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Framing depression in a SN(a)Pshot

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2013

document version

Publisher's PDF, also known as Version of record

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citation for published version (APA)

Woudstra, S. (2013). *Framing depression in a SN(a)Pshot: Imaging risk factors of MDD.* [, Vrije Universiteit Amsterdam].

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Chapter 1

General introduction

*Zodra de dag als een dreigbrief
in mijn kamer wordt geschoven,
worden de rode zegels van de droom
door snelle messen zonlicht losgebroken.*

*Huizen slaan traag hun bittere ogen op
en sterren vallen doodsbleek uit hun banen.*

*Terwijl de zwijgende schildwachten,
nachtdroom en dagdroom, haastig
elkaar hun plaatsen afstaan,
legt het vuurpeloton van de twaalf
nieuwe uren bedaard op mij aan.*

– ‘*Changement de Décor*’ door Ellen van Warmond uit *Proeftuin*, 1953 –

This thesis is about imaging parameters associated with the occurrence and recurrence of major depressive disorder (MDD). In **part I** of this thesis, genetic neuroimaging was used to study the relationship between a single nucleotide polymorphism (SNP) associated with depression and regional brain dysfunction underlying abnormal emotion processing and executive function. In **part II**, brain morphology and executive dysfunction in MDD were investigated in a longitudinal design.

Clinical characteristics of MDD

MDD is a common, multifactorial psychiatric disorder and is one of the leading causes of years lost due to disability (World Health organization (WHO), 2005; World Health organization (WHO), 2009). It has a severe impact on daily functioning, and is associated with significant morbidity, mortality, and public health costs. Remission is the most favourable outcome, although approximately 50% of MDD patients with remitted MDD experience recurrence of MDD within 5 years. Available treatments, though effective, have only modest response rates (Trivedi & Daly, 2008). Recurrent MDD is not only a burden for those with depression; it is also a major annual cost for society, of an estimated 1.3 billion Euro (in the Netherlands). Early prediction of recurrent depression is key for preventing relapse, the development of effective preventive (pharmaco)therapies, and thus for reducing costs associated with MDD.

The core symptoms of MDD are affective abnormalities, characterized by depressed mood accompanied by low self-esteem and/or loss of interest in normally enjoyable activities. Other MDD symptoms include cognitive impairments, such as impaired ability to think and concentrate, and planning problems. At least five out of nine symptoms must be present for an MDD diagnosis according to the Diagnostic and Statistical Manual of Mental Disorder, fourth edition, text revision (DSM-IV, TR; table 1.1).

The different genetic, biological, and psychosocial factors make MDD multifactorial by origin. This multifactorial character of the development and course of MDD makes it a complex and heterogeneous disorder, of which the underlying mechanisms are still unclear.

Table 1.1: Major Depressive Disorder Diagnostic Criteria according to DSM-IV-TR

	Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning. At least one of the symptoms is (1) depressed mood or (2) loss of interest or pleasure.
A	<ol style="list-style-type: none"> 1. Depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others. 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day. 3. Significant weight loss when not dieting or significant gain, or decrease or increase in appetite nearly every day. 4. Insomnia or hypersomnia nearly every day. 5. Psychomotor agitation or retardation nearly every day. 6. Fatigue or loss of energy nearly every day. 7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick). 8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others) 9. Recurrent thought of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide.
B	The symptoms do not meet the criteria for a mixed episode.
C	The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.
D	The symptoms are not due to the direct physiological effects of a substance (for example, a drug of abuse, a medication), or a general medical condition (for example, hyperthyroidism).
E	The symptoms are not better accounted for by bereavement, i.e. after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms or psychomotor retardation.

[Source: American Psychiatric Association. *DSM-IV-TR. Diagnostic and statistical manual of mental disorders, 4th edition, 2003.*]

Neuroimaging

Mechanisms underlying MDD can be studied using neuroimaging techniques, and Magnetic Resonance Imaging (MRI) is a non-invasive technique to study brain function and structure. Brain function can be studied using the Blood Oxygenated Level Dependent (BOLD) signal, which serves as a derivative for neuronal activity and has been used in this thesis to study task related functional activity of the brain. Structural abnormalities of grey matter volume related to MDD can be studied on a macroscopic level by using so called T1 weighted scans. A more detailed description of the techniques used can be found in e.g. Weishaupt *et al.* (2006).

Neuroimaging in MDD

The presence and severity of both affective and cognitive symptoms can be evaluated by neuropsychological assessments (Weiner *et al.*, 2003), and may be reflected in altered regional

brain activity as measured using functional MRI (fMRI) (Demenescu *et al.*, 2011; Savitz & Drevets, 2009; van Tol *et al.*, 2011).

Affective symptoms in MDD may partly result from an attentional bias towards mood-congruent (i.e. negative) information (Stuhrmann *et al.*, 2011). Using neuropsychological assessments (Rude *et al.*, 2002), it has been shown that a negative emotion processing bias may be predictive of depression symptoms and may represent a state marker of MDD. It is thought that this negative bias is associated with abnormal responsiveness of brain regions involved in emotion processing, as well as disruption of cortico-limbic connections that are important for regulating emotional responses (Browning *et al.*, 2010; Leppänen, 2006). Identification of emotional facial expressions is reportedly impaired in MDD (Surguladze *et al.*, 2004). Using an emotional faces task in healthy controls (HC) (Fusar-Poli *et al.*, 2009), functional imaging studies have shown activity of emotional face processing related areas, including the amygdala, striatum, insula, parahippocampal area, and dorsolateral prefrontal cortex (PFC). Abnormal responses during recollection of negative faces have been associated with MDD, which may reflect activation of negative schemas (van Wingen *et al.*, 2011). Dysfunctional emotional memory processing is thought to ensue from, or reinforce symptoms of negative mood, lack of positive affect, and attentional impairments. Left ventral insular activation during negative encoding has been identified as a trait-like effect of MDD (van Tol *et al.*, 2012), and may reflect a generally increased sensitivity for negative information (as suggested by Surguladze *et al.*, [2010]).

Attentional bias towards positive information (so called mood-incongruent bias) has been associated with MDD as well (Burt *et al.*, 1995; Heller *et al.*, 2009; Shestyuk *et al.*, 2005) and may negatively affect memory formation for positive as compared to negative and neutral stimuli. Using event related potentials (ERP), Shestyuk *et al.* observed smaller slow wave amplitudes to positive self-relevant words in MDD relative to controls, whereas group differences for negative or neutral stimuli were absent (Shestyuk *et al.*, 2005). In a previous study (van Tol *et al.*, 2012) it was shown that MDD patients showed abnormal processing of positive information, as reflected in decreased hippocampal activation. Together these results suggest that positive information is remembered worse than negative or neutral information, which may lead to enhancing the negative mood.

Taken together, negative and positive biases may lead to reinforcement of negative mood and abnormal memory formation, which, subsequently, may further contribute to a chronic course of the disorder (Elliott *et al.*, 2002; Wagner *et al.*, 1998).

The symptoms of impaired ability to think and concentrate have been related to deficits in memory, attention, and executive functioning (EF; Frodl *et al.*, 2006). Deficits in EF are key factors in prohibiting full rehabilitation in social functioning, and can have a severe impact on the depressed patient's ability to cope with the demands of daily living, which may increase their risk for relapse (Gotlib & Hamilton, 2010). A major feature of EF is planning, the process of thinking about and organizing the steps required to achieve a desired goal. EF has been reported to be impaired in MDD (Rogers *et al.*, 2004). Studies in MDD assessing EF have shown abnormal task performance and increased activity in task-related brain areas (Fitzgerald, Sr., 2008; Matsuo *et al.*, 2006; McClintock *et al.*, 2010; Rose *et al.*, 2006; van Tol *et al.*, 2011; Wagner *et al.*, 2006), during the Tower of London visuospatial planning task (ToL) and the n-back working memory task, although reduced activity has also been reported

(Elliott *et al.*, 1997; Goethals *et al.*, 2005). These inconsistencies may be due to limited power, or differences in scanning modalities and clinical characteristics of patient groups, including medication use. In healthy controls, visuospatial planning has been consistently associated with activation of a dorsal prefrontal-parietal-striatal circuit (van den Heuvel *et al.*, 2003; van Tol *et al.*, 2011).

These findings of MDD related altered activity in task-related brain areas can be incorporated in three well-known models for MDD: Mayberg's limbic-cortical dysregulation model, Phillips's dorsal-ventral model, and Beck's cognitive model of depression. In short, Mayberg proposed a model with hyperactive ventral paralimbic regions, and hypoactive dorsal neocortical regions (Mayberg, 1997; updated in 2004 by Seminowicz *et al.*). Like Mayberg, Phillips suggested that the combination of a hyperactive ventral system and a hypoactive dorsal system is responsible for sad mood and impaired regulation of emotional responsiveness in MDD (Phillips *et al.*, 2003). Whereas Mayberg and Phillips used their models to describe the neuroanatomical underpinnings of disturbances of emotion perception and regulation in depression, the cognitive model of Beck (Beck, 1967) is based on latent cognitive schemas influencing emotion processing. Recently, Beck and colleagues (Disner *et al.*, 2011) extended the cognitive model of depression by integrating cognitive dysfunction and emotional biases. They suggested that the negative cognitive biases in depression are associated with increased activity in subcortical emotion processing regions combined with attenuated top-down cognitive control. Areas associated with biased attention for negative stimuli are thought to include the anterior cingulate cortex (ACC), dorsolateral PFC, ventrolateral PFC and superior parietal cortex (SPC). Taken together, influences from subcortical emotion processing regions combined with attenuated top-down cognitive control are thought to underlie depression. However, although these models are straightforward if not simplistic, neuroimaging studies on abnormal activation in depression are not consistent in their findings.

Clinical symptoms of MDD have also been related to structural brain changes. Structural neuroimaging studies have shown smaller volumes of areas related to MDD, including limbic areas, such as amygdala, insula, hippocampus (Hatton *et al.*, 2012; Frodl *et al.*, 2008c; MacQueen *et al.*, 2003; van Tol *et al.*, 2010), and prefrontal areas, such as ACC and dorsal medial PFC (Frodl *et al.*, 2008c). These regions have been implicated in emotion processing as well as executive function. Most studies to date investigating the neural correlates of MDD are cross-sectional, and, therefore, cannot elucidate whether abnormalities in e.g. planning related activation in MDD and structural changes are a result of the active disease process (i.e. *state* characteristic of MDD) or rather precede the acute disease (i.e. *trait* characteristic of MDD) (Amico *et al.*, 2011).

Risk factors

Multiple factors have been proposed to contribute to the development of depression. Identifying these so-called risk factors is important for the understanding of the underlying mechanisms of MDD. The genetic factor is an example of a risk factor that plays an important role in the development of MDD, which is indicated by family, twin, and adoption studies. Also, genetic factors may uncover important information about underlying disease

mechanisms. More specifically, the variation in genes can be considered as risk factors: they likely contribute to the vulnerability and maintenance of depressive symptoms by influencing emotional information processing or executive function. The variation may alter the structure of the protein that is translated from the gene, which is likely to start a cascade of alterations that in turn may influence the firing rate of neurons underlying emotion processing or executive function.

Risk factor: Genetics

We all carry deoxyribonucleic acid (DNA), the building bricks of our body. It determines the colour of our hair, partially our intelligence and partially whether we get depressed. We all are unique because of genetic variation. This variation takes place at the level of the nucleotide; the bricks that form DNA. One type of genetic variation is called a SNP (pronunciation: snip), a single nucleotide polymorphism. This is a DNA sequence variation arising by change of a single nucleotide (A [adenine], C [cytosine], T [thymine], or G [guanine]). SNPs can be associated with the clinical phenotype of depression, or with an intermediate phenotype of depression, such as regional brain function (Human Molecular Genetics, Third Edition).

Twin studies have shown that up to 40% of MDD is genetically determined. Since the beginning of genetic investigations in MDD, several methods have been used to detect associations between genetic variation and MDD. Linkage and association studies are complementary methods of locating susceptibility genes for MDD. Briefly, linkage is looking at physical segments (so-called quantitative trait loci; QTL) of the genome that are associated with depression and can be detected over comparatively large distances of the genome (for a more detailed description, see box 1). However, power is problematic when searching in genome-wide scans for QTLs with small effect sizes. By contrast, traditional association studies are investigating small genetic variations in the genome and are then looking for different traits that are associated with those different segments of genome. (Cohen-Woods *et al.*, 2013).

Since Joseph Schildkraut (1965) first proposed the monoamine hypothesis of depression, a great deal of research has investigated the effects of the putative lack of monoamines in the brain on depression (Ruhé *et al.*, 2007). The monoamine hypothesis proposes that the underlying biological or neuroanatomical basis for depression is a deficiency of central noradrenergic and/or serotonergic systems and that targeting this deficiency with an antidepressant would tend to restore normal function in depressed patients (Hirschfeld, 2000). As the most widely prescribed antidepressants prevent reuptake of serotonin in the synaptic cleft (i.e. selective serotonin reuptake inhibitors or SSRI's), most candidate gene studies have been focussing on genes influencing serotonergic pathways. However, given the many inconsistencies in candidate gene studies, a hypothesis-free approach might be more useful to identify possible genetic variants that contribute to MDD. Moreover, using a hypothesis-free approach might point us towards other systems than the serotonergic system involved in MDD.

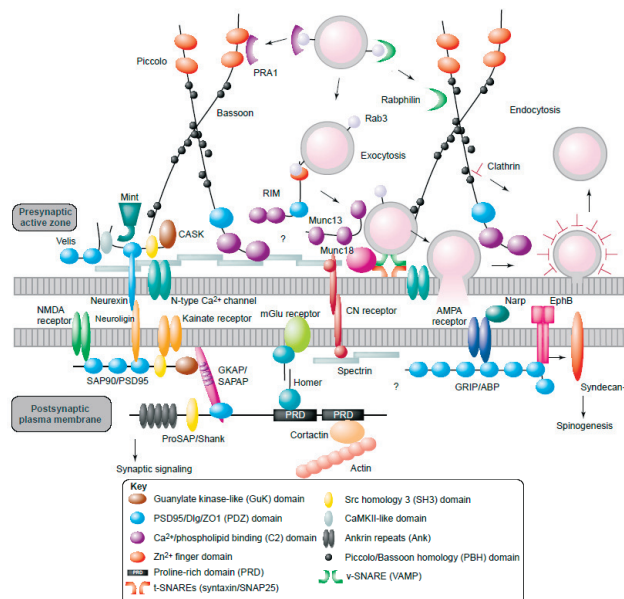
GWAS

The genome-wide association study (GWAS) method combines the advantages of the scope of linkage with the power of association, and no *a priori* hypothesis is required. Therefore, the GWAS approach is also called a hypothesis-free approach.

In a typical GWAS study, a case-control design is used to test for an association with disease and any of the 500,000 tagged SNPs in each individual. The first GWAS on depression resulted in the discovery of piccolo (PCLO) (Sullivan *et al.*, 2009; box 1.1), a gene involved in monoaminergic neurotransmission, although this GWAS could not be consistently replicated (Hek *et al.*, 2010; Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium, 2013; Wray *et al.*, 2012). Possibly, the clinical phenotype of MDD may have been to heterogeneous to be associated with SNPs in the genome.

Box 1.1: Piccolo/PCLO

Recently a GWAS for depression yielded a SNP in the PCLO gene. Using ~500,000 single nucleotide polymorphisms (SNPs), one SNP (rs2522833) located at position 82453708 (hapmap genome build 37.1) in the piccolo gene (PCLO) showed in particular to be of interest in the genetic model for MDD. Further research showed that this is most likely the true causal variant for association with depression. This association was replicated in some studies, but not in others. The rs2522833 SNP changes the hydrophilic, uncharged amino acid serine to the charged amino acid alanine in the calcium binding C2A domain of PCLO and may affect protein stability. The PCLO protein is localized at the cytomatrix of the presynaptic active zone and is important in monoaminergic neurotransmission in the brain. Recently, Schuhmacher *et al.* showed that the PCLO SNP rs2522833 is associated with antidepressant treatment response, supporting the involvement of PCLO in MDD. The mechanism through which this PCLO risk allele contributes to MDD is not known, but its primary role in monoaminergic neurotransmission suggests that it may affect activity of brain circuitry involved in emotional information processing and/or executive functioning in MDD (from chapter 2 of this thesis).



source image: Zhen & Jin, 2004 *Current opinion in Neurobiology*

Getting closer to genes

Obviously, the clinical phenotype of MDD is not directly coded by genes itself. Genetic variants more likely affect the functional or structural integrity of neural circuitries of emotion processing and executive function through molecular and cellular mechanisms (Meyer-Lindenberg & Weinberger, 2006; Scharinger *et al.*, 2011). The neurobiological substrate of emotion processing and executive function itself have been used as intermediate phenotype for MDD in candidate gene studies. To date, most studies describing the association between emotion processing and candidate genes in MDD reported genes from the serotonergic system to be associated with emotion processing related brain regions (Linden & Thome, 2011). Regarding executive functions, most genetic association studies found genes from the monoamine systems, including the serotonergic system to be involved. The association of executive function with monoaminergic neurotransmission is thought to be bidirectional: PFC function is shaped by monoaminergic neurotransmission, but modulatory monoaminergic systems may also be affected by the PFC (Robbins & Arnsten, 2009). Studies suggest that the PFC is able to recruit monoamine systems in specific circumstances, for example in rats, to optimize the coping strategy for stress (Amat *et al.*, 2005; Giorgi *et al.*, 2003; Hasler *et al.*, 2004). However, genetic association studies linking candidate genes from the serotonergic system to emotion processing and executive function in depression are inconclusive and not well replicated (Bosker *et al.*, 2011). This suggests that a hypothesis-free GWAS, using neuroimaging data as intermediate phenotype, might be more useful to identify mechanisms of action that contribute to emotion processing.

Risk factor: Course of depression

Clearly, genetic variants are important risk factors for depression. However, studies examining neuronal processes that link genes to the psychopathology of depression have yielded inconsistent findings and GWAS studies on depression partially failed to replicate. Looking for additional risk factors to understand the underlying mechanisms of depression is therefore essential. Using the intermediate phenotype of neuroimaging to investigate the course of depression is described in **part II** of this thesis.

The number of previous depressive episodes is an important risk factor for recurrent depression. Circa 50% of MDD patients experience recurrence of MDD in their lives within 5 years after an episode, and 80% of patients with a history of two episodes will have another recurrent depression (Burcusa & Iacono, 2007). In terms of outcome, recurrence or chronic depression is the least favourable course of depression. Moreover, full social rehabilitation may be hampered in MDD by EF impairments, which can have a severe impact on the ability to cope with the demands of daily living, thereby increasing the risk of relapse (Gotlib & Hamilton, 2010). EF impairments in MDD are thought to be stable neuropsychological (trait)-characteristics, present in both chronic depression (Bhardwaj *et al.*, 2010; Reppermund *et al.*, 2009; Westheide *et al.*, 2007) and remission (Neu *et al.*, 2005; Paelecke-Habermann *et al.*, 2005; Weiland-Fiedler *et al.*, 2004), although inconsistent findings have been reported (Maalouf *et al.*, 2011; van Tol *et al.*, 2011).

So far, a limited number of studies have focused on morphometric abnormalities to predict disease course (i.a. Baldwin *et al.* 2000). In MDD outpatients, preserved grey matter (GM) volume of the ACC was shown to predict good clinical outcome (Frodl *et al.* 2008b). Smaller hippocampal volume has often been found in MDD (i.a. Neumeister *et al.* 2005), albeit not consistently (Eker *et al.* 2010; van Tol *et al.* 2010), and may relate to disease load (Frodl *et al.* 2008c).

One theory on the association between MDD and structural changes is that smaller volume of limbic regions, such as amygdala, insula, hippocampus (Frodl *et al.*, 2008c; Hatton *et al.*, 2012; MacQueen *et al.*, 2003) and prefrontal regions, such as ACC and dorsal medial PFC (Frodl *et al.*, 2008c) may result from prolonged duration of the disorder (i.e., ‘scarring’ [McEwen, 2001; Sheline, 2000]). These smaller volumes may be due to chronically elevated levels of stress hormones (Post *et al.*, 2012) and possibly abnormal BDNF levels (Gonul *et al.*, 2010). Such so called scarring could explain the heightened vulnerability for new depressive episodes, as these morphological abnormalities may underlie functional impairments in emotion processing and mood regulation. However, empirical support for the scar hypothesis is ambiguous (Santesso *et al.*, 2008; Zeiss & Lewinsohn, 1988), and comparisons between studies investigating the effects of disease burden of depression on regional brain volumes are hampered by low power (Cho *et al.*, 2010; Frodl *et al.*, 2008a; Frodl *et al.*, 2004; Frodl *et al.*, 2008c), the inclusion of selected patient subgroups (Chen *et al.*, 2010; Nifosí *et al.*, 2010), clinical heterogeneity (Lagopoulos *et al.*, 2012), and the use of different data-analytical strategies. Furthermore, most studies to date were cross-sectional, and were therefore unable to disentangle state and trait effects of the disease.

An alternative hypothesis would be that structural abnormalities and EF impairments in fact represent a premorbid vulnerability factor, possibly associated with genetic or familial risk for depression, that can be regarded a predictor rather than a consequence of chronic course. A direct prediction from this hypothesis is that prolonged duration of the disorder is not accompanied by progressive volume loss or aggravation of disturbances in dlPFC activity, but regional brain volume decreases and altered EF related dlPFC activity differentiates those with an unfavourable course from those with a favourable course early in the disease, or even before onset of the disease. Previous work seems to support this suggestion (Chen *et al.*, 2007; Cho *et al.*, 2010; Frodl *et al.*, 2008c; Holmes *et al.*, 2010; Lagopoulos *et al.*, 2012; Samson *et al.*, 2011), but results may have been confounded by clinical status of patients, or use of antidepressant medication. Moreover, in these studies, manual delineation techniques were applied, limiting the analysis to a small number of regions. In a previous cross-sectional whole-brain study in MDD patients and HC, we found smaller GM volumes of the rostral ACC, inferior frontal gyrus (IFG), and posterior cingulate cortex (PCC) in a large sample of MDD patients relative to controls (van Tol *et al.*, 2010). However, as this was a cross-sectional study, conclusions on the predictive value of these results for MDD outcome could not be drawn.

Aim of the present study

Neuroimaging Genetics

Until now, neuroimaging genetic association studies in MDD have yielded important insights in downstream effects of genetic variants. In addition, using a hypothesis-free approach, GWAS have identified risk alleles (including the PCLO risk allele rs2522833) for MDD, but about their function little is known. Only very recently, researchers have started to use structural and functional neuroimaging in GWA studies to find risk alleles for specific brain dysfunction and volume alterations (Brown *et al.*, 2012; Stein *et al.*, 2012). Moreover, follow up of risk alleles identified in GWAS for MDD with an intermediate phenotype, such as functional and structural neuroimaging, has not been performed yet.

Longitudinal Neuroimaging

The answer to the question whether brain abnormalities associated with depression are present before the onset of the disorder remains still unclear. Moreover, improvement of social rehabilitation by lowering EF impairment is desired. To elucidate more on the theories of the association between MDD and structural changes and to find improvement for social rehabilitation, longitudinal neuroimaging are crucial. Longitudinal studies published so far were likewise low-powered (Chen *et al.*, 2007; Frodl *et al.*, 2008a; Frodl *et al.*, 2004; Frodl *et al.*, 2008c; Hou *et al.*, 2012), or were conducted in elderly (Hickie *et al.*, 1997; Hou *et al.*, 2012; O'Brien *et al.*, 2004; Soriano-Mas *et al.*, 2011). Moreover, this limited number of current longitudinal studies did not investigate EF impairment in MDD.

The overall aim of the studies presented in this thesis is to identify imaging characteristics associated with the occurrence and recurrence of depression. Two perspectives were chosen: In **part I** the association between the PCLO genotype and the neural substrates of emotion processing, executive function, and memory processing is investigated, while controlling for antidepressant medication and volumetric differences. In **part II**, following the 'vulnerability' hypothesis, we investigated whether regional brain volumes and planning related brain activity in regions associated with the neuropathology of MDD at baseline were predictive of MDD recurrence or remission after two years. Moreover, following the scar hypothesis, it was tested whether structural and functional changes, seen in MDD, further aggravated with prolonged MDD course. The effects of illness severity and use of selective serotonin reuptake inhibitors (SSRI) were taken into account as potential confounders. The studies described in this thesis were part of the Netherlands Study for Depression and Anxiety, which is an ongoing longitudinal cohort study (box 1.2).

Outline thesis

Part I

Chapter 2 describes whether the PCLO risk allele is associated with similar changes in activity in emotion processing and executive function related brain areas as have been described in MDD. In addition, the relationship of PCLO with current psychopathology during emotional face processing and executive function is studied.

Chapter 3 outlines the association between the PCLO genotype and the neural substrate of the memory processing of positive and negative information. In addition, this study investigated whether the PCLO risk allele was associated with volumetric abnormalities in the regions related to memory processing, which could in part explain functional deficits. This study also explored whether PCLO genotype effects on the brain were different in the presence of MDD psychopathology.

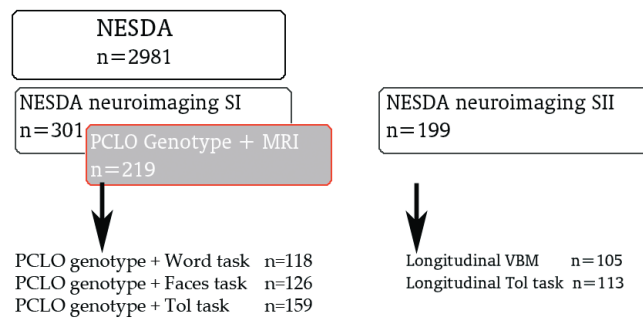
Part II

In **chapter 4** it was studied whether volumes of regions associated with the neuropathology of MDD at baseline were predictive for remission of MDD at two-year follow-up. In the context of the ‘scar’ hypothesis, it was investigated whether structural changes seen in MDD further decline with prolonged course of MDD. In **chapter 5** the predictive value of executive dysfunction related brain activity in MDD was investigated in terms of outcome. Next, this study described whether executive function related brain activity in MDD aggravates with chronic course and/or normalizes with stable remission at follow-up. In addition, it was investigated to what extent structural changes and executive dysfunction are influenced by severity of depression, and the use of selective serotonin reuptake inhibitors (SSRIs).

Chapter 6 summarizes and discusses the results. In addition, implications for future treatment and recommendations for future research are presented.

Box 1.2: Netherlands Study for Depression and Anxiety

Genetic factors, course of depression, and more factors are studied in the Netherlands Study for Depression and Anxiety (NESDA). NESDA is an ongoing longitudinal cohort study, that aims to (1) describe the long-term prognosis of depressive and anxiety disorders in terms of course (chronicity, recurrence, development of comorbidity, suicidal behavior) and public health consequences (disability, mortality, costs), (2) examine clinical, psychosocial, biological and genetic determinants of the long-term course and consequences of depressive and anxiety disorders, (3) examine patient’s expectations, evaluation and provision of (mental) health care and their association with the long-term course and consequences of depressive and anxiety disorders.



NESDA and the study samples; NESDA neuroimaging SII is measured two years after NESDA neuroimaging SI