration problems. A diagnosis of MDD or any other mental disorder, except for posttraumatic stress disorder, is solely based on the presented symptoms. Aetiological or biological factors including a positive family history of depression and anxiety, genetics, adverse life events, and childhood trauma are not considered in the process of diagnostics. Nevertheless, these factors have been recognized to play an important role in the aetiology of MDD (Belmaker & Agam, 2008). Appendix 1 lists the diagnostic criteria of MDD according to the Diagnostic and Statistical Manual of mental disorders (DSM) version IV.

About 20-30% of the male population and 30-40% of the female population in western countries will experience at least one episode of MDD (Kruijshaar et al., 2005). At any point in time, four to ten percent of the population will suffer within one year from a major depressive episode that will typically last 24 weeks (Kruijshaar et al., 2005). Also, risk of recurrence is high, and most strongly predicted by illness severity and comorbidity of (social) anxiety disorders (Melartin et al., 2004). In the outpatient setting, approximately one-third will recover from MDD, whereas two-third of the MDD patients will experience at least one more episode of MDD within 5 years (Holma, Holma, Melartin, Rytala, & Isometsa, 2008). MDD is associated with increased mortality rates, illness costs, and loss of productivity (Cassano & Fava, 2002).

Ten to 30% of those who suffer from MDD also meet criteria for an anxiety disorder, such as social anxiety disorder, panic disorder, and generalized anxiety disorder (Gorman, 1996; Gorman & Coplan, 1996; Ressler & Mayberg, 2007). Panic disorder is characterized by an excessive fear for panic attacks, social

anxiety disorder by extensive fear for social situations, and generalized anxiety disorder by excessive general worrying. Diagnostic criteria for these anxiety disorders are listed in detail in Appendix 1. Prevalence of anxiety disorders is also high, with a mean life-time prevalence of 28% (Ressler & Mayberg, 2007). The economic burden of anxiety disorders is comparable to that of MDD in terms of loss of productivity, quality of life decrement, and medical care utilization (Hoffman, Dukes, & Wittchen, 2008).

Approximately 50% of persons who suffer from an anxiety disorder will suffer from at least one major depressive episode in their lives (Gorman, 1996), although comorbidity figures vary between 20% and 90%. The comorbid condition of depression and anxiety disorders has been associated with more severe psychopathology (Kessler, Chiu, Demler, & Walters, 2005; Roy-Byrne et al., 2000; Rush et al., 2005), increased disability (Gorman, 1996), and worse outcome compared with patients with only a diagnosis of MDD or anxiety disorders (Bruce et al., 2005; Gorman, 1996; Gorman & Coplan, 1996; Melartin et al., 2004; Roy-Byrne et al., 2000; Rush et al., 2005). Because of these differences, it has been suggested that MDD with comorbid anxiety disorders and MDD without comorbid anxiety disorders should be considered as different diagnostic groups (Penninx et al., 2010). At the same time, MDD and anxiety disorders might share a common neurobiological pathology. This is suggested because of their high comorbidity, but also because patients with MDD and anxiety disorders tend to respond to the same treatment strategies such as treatment with Selective Serotonin Reuptake Inhibitors (SSRIs)¹ and cognitive behavioral therapy² (Ressler & Mayberg, 2007). Furthermore, MDD and anxiety disorders show overlap in symptoms, such as restlessness, irritability, feelings of rejection, dysphoria, sleep and appetite disturbances, increased self-consciousness, and oversensitivity to criticism (Gorman, 1996). Both MDD and anxiety disorders are associated with increased vulnerability to psychosocial stress, as reflected by an abnormal cortisol response of the hypothalamus-pituitary-adrenal (HPA)-axis³ (Veen et al., 2009; Vreeburg et al., 2009; Vreeburg et al., 2010), although findings have been inconsistent (Chida & Steptoe, 2009). Also, MDD and anxiety disorders are associated with common risk factors, including neuroticism, a positive family history of depression and anxiety, childhood trauma, and aversive life events (Spinhoven et al., 2010; Warner, Mufson, & Weissman, 1995; Weinstock & Whisman, 2006). These shared risk factors also suggest a shared aetiology in MDD and anxiety disorders.

DIAGNOSTIC CLASSIFICATION

The discussion whether MDD and anxiety disorders should be considered separate diagnostic categories with specific phenomenological and neurobiological characterizations, or should be considered different manifestations of the same disorder is not new. Since the late 1960's researchers attempted to find shared and unique phenomenological, treatment, course and outcome characteristics of MDD, anxiety disorders, and comorbid depression-

1 Since the 1950's, successful treatment of MDD with tricyclic medication led to the monoamine hypothesis of MDD and anxiety disorders. This hypothesis predicts that MDD and anxiety disorders are characterized by deficient monoaminergic transmission. Nowadays, selective serotonin reuptake inhibitors (SSRIs) and to a lesser extent selective noradrenalin reuptake inhibitors (SNRIs) are administered. These medications produce fewer side effects than the older tricyclic medication. SSRIs and SNRIs primarily act by preventing uptake of the monoamines by the pre-synaptic receptors, thereby promoting uptake of the agents by the post-synaptic receptors. However, up to 60% of patients may not achieve a sufficient response (Ressler & Mayberg, 2007).

2 Cognitive behavioral therapy is based on the hypothesis that MDD and anxiety disorders are in part the product of a maladaptive set of depressive or anxious cognitions. In cognitive-behavioral therapy, these cognitions are challenged and exchanged for more adaptive cognitions and behavior.

3 The HPA-axis is the body's primary stress-response and feed-back system. Cortisol, a glucocorticoid, is the primary human stress hormone that is synthesized in the adrenal glands. Cortisol is the end product of a cascade initiated by hormones released by the hypothalamus. The stress hypothesis of MDD and anxiety disorders states that a disrupted homeostasis of the human stress system is at the base of the disorder.

anxiety (Stavrakaki & Vargo, 1986). A problem in psychiatric classification is that psychiatric disorders are not discrete biomedical entities with clear phenotypic boundaries. Consequently, classification of psychiatric disorders is not stable and subject to ongoing discussion between scientist and clinicians. For instance, before 1994, the year that version IV of the DSM was published, symptomatology of panic disorder and generalized anxiety disorder was considered as one entity and referred to as anxiety neurosis. In contrast, generalized anxiety disorders is currently considered a separate disorder that is principally related to MDD owing to the large overlap in symptomatology. It has also been suggested that MDD and anxiety disorders should be characterized along one continuum from anxiety to depression (Stavrakaki & Vargo, 1986). Such an approach could explain the overlapping symptomatology and the high 'turn-over' rate, that is the 'replacement' of a primary diagnosis of an anxiety disorder with a primary diagnosis of MDD over the course of the disease. Models including more than one continuum have been proposed as well (Clark & Watson, 1991; Goldberg, 2000; Wardenaar et al., 2010a; Wardenaar et al., 2010b), including dimensions of general distress, physiological or anxious arousal, anhedonia/lack of positive affect, mood and cognition/negative affect, and sleep.

Such dimensional approaches have the advantage of avoiding problems associated with a categorical classification, especially when studying biological factors associated with MDD and anxiety disorders. Describing patients along dimensions of depression and anxiety symptomatology avoids artificial comorbidity that may arise owing to the large overlap in symptoms. Next, no strict dichotomy between healthy and ill is needed, and subsyndromal levels of depressed and/or anxious symptoms are not systematically overlooked. Finally, the use of a categorical disorder classification system to describe patients leads to high levels of heterogeneity within diagnostic classes: e.g. in MDD, patients receive the same diagnosis even if they only overlap on one of nine symptoms.

For the forthcoming version of the DSM, version V, it has been proposed to include a dimensional characterization of mood and anxiety symptoms next to the categorical classification for the diagnosis of mood and anxiety disorders. Such an approach may fill the gap between clinicians and scientist in an attempt to further identify and acknowledge the shared and unique phenomenological and neurobiological characteristics of various psychiatric disorders. Importantly, taking into account aetiological factors (e.g., childhood trauma, negative life events, family history), psychological factors (e.g., personality factors, dysfunctional cognitive schemas), and laboratory findings (e.g. neuroimaging findings, genetics, stress hormone measurements) could have implications for the psychiatric nomenclature (Rounsaville et al., 2002). Considering information on aetiology, symptomatology, and neurobiology could help answer the question of how to regard MDD and prevalent anxiety disorders: consider the symptomatology as manifestations of the same disorder, classify the disorders as distinct diagnostic groups, or characterize

patients along axes within a multi-dimensional space. However, as of yet, the common and disorder specific neurobiological characteristics of MDD and prevalent anxiety disorders have not been studied extensively. Also, support for the suggestion that MDD with and without comorbid anxiety disorders should be considered as different entities, with respect to their neurobiological profile, is limited. Moreover, the neurobiological impact of risk factors of depression and anxiety disorders has been hardly studied. Importantly, neurobiological insights could contribute to the discussion of how to regard MDD, anxiety disorders, and the comorbid condition of depression-anxiety. Accurate characterization of the disorders is important because the way patients are diagnosed has implications for both treatment and prognosis.

NEUROIMAGING

One approach in studying the neurobiological underpinnings of MDD and anxiety disorders is to focus on brain morphology and brain functioning. Technological developments in the past 30 years have made it possible to study the brain in a non-invasive way in vivo. Neuroimaging techniques such as Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) have contributed enormously to the knowledge of brain structure and function in healthy individuals and in psychiatric patients. Using PET, a radioactive tracer is injected in the bloodstream. Frequently used tracers are ^{18}F -labeled glucose (Fluorodeoxyglucose [FDG]) and ^{15}O -labeled water⁴. Subsequently, distribution of the radioactively labeled glucose or water is imaged, giving an estimate of energy consumption (glucose metabolism) or perfusion across the brain. MRI does not require the administration of a radioactive tracer. Using functional (f)MRI, scans are acquired that are sensitive to changes in the ratio of oxygen bound to haemoglobin molecules in venous blood. This is called the Blood Oxygenation Level Dependency (BOLD) effect, and is reflective of neuronal activity (Logothetis, 2002). Using both ^{15}O -PET and BOLD-fMRI, perfusion or activity in reaction to certain stimuli or responses are usually compared with a chosen baseline, and therefore provide relative measurements. In the last 10 years, researchers became increasingly interested in the low frequency fluctuations of the BOLD signal. These low frequency fluctuations are used to study synchronicity of time courses across the brain, providing an estimate of the functional connectivity of separate brain regions. Major advantages of fMRI are that scans are acquired without exposure to radiation, and that both the spatial and temporal resolution is better than for PET. MRI can also be used for structural imaging of brain volume (gray matter, white matter, and cerebrospinal fluids), diffusion, and white matter tracts.

⁴ Other nuclear imaging applications of PET for biochemical imaging exist but will not be discussed in this thesis.

Neuroimaging in MDD

Up to 2005, brain activation has been studied in MDD predominantly with PET during the 'resting state', that is when patients are not engaged in a task. From 1998 on, researchers started using fMRI to study brain activity in MDD using

various emotional and cognitive tasks. Most consistent metabolism/perfusion (PET) and BOLD (fMRI) abnormalities have been observed in the cingulate gyrus, dorsolateral prefrontal cortex, orbitofrontal cortex, insula, hippocampus, and putamen, although little overlap is found between different activation studies (Fitzgerald, Laird, Maller, & Daskalakis, 2008). Emotional processes have been most frequently studied in MDD, such as emotional face viewing, emotional autobiographical script processing and emotional picture viewing. Such emotional paradigms have been used to test the hypothesis of abnormal limbic activation to disorder relevant information. Abnormal sensitivity of limbic areas might explain the heightened responsiveness to stress and negative emotions associated with MDD.

Cognitive theories of MDD predict that MDD is the product of automatic maladaptive thoughts and cognitions (i.e., negative views of the self, the world, and the future) and associated selective processing of negative information (Beck, 1976). When encountering negative events, only a limited pallet of stereotyped ideas is available, further biasing the view of self, the world, and the future in a negative way. Such biased information processing towards negative information is referred to as the mood-congruent bias, whereas biased information processing away from positive information has been referred to as the mood-incongruent bias (Beck, 1976; Bower, 1981; Bradley, Mogg, & Williams, 1995). These mood-congruent and mood-incongruent processing biases may affect memory formation and thereby further affect the course of the disorder in a negative way (Elliott, Rubinsztein, Sahakian, & Dolan, 2002). Also, cognitive abnormalities in depression have been related to deficits in effortful processing (Elliott, 1998; Hartlage, Alloy, Vazquez, & Dykman, 1993). Some researchers have proposed that stressful conditions, including depression and anxiety reduces cognitive capacity, resulting in diminished available attentional resources (Hasher & Zacks, 1979). Others proposed that cognitive capacity in MDD is unaffected, but that attentional resources in a depressed state are allocated to depression-relevant thoughts and information. This 'narrowed attention' is proposed to be the result of the availability of more relevant 'nodes' to link negative information to or by the incapacity to inhibit negative information flow (see Hartlage et al., 1993 for an overview). As a result, less attentional resources are available for (external) task-relevant processes.

In support of these theories, researchers observed abnormal activity of (para) limbic regions during 'mood-congruent' and 'mood-incongruent' information processing (Epstein et al., 2006; Fossati, Ergis, & Allilaire, 2002; Keedwell, Andrew, Williams, Brammer, & Phillips, 2005b; Sheline et al., 2001; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007). Next, cognitive processes such as selective and sustained attention and executive control that are often reported to be abnormal in MDD (Fossati et al., 2002) have received attention in neuroimaging studies. Executive tasks are considered effortful, and therefore thought to be affected in MDD (Elliott, 1998). Importantly, these executive processes are thought to rely on cortical prefrontal cortex (PFC) regions, such

as the ventrolateral PFC, dorsolateral PFC, and anterior cingulate cortex (ACC) that are also implicated in mood regulation. Therefore researchers administered these cognitive tasks to test the functional integrity of these regions during non-emotional processes. Abnormal executive performance and associated abnormal activity of dorsolateral PFC and ACC regions have been observed (Fossati et al., 2002) and support the effortful processing hypothesis of depression. However, results have been inconsistent.

MRI has also been used to study brain morphometry in MDD. Structural abnormalities (gray matter volume reductions) in MDD have been most consistently found in the ACC and orbitofrontal cortex, and moderate volumetric reductions have been observed in the hippocampus, putamen and caudate nucleus (Koolschijn, van Haren, Lensvelt-Mulders, Hulshoff Pol, & Kahn, 2009). These volumetric abnormalities have been explained in light of the abnormal stress and emotion regulation associated with MDD.

Overall, brain imaging studies in MDD often lack an adequate sample size. Also, results may have been confounded by the inclusion of MDD patients with a variety of comorbid psychiatric disorders including anxiety disorders, posttraumatic stress disorder, obsessive compulsive disorder, and attention deficit hyperactivity disorder. Also, use of antidepressant medication may have confounded the results. Antidepressive drugs such as benzodiazepines, tricyclic antidepressants (TCAs), and antipsychotics could influence the cerebral blood flow (Matthew et al., 1995; Ngan, Lane, Ruth, & Liddle, 2002) and thereby the BOLD signal. In conclusion, imaging studies in MDD patients with adequate sample sizes that are able to control for confounding factors including psychiatric comorbidity and medication use are rare.

Neuroimaging in anxiety disorders

The literature on brain function and structure in the highly prevalent anxiety disorders panic disorder, social anxiety disorder, and generalized anxiety disorder is limited. The less prevalent anxiety disorders posttraumatic stress disorder and obsessive-compulsive disorder have been most extensively studied. As mentioned earlier, a diagnosis of posttraumatic stress disorders is made only in the presence of a traumatic experience in the (near) past. Other anxiety disorders are diagnosed solely based on presented symptomatology without including aetiological factors in the diagnostic process. Obsessive-compulsive disorder on the other hand has been characterized by a different neurobiological profile compared with other anxiety disorders (Radua, van den Heuvel, Surguladze, & Mataix-Cols, 2010; Rounsaville et al., 2002; van den Heuvel et al., 2005b). Also, for the new version of the DSM, obsessive compulsive disorder has been proposed for possible reclassification in another or separate diagnostic category. Therefore, these anxiety disorders and their associated neurobiological abnormalities may not be representative of the cluster of anxiety disorders at large.

The focus of activation studies in anxiety disorders has traditionally been on

threat perception and fear-conditioning, and hardly any studies focused on executive and attentional processes. Overall, generalized anxiety disorder has received very limited attention in the field of neuroimaging. In social anxiety disorder, emotional paradigms most consistently demonstrated increased responsiveness of the amygdala and the insula (Etkin & Wager, 2007). In anxiety disorders, studies investigating dorsal involvement in emotional processes are limited in number. In one paper normal attentional control and related prefrontal activation was reported during non-emotional task in patients with panic disorder, but compromised functioning was observed under emotional distraction (van den Heuvel et al., 2005b). Overall, few studies have studied whether effortful processing is compromised in anxiety disorders as well.

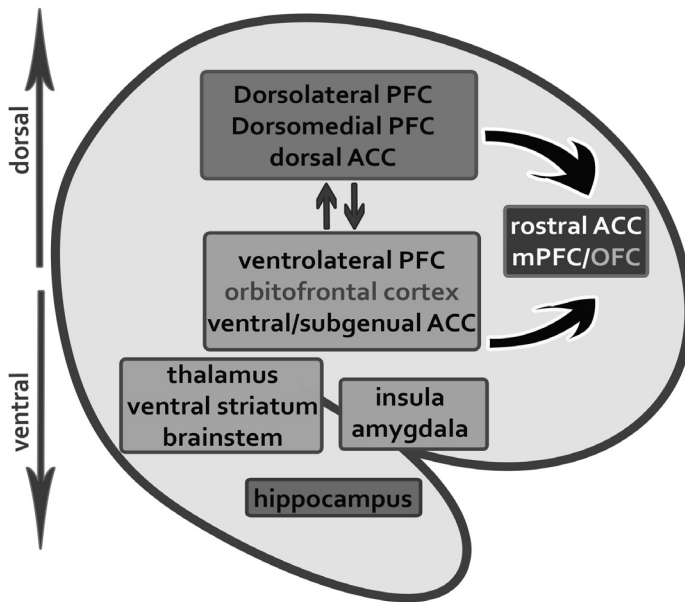
The focus of most structural imaging studies in anxiety disorders has been on panic disorder, and researchers reported decreased amygdalar, insular, dorsal ACC volume (Asami et al., 2008; Massana et al., 2003; Uchida et al., 2008). A recent meta-analysis showed that reduced dorsal ACC and putaminal volume are the most consistently observed abnormalities in panic disorder (Radua et al., 2010), although considered together with posttraumatic stress disorder. Similar to the research in MDD, most studies in anxiety disorders lack sufficient sample size and adequate controlling for comorbidity and medication use.

NEUROANATOMICAL MODELS OF MOOD AND ANXIETY DISORDERS

Based on the variety of brain regions associated with abnormal structure or function, MDD and anxiety disorders are not considered disorders of a single brain region; Instead, MDD and anxiety disorders are considered the result of complex deficient interactions between highly integrated networks of limbic-cortical regions (Seminowicz et al., 2004). Several neuroanatomical models have been proposed in an attempt to explain the variety of symptoms observed in MDD including depressed mood, anhedonia, somato-vegetative dysregulation, and concentration problems. These models propose that symptoms are based on abnormal functioning of both (para)limbic and neocortical brain regions. (Para)limbic regions are primarily associated with perception of emotional information and the generation of a primary emotional response, whereas the neo-cortical regions are mainly associated with cognitive and emotional control. (Para)limbic, or 'ventral'⁵, regions include amongst others the amygdala, insula, ventral striatum, thalamus, and subgenual ACC. Dorsolateral PFC, dorsal ACC, and dorsomedial PFC are considered 'dorsal' regulatory neocortical areas, in the context of emotion regulation models.

In a prominent neuroanatomical model of limbic-cortical dysregulation developed by Helen Mayberg in 1997 and updated in 2004 (Seminowicz et al.), increased activation of ventral paralimbic regions and decreased activation of dorsal neocortical regions are proposed as prominent features of MDD, responsible for sad mood. The Mayberg model emphasizes the importance of a third 'emotion-cognition integration component', including the rostral ACC,

⁵ 'Ventral' or 'inferior' refers to the lower portion of the brain. 'Dorsal' or 'superior' refers to the top portion of the brain.

**FIGURE 1:**

Graphical representation of the combined models of Mayberg (1997; Seminowicz et al., 2004) and Phillips (Phillips, Drevets, Rauch, & Lane, 2003b) displayed within the contours of the brain, as viewed from the side. In this model the orbitofrontal cortex (OFC), is depicted in gray, as it serves a different role in the two models. Finally, the hippocampus is also depicted in gray, as in both models, this structure is considered to serve a dorsal regulatory role, despite its ventral location. In Box I, an overview of functions of several ventral and dorsal regions and their relation with the psychopathology in MDD and anxiety disorders is presented.

medial PFC, and orbitofrontal cortex. In his model, the rostral component serves as a modulatory hub between ventral 'autonomic integration' regions (e.g., sub-genual ACC, thalamus) and dorsal 'sensory-cognitive integration' regions (e.g., dorsolateral PFC, hippocampus) and is implicated in normal mood regulation.

A second neuroanatomical model, developed by Mary Phillips and colleagues (2003b) proposes that direct deficient interactions between 'ventral' ((para) limbic) and 'dorsal' (neocortical) regions could result in the symptomatology of a range of psychiatric disorders such as schizophrenia, bipolar disorder, and MDD. This Phillips model predicts that excessive activity of ventral and decreased activation of dorsal structures gives rise to the experience of inappropriate threat and a decreased range of emotional states. Figure 1 depicts the models of Mayberg and Phillips combined for the purpose of this thesis.

Although frequently associated with salience detection (See box I), and therefore an evident region of interest, the amygdala is not included in every model of mood regulation in MDD and in the most consistent functional or structural abnormalities reported to date in MDD (Seminowicz et al., 2004). In the study of anxiety disorders, disrupted interaction between amygdalar nuclei and dorsal PFC structures has been proposed to underlie the symptomatology (Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010; Etkin, Prater, Schatzberg, Menon, & Greicius, 2009), giving a more central role for the amygdala in the pathophysiology of anxiety disorders than in the models of MDD. The model

of Mayberg (1997) is primarily proposed for MDD, whereas the model of Phillips (2003b) is considered a more general framework for psychiatric disorders, such as posttraumatic stress disorder and schizophrenia. To what extent these models are applicable to the functional and structural neuropathology of prevalent anxiety disorders and to comorbid depression-anxiety is barely studied.

AIM OF THE PRESENT STUDY

Most studies performed to date focused either on MDD or on anxiety disorders and failed to systematically exclude comorbid psychiatric disorders. Also, studies performed to date failed to test for shared and unique characteristics in brain function and structure of MDD and anxiety disorders. Importantly, no study explicitly studied the comorbid condition of MDD and anxiety disorders and compared the neurophysiological profile of this comorbid condition with 'singular' (i.e. without comorbidity) MDD and anxiety. Also, owing to the small numbers of participants included in most studies, comorbidity of MDD on the correlates of anxiety, and vice versa could not be controlled for. This limited power (small sample size) constitutes a further problem, as it has been shown that reliable and replicable task effects in fMRI studies are only obtained in samples of over approximately 15 persons (Thirion et al., 2007). Small sample sizes lead to unreliable results and do not allow one to control for important confounders, such as use of antidepressive medication, illness severity, and psychiatric comorbidity. The inconsistencies in imaging results reported so far could be the result of such factors.

In addition to including predominantly medicated patients, the inclusion of severely ill, hospitalized patients in previous studies may have confounded results. Hospitalization may be a very stressful experience itself, which often involves change of medication or administration of a sedative drug. Including patients who suffer from concentration problems related to the negative side effects of hospitalization or use of psychotropic acting drugs may result in activation abnormalities. Subsequently, these abnormalities might be falsely attributed to the psychopathology. Also, cognitive dysfunction may be an important predictor for hospitalization (Jaeger, Berns, Uzelac, & vis-Conway, 2006). Therefore, inpatients may be characterized by a distinct symptom- or functional impairment profile than outpatients.

Furthermore, few studies have investigated whether functional and structural abnormalities that are observed in the 'active' depressed or anxious state continue into the remitted phase. PET studies have demonstrated abnormal orbitofrontal, ACC and dorsolateral PFC perfusion in the remitted state in MDD in a mood provocation paradigm, indicating a functional vulnerability that could explain the heightened sensitivity to relapse into another MDD episode. Recent evidence exist that those who reach full remission after six weeks of SSRI treatment, differ in both brain morphology and cognitive functioning from patients who do not reach remission (Li et al., 2010). However, whether

such 'trait' phenomenon are observed during cognitive and emotional tasks in MDD patients, or are observed in patients with remitted anxiety disorders, is barely studied.

In anxiety disorders, studies primarily focused on the signaling function of ventral regions in response to negative or threat eliciting stimuli. Dorsal PFC involvement during cognitive tasks has hardly been studied in panic disorder, and studies on PFC involvement in social anxiety disorder and generalized anxiety disorder are virtually absent. Studying fMRI correlates of cognitive tasks that depend on intact functioning of dorsal PFC regions such as the dorsolateral PFC, dorsal ACC and inferior frontal gyrus is important because of the role these regions play in (models of) emotional regulation.

The studies presented in the current thesis aimed to overcome such limitations by studying both cognitive and emotional processes in a large sample of outpatients with MDD and anxiety disorders (panic disorder, social anxiety disorder, generalized anxiety disorder), and healthy controls. Participants were recruited from the Netherlands Study of Depression and Anxiety (NESDA; described below), a large-scale, observational study in the outpatient setting. This allowed for the inclusion of large numbers of participants and to study MDD and anxiety in a 'real-life' setting. By including a large sample of patients with both MDD and anxiety disorders, the shared and unique correlates in MDD and anxiety disorders could be studied. At the same time, this set-up allowed to explicitly test for the effect of comorbidity of depression and anxiety, use of antidepressant medication, and illness severity.

THE NETHERLANDS STUDY OF DEPRESSION AND ANXIETY

The Netherlands Study of Depression and Anxiety (NESDA) is a multi-center, longitudinal, observational cohort study, that aims to (1) gain insight in the long-term prognosis of depression and anxiety disorders in terms of course and public health consequences, (2) study depression and anxiety in concert, and (3) integrate biological and psychosocial paradigms of mood and anxiety disorders. NESDA has been designed to be representative of those with depressive and anxiety disorders in different health care settings and stages of developmental history. Therefore, the sample is stratified for setting (community, primary care and specialized mental health) and set up to include a range of psychiatric disorders. NESDA has a focus on MDD, dysthymia, social anxiety disorder, panic disorder, and generalized anxiety disorder. Persons diagnosed with a primary clinical diagnosis of a psychiatric disorder not subject of NESDA that is likely to affect course trajectory, such as posttraumatic stress disorder, personality disorders, and obsessive-compulsive disorder, were not included in NESDA.

Amongst the psychosocial and biological measures included in NESDA are: Demographic interview, current and life-time psychopathology interview, personal history interview (trauma, life events), health consequences interview (medication use, loss of productivity, disability), perceived need for care questionnaires, current depressive and anxiety state questionnaires,

personality measures, worrying,- depressive and anxious cognitions measures, health behavior interview (sports, smoking, alcohol, drugs use, sleep), saliva sampling for cortisol measures, measures of heart-rhythm variability, and genetic measures. For a complete description of the instruments included in NESDA, see Penninx et al. (2008). Most important for this thesis is the inclusion of functional and structural MRI in NESDA.

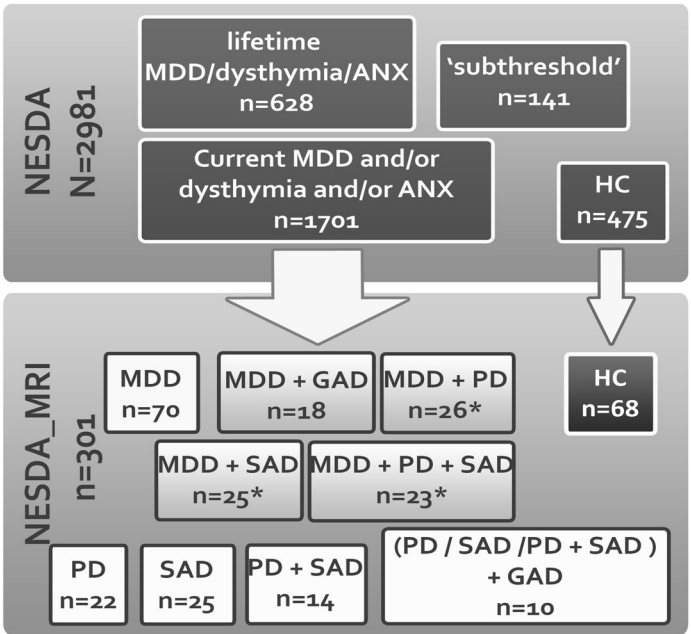
NESDA NEUROIMAGING STUDY

A subsample (n=301; 200 female, age range: 18-57) of the total NESDA sample (N=2981) (See Figure 2 for a flow chart and a graphical representation of the MRI sample), was invited to participate in the NESDA neuroimaging study between October 2004 and April 2007. The NESDA neuroimaging study is a longitudinal study that was designed to study cognitive and emotional processes, as well as brain structure in MDD and anxiety disorders. In this thesis ‘anxiety disorders’ refers to panic disorder, social anxiety disorder and generalized anxiety disorder, unless otherwise specified.

Aims of the NESDA neuroimaging study at large, that include aims beyond the scope of this thesis, were to: (I) Study shared and unique neurophysiological correlates of MDD and anxiety disorders in an outpatient sample, related to basic cognitive processes, emotional processes, ‘resting state’, and variations in brain structure; (II) study the comorbid condition of MDD and anxiety disorders and make a comparison with both MDD and anxiety disorders on measures named in (I); (III) describe patients with MDD and anxiety disorders with respect

FIGURE 2:

NESDA flow-chart. * indicates that the subsample also includes patients with comorbid GAD. Current diagnosis refers to a half-year diagnosis. All MRI participants were selected from the NESDA ‘current diagnosis’ sample and the HC sample. In this figure, patients with a current diagnosis are not included in the ‘life-time’ sample. Approximately one-third of the included patients used anti-depressant medication at the time of scanning.



to their course, to identify neurophysiological correlates that are associated with outcome (recovery, recurrence, development of comorbidity; (IV) describe neurophysiological correlates of risk factors of MDD and anxiety disorders, including genetic variations; (V) test whether a dimensional model of psychopathology for MDD and anxiety disorders (to be developed in NESDA) would describe the functional and structural pathophysiology more accurate than a categorical classification system (DSM-IV classes). MRI measurements were planned at To (baseline measurement), T₁ (follow up after two years), T₂ (four or six years after the baseline measurement). Several tasks were administered to all participants during functional MRI: A non-emotional visuospatial planning task (Tower of London; ToL), an emotional word encoding and recognition task, and an emotional face viewing task. In addition, structural imaging for measurement of regional brain volume and white matter integrity measurements and functional imaging for 'resting state' fMRI was applied to study the brain's intrinsic organization when participants were not engaged in a task. Data acquired during execution of the Tower of London visuospatial planning task and the word encoding task will be discussed in this thesis, in addition to the structural MRI data.

OUTLINE OF THE THESIS

The main objective of this thesis is to describe the common and unique functional and structural MRI correlates of MDD and anxiety disorders, while explicitly testing for the effects of their comorbidity. The thesis is structured into two sections: in SECTION I, the functional and structural MRI correlates of a current diagnosis of MDD and/or anxiety disorders are investigated, while the effects of antidepressant medication use and illness severity are being studied as well. In SECTION II, the focus is on factors that are considered risk factors for developing mood and anxiety disorders.

In **Chapter 2**, common and unique neuroanatomical correlates of MDD and anxiety disorders are studied with an optimized voxel based morphometry (VBM) approach, a method that allows detecting regional volumetric differences across the whole brain. Aim of this study is to investigate whether emotional disturbances in MDD and anxiety could at least in part be explained by volumetric variations in regions related to emotional processing.

In **Chapter 3**, common and unique neurophysiological correlates of encoding and recognizing emotional words in MDD and anxiety disorders are investigated. Aim of this study is to test whether disorder specific biases towards negative and away from positive information result in altered memory formation and performance that could explain the prolonged course of the disease.

In **Chapter 4**, fMRI correlates of a visuospatial planning task are discussed. Visuospatial planning is an executive process that depends heavily on dorsal prefrontal integrity. Aim of this study is to test whether dorsal prefrontal involvement during executive processes is equally compromised in both

SECTION I

depression and anxiety, or whether it should be considered an MDD specific phenomenon.

In **Chapter 5**, we focus on the intrinsic organization of subcortical and cortical brain structures during an emotional word categorization task in MDD. As MDD is considered the result of complex deficient interactions between highly integrated networks of limbic-cortical regions, we aim to study intrinsic functional connectivity between both dorsal and lateral cortical regions on the one hand and subcortical and limbic regions on the other hand, while patients are engaged in an emotional task.

SECTION II

Chapter 6 focuses on the effects of childhood emotional trauma or abuse on regional brain volume across patients with depression and anxiety disorders. Early life trauma is one of the major risk factors for developing emotional disturbances. Aim of this study is to indicate a possible neuroanatomical vulnerability for developing depression and anxiety disorders resulting from early life abuse.

In **Chapter 7**, we present a study that focuses on the influence of the personality factors neuroticism and extraversion on brain structure. Neuroticism and extraversion are personality factors that have been associated with both increased and lower risk of developing mood and anxiety disorders. To avoid the possible confounding effect of current psychopathology, we focus on personality correlates in healthy controls.

In **Chapter 8**, results are summarized and discussed. Also, recommendations will be provided for implementing (f)MRI in an observational study.

INVOLVEMENT OF VENTRAL AND DORSAL REGIONS IN MDD AND ANXIETY DISORDERS: A SUMMARY

The amygdala, a limbic structure, is primarily associated with salience detection and processing of emotional cues, also in the context of memory processes (Hamilton & Gotlib, 2008). In MDD and panic disorder, the amygdala has found to show abnormal gray matter volume (Asami et al., 2009; Hamilton, Siemer, & Gotlib, 2008; Hayano et al., 2009; Massana et al., 2003; Wagner et al., 2008). An increased BOLD response during (masked) negative face viewing (Sheline et al., 2001) and a prolonged response during emotional word classification (Siegle et al., 2007) has been observed in MDD. In social anxiety disorders, the amygdala has also been associated with an elevated (Stein, Goldin, Sareen, Zorrilla, & Brown, 2002) and delayed response (Campbell et al., 2007) during negative (contemptuous and angry) face viewing. In both MDD and anxiety disorder, amygdala hyperactivation has been found to normalize after successful treatment (Ressler & Mayberg, 2007).

The hippocampus has been regarded as an affective state regulatory structure (Phillips, Drevets, Rauch, & Lane, 2003a) and has been repeatedly found to be reduced in volume in MDD (Campbell & MacQueen, 2006). The hippocampus is an important structure related to HPA-axis functioning, the primary stress-regulatory system of the human body, and is thought to be implicated in the feed-back loop on adrenal cortisol secretion (Jacobson & Sapolsky, 1991). Volumetric reductions in this region have been linked to the neurotoxic effects of excessive cortisol (McEwen, 2005; Sapolsky, 2000). Functionally, the hippocampus has been associated with contextual memory processes (McEwen, 2000), and reduced neurogenesis of hippocampal cells due to excessive cortisol may lead to compromised memory functions, as has been found in MDD (Zakzanis, Leach, & Kaplan, 1998). Although abnormal hippocampus activation is not a commonly observed phenomenon, the hippocampus has been found to abnormally inhibit dorsal prefrontal regions in MDD and at the same time facilitate ventral prefrontal regions (Hamilton, 2010). These abnormal projections may be at the base of depressive symptomatology. Also in the study of anxiety disorders, abnormal interactions of the hippocampus with the amygdala and cortical areas has been observed (Etkin et al., 2010; Etkin et al., 2009).

The insular cortex has extensive connections with the amygdala, hypothalamus, and peri-aqueductal gray, and has been associated with regulation of the autonomic nervous system (Etkin & Wager, 2007). The insula has been related to disgust processing (Phillips et al., 1997; Small, 2010), homeostatic regulation (Small, 2010), fear conditioning (Buchel, Dolan, Armony, & Friston, 1999), and anticipation of negative reward (Phelps et al., 2001). Abnormal insular

functioning in MDD has been observed during aversive emotional paradigms (Surguladze et al., 2010) and is thought to reflect the somato-vegetative symptoms, such as abnormal sleep and appetite (Wiebking et al., 2010). Also, in social anxiety disorder, increased insular activation is among the most consistently observed phenomena during emotional paradigms and is associated with increased activation of a network related to producing fear responses to symptom provoking material (Etkin & Wager, 2007).

The ventral striatum, including the nucleus accumbens, and the ventro-medial PFC have been associated with reward processing, and abnormal activation of these regions in MDD has been associated with the MDD core symptom of anhedonia as reflected in decreased activation during processing of positive stimuli (Epstein et al., 2006), positive mood induction (Keedwell et al., 2005b), and with a failure to sustain activation over time during upregulation of positive emotional states (Heller et al., 2009). In the study of anxiety disorders, the ventral striatum has been a target for deep brain stimulation, an invasive therapy that aims to influence activation of specific brain targets in order to relieve symptom burden. Studies on the results of the effects of deep brain stimulation in anxiety disorders, including obsessive compulsive disorder, have proposed that the ventral striatum serves as a modulatory hub in the information flow between the amygdala and the basal ganglia, thalamus and PFC (Sturm et al., 2003).

The subgenual ACC, the most ventral region of the cingulate cortex, has been associated with processing emotional and motivational information and the production of affective states (Bush, Luu, & Posner, 2000; Phillips et al., 2003a). In MDD, reduced volume of the subgenual ACC has been observed (Botteron, Raichle, Drevets, Heath, & Todd, 2002) and blunted regional blood flow in the subgenual ACC has been observed during mood induction, even in remitted (recovered) MDD patients (Liotti, Mayberg, McGinnis, Brannan, & Jerabek, 2002). The subgenual ACC has been linked to the treatment response to cognitive behavioral therapy in both MDD and social anxiety disorder (Ressler & Mayberg, 2007).

The orbitofrontal cortex has been associated with behavioral inhibition, impulsivity, decision making, and interpreting other people's mood (Elliott, Zahn, Deakin, & Anderson, 2010; Milad & Rauch, 2007). The orbitofrontal cortex has been related to the autonomic regulation of emotional behaviour (Phillips et al., 2003a) and reward related behaviour (Milad & Rauch, 2007). Related to mood regulation, the orbitofrontal cortex has been found to exert inhibitory control over amygdalar activation (Milad & Rauch, 2007). In MDD, orbitofrontal cortex metabolism has been related to symptom improvement after successful treatment (Brody et al., 1999). In the study of anxiety disorders, orbitofrontal functioning has been linked to a failure to inhibit inappropriate anxiety and fear

responses ((Milad & Rauch, 2007).

Dorsal prefrontal cortex (PFC) regions, including the dorsolateral PFC, dorsal ACC, inferior frontal gyrus (IFG), and dorsomedial PFC have been predominantly linked to executive and attentional control functions, such as sustained attention (dorsal ACC), selective attention (IFG) and executive processes (dorsolateral PFC), during working memory tasks, switching tasks, planning tasks, and verbal fluency tasks; tasks that all have been found to be mildly impaired in MDD (Fossati et al., 2002). Verbal fluency and switch functions also have been found to depend on involvement of the orbitofrontal cortex. In the study of MDD, both increased and decreased activation of these regions have been observed (Fossati et al., 2002). In patients with social anxiety disorder, viewing of negative (disgust) facial expressions has been associated with increased ACC activation (Amir et al., 2005). In generalized anxiety disorder, failure of the ACC to dampen the amygdalar response has been associated with a failure to regulate emotional conflict (Etkin et al., 2010). Thus, next to executive and attentional control, dorsal PFC regions have been thought to exert top-down control over the ventral emotional appraisal regions, possibly via the ACC and medial PFC (Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007).

