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Table of Contents

1 Introduction

Depression is among the four leading causes of disease burden throughout the world and is associated with medical morbidity and mortality across the lifespan (Wong et al. 2001; Evans et al. 2005). Besides being the most prominent psychiatric disorder, major depressive disorder (MDD) is also associated with many other chronic medical conditions. Recent studies have shown that MDD is not only a side-effect of severe medical conditions but additionally an independent risk-factor or pre-cursor being associated with different illnesses, such as ischemic heart disease, stroke, cancer, and epilepsy (Evans et al. 2005). Moreover, MDD is often accompanied by comorbid psychiatric disorders, most prominently anxiety disorders (Nemeroff et al. 2002).

Given the importance of shedding light on the neurobiological underpinnings of MDD, chapter one and the following subchapters outline the neurobiological basis of MDD on a genetic, molecular, cellular and systemic level, focussing on functional and structural alterations in cognitive and emotional processing, including phylogenetic and ontogenetic mechanism, reported by a large body of literature.

Chapter 1.1 and its subchapters delineate the neurobiological circuits involved in the pathophysiology of MDD and its functional and structural correlates, including data derived from human studies with acute MDD and remitted MDD patients. Since a lot of evidence in the neurophysiology of MDD within the last 15 years comes from neuroimaging studies, the present diploma thesis particularly focuses on corresponding data within the neuroimaging literature. However, since there is a lot of speculation and discussion about the genetic, molecular and cellular underpinnings of these functional and structural alterations, this field of research will be also tackled in the course of the following subchapters.

Within the chapters 1.2 – 1.4 the focus lies on the structural aspects of MDD. Thus, developmental mechanisms concerning the human cerebral cortex and its

morphology will be thoroughly discussed, before thematic emphasis will be put on the molecular and cellular basis of cortical thickness as a measure of the morphology of the human cerebral cortex. Based on these results on a microscopic level, recent structural neuroimaging findings relying on cortical thickness as a structural marker distinguishing between healthy subjects and patients with neurological or psychiatric diseases will be reviewed extensively. Finally, the goal of the present diploma thesis will be briefly described in chapter 1.5.

1.1 The Neurobiology of Depression

MDD is symptomatically characterized by depressed mood, irritability, reduced self esteem, feelings of hopelessness and guilt, cognitive disabilities like aberrant functioning of memory and attention and abnormalities in sleep, appetite and social interaction (Nestler et al. 2002). The diversity of cognitive, emotional and vegetative symptoms in MDD reflects the underlying, complex pathophysiology. Several lines of evidence indicate that the pathophysiology of MDD is a result of a dysfunctional interplay between several brain regions and neurotransmitter systems. Converging biochemical, pharmacological, post-mortem and neuroimaging studies evidence suggests MDD to be a system-level disorder (Mayberg et al. 2005; Drevets et al. 2008).

1.1.1 Neural Circuitry of MDD

Recent advantages in brain imaging techniques shed light on the neuroanatomical underpinnings of the pathophysiology of MDD on a system level. Especially prefrontal and limbic regions have been implicated in the pathogenesis of MDD. Mayberg (1997) has proposed a model of MDD based on the notion of a dysfunctional coordination of different brain areas within the framework of a distributed cortical network. It distinguishes between the *dorsal compartment* which includes the neocortical and the midline limbic regions, such as the

dorsolateral prefrontal cortex (DLPFC), the dorsal anterior cingulate cortex (dACC), the inferior parietal cortex, and the striatum and the *ventral compartment* comprising the paralimbic cortical, the subcortical and the brainstem regions, such as the hypothalamic-pituitary-adrenal axis (HPA), the insula, the subgenual anterior cingulate cortex and the amygdala. The dysfunctional coordination of these interconnected regions encompasses activity decreases in the dorsal compartment, especially the DLPFC and the dACC and activity increases in the ventral paralimbic areas measured by regional blood flow changes during positron emission tomographic (PET) measurements. Consequently, remission from MDD can be achieved by inhibition of the hyperactivated ventral compartment and restoring normal functioning of the dorsal compartment exerting control over ventral areas by modulating their levels of activity (Mayberg 1997; Mayberg et al. 1999).

Phillips et al. (2003) have extended and refined the aforementioned model of depression focussing on the neurobiological basis of abnormal emotion processing in depressive patients. Within that framework, aberrant functioning of the ventral and the dorsal system mediate different aspects of emotional dysregulation. The ventral system, consisting of the amygdala, insula, ventral striatum, ventral anterior cingulate gyrus, and prefrontal cortex plays a major role in detecting the emotional importance of a stimulus, producing affective states and regulating emotional responses. On the other hand, the dorsal system, including the hippocampus, dorsal anterior cingulate gyrus, and prefrontal cortex is mainly implicated in executive functioning, such as selective attention, planning and the effortful regulation of affective states. In MDD executive and emotional processing is impaired with patients identifying and experiencing emotional stimuli primarily within a negative context resulting in depressed mood and anhedonia (Phillips et al. 2003).

Those circuits regulating and modulating the experience and evaluation of emotional events, are also discussed within an extended network, including limbic-cortical-striatal-pallidal-thalamic circuits (LCSPT), formed by connections between

the orbital and medial prefrontal cortex, amygdala, hippocampal subiculum, ventromedial striatum, mediodorsal and midline thalamic nuclei and ventral pallidum, the orbital prefrontal network, encompassing sensory association and somato-sensory areas and the medial prefrontal network, consisting of the dorsomedial/dorsal anterolateral prefrontal cortex, the mid- and posterior cingulate cortex, and the entorhinal and posterior parahippocampal cortex (Ongur et al. 2003; Saleem et al. 2008). The medial prefrontal network might be of special interest as it is not specifically linked to the sensory system, but interacts with limbic regions as well as the hypothalamus. By that, it mediates visceromotor functions producing and regulating visceral reactions to emotional stimuli which seem also to be impaired in MDD (Drevets et al. 2008).

1.1.2 Brain Activation Abnormalities in MDD

The pathophysiology of MDD may be explained by functional abnormalities in distributed networks of cognitive and emotional processing. Indeed, neuroimaging studies have shown global and regional changes in cerebral blood flow and glucose metabolism in depressed patients compared to normal controls (Soares et al. 1997; Fitzgerald et al. 2008). Meta-analyses of functional magnetic resonance imaging (fMRI) and PET studies measuring brain activation in MDD have demonstrated several brain areas consistently implicated in the pathophysiology of MDD. Especially, aberrant functioning of two neural networks has been identified in several studies. The first includes the dorsal/pregenual anterior cingulate, bilateral middle frontal gyrus (DLPFC), insula and the superior temporal gyrus which show decreased activity to negative emotion induction and increased activity after selective serotonin reuptake inhibitor (SSRI) treatment. The second neural circuit involved in the pathophysiology of MDD consists of the medial and inferior frontal cortex, the basal ganglia, the amygdala and the thalamus which display hyperactivity during negative emotion induction and reduced activity in response to SSRI treatment (Fitzgerald et al. 2008).

Several neuropsychological studies have provided evidence that MDD is not only characterized by dysfunctional emotional processing, but also by abnormal functioning of cognitive processing (Westheide et al. 2007).

The memory system is one of the most affected neurocognitive systems in MDD. Studies have demonstrated deficits in memory encoding and retrieval in episodic, semantic and working memory in patients (Zakzanis et al. 1998; Rose et al. 2006). Consistent with these neuropsychological studies, neuroimaging findings have reported abnormal functioning in working memory associated brain areas, prominently the DLPFC. However, findings are conflicting, showing underactivated prefrontal cortex during working memory associated tasks (Barch et al. 2003; Okada et al. 2003) whereas other studies report hyperactivation of the prefrontal cortex (Matsuo et al. 2007).

Within the framework of the aforementioned circuitry models of depression, dysfunctional activation of the prefrontal cortex might contribute to an abnormal evaluation and response to emotional stimuli frequently associated with MDD. The frequent observation that prefrontal hyperactivation is not correlated with deficits in behavioural performance provide some evidence that MDD patients need higher activation of working memory associated areas in order to maintain the same level of performance in solving given tasks.

Another important area which might contribute to the pathophysiology of MDD is the anterior cingulate cortex (ACC). Neuroimaging studies have shown that the ACC, similar to recent findings focussing on the DLPFC, displays hyperactivation in patients compared with healthy controls (Harvey et al. 2005; Matsuo et al. 2007). The role of the ACC in depression has been extensively discussed within the scientific literature (Bush et al. 2000; Drevets et al. 2008). A large body of evidence suggests that the ACC is both involved in emotional and cognitive processing. Whereas the dorsal part of the ACC subserves cognitive functions, such as working memory, attention, conflict monitoring and error processing (Bush et al. 2000; Mulert et al. 2007; Sohn et al. 2007), the ventral compartment plays a

key role in emotional assessment and regulation of behavioural responses (Whalen et al. 1998).

The strong connections of the ACC with other cortico-limbic regions, such as the DLPFC, the amygdala, the hippocampus, the nucleus accumbens, the hypothalamus or the orbitofrontal cortex, which are also involved in the pathophysiology of depression, facilitates the hypothesis that a dysfunctional cortico-limbic network is the main contributor to the pathogenesis of MDD. Especially the amygdala has been shown to be involved in emotional dysregulation, displaying increased activity when confronted with fearful faces (Sheline et al. 2001).

In addition to the involvement of the cortico-thalamo-limbic circuitry, other regions, such as the posterior cingulate, medial temporal lobe and the cerebellum also seem to contribute to the pathophysiology of MDD (Fitzgerald et al. 2008). Interestingly, the ventral part of the posterior cingulate cortex has direct connections to the subgenual anterior cingulate as well as the orbitofrontal cortex (Vogt et al. 2006) both of which functioning abnormally in MDD (Drevets 2007; Drevets et al. 2008).
It has been proposed that the ventral posterior cingulate and the subgenual anterior cingulate are involved in the assessment of emotional content which is consistent with the notion of deficits in emotional evaluation and regulation in depressed patients. The subgenual anterior cingulate cortex has been intensively investigated within the last years with studies showing elevated activation of this structure in MDD patients (Mayberg et al. 1999; Drevets et al. 2008). Pezawas et al. (2005) have shown that a polymorphism in the 5' promoter region (5-HTTPLR) of the human serotonin transporter gene (SLC6A4) is related to altered
structural covariation between the amygdala and perigenual ACC, reflecting weaker functional coupling between these two areas resulting in stronger amygdala reactivity in S allele carriers.

As already mentioned before, dysfunctional fronto-limbic coupling described as loss of top-down control of the prefrontal cortex over limbic regions, such as the amygdala, has been a favoured model to describe the pathophysiology of MDD. Functional decoupling of this circuitry would mean a loss in cognitive control and consequently, elevated emotional responses which might be reversed with antidepressant treatment by strengthening fronto-limbic connections (Chen et al. 2008).

1.1.3 Brain Structure Abnormalities in MDD

A large body of evidence suggests morphological changes in depression-related neural circuits. Primarily, structural changes in regions of the cortico-limbic network have been implicated in the pathophysiology of MDD (Sheline 2003; Koolschijn et al. 2009). Consistently replicated by structural neuroimaging studies are volume reductions in frontal regions, such as the ACC, the prefrontal cortex and the orbitofrontal cortex as well as in limbic regions including the amygdala and the hippocampus (Konarski et al. 2008). Other regions shown to be involved in the dysfunctional changes in MDD are the thalamus, the basal ganglia, the pituitary and the cerebellum (Konarski et al. 2008). However, besides those studies finding changes in structure between patients and healthy controls, some studies have reported no significant differences (see e.g. reviews of Sheline 2003; Konarski et al. 2008).

Several studies have demonstrated that volume loss in cortico-limbic areas is particularly associated with stress-induced HPA-axis dysregulation which leads to increased levels of cortisol (Bao et al. 2008). Hypercortisolemia, elevated levels of cortisol, might be one causal factor producing volume loss including neuronal atrophy and/or inhibition of neurogenesis (Rajkowska et al. 1999; Czeh et al. 2007).

Additional mechanisms have been proposed linking the volume loss of several regions to stress and subsequently to MDD. Besides hypercortisolemia, reduction

in neurotrophic factors or glial cell loss, the latter of which has been found in the amygdala (Hamidi et al. 2004), might also account for reduced volume (Duman et al. 1997).

Summing up, glucocorticoid (GC)-mediated neurotoxicity (Sapolsky 2000), might be one explanation for atrophic processes observed in MDD patients accounting for decreases in volume. The fact that cortico-limbic structures, primarily the hippocampus, amygdala and the prefrontal cortex display high concentrations of GC receptors (Sheline 2003), supports the glucocorticoid (GC)-mediated neurotoxicity hypothesis explaining volume reductions in MDD. Additionally supportive for that hypothesis are findings which show increases in pituitary volume in depressed patients (Krishnan et al. 1991).

As already mentioned before, Pezawas et al. (2005) reported attenuated coupling between the amygdala and perigenual ACC in subjects with a polymorphism in the 5' promoter region (5-HTTPLR) of the human serotonin transporter gene (SLC6A4). Those short-allele carriers also display reduced grey matter volume in limbic regions involved in processing of negative stimuli, particularly the amygdala and perigenual cingulate cortex, eventually making them more vulnerable developing MDD.

1.1.4 Molecular Mechanisms in MDD

On a molecular basis, alterations in the network responsible for emotional and cognitive processing, might be induced by aberrant functioning of neurotransmitter systems, impairments in neurotrophin action and/or dysfunctions within the neuroendocrine system (Nestler et al. 2002; Krishnan et al. 2008). One favoured model, the so-called "monoamine hypothesis", states that depression is caused by decreases in monoamine function (Krishnan et al. 2008). Antidepressant treatment with SSRIs or monoamine oxidase inhibitors have been shown to increase serotonin (5-HT) and and the latter one also noradrenaline neurotransmission (Berton et al. 2006; Pittenger et al. 2008). Animal studies report altered 5-HT

signalling in response to stress accompanied with changes in behaviour (Gaspar et al. 2003; Gross et al. 2004).

Since 5-HT neurotransmission is regulated by receptors and transporters, it is hypothesized that aberrant functioning of these components of the 5-HT system is a key factor in the pathogenesis of depression. Different receptor types and transporters and their abnormal functioning in depression have been highlighted by genetic, pharmacological and neuroimaging studies (Staley et al. 1998). One of the most promising candidates suggested to be involved in the processes underlying dysfunctional 5-HT neurotransmission seems to be the 5-HT_{1A} receptor subtype which is one of at least 14 different 5-HT receptor types been identified yet (Hoyer et al. 2002).

5-HT_{1A} receptors are pre- and postsynaptic G protein-coupled receptors expressed in a large number of brain regions including the frontal cortex, septum, amygdala, hippocampus and the hypothalamus which are terminal fields of serotonergic projections originating from the raphe nuclei in the brainstem. Activation of presynaptic 5-HT_{1A} receptors leads to hyperpolarization of the serotonergic neuron resulting in an inhibition of neurotransmitter release. Consequently, the overall release of 5-HT neurotransmitters in the serotonergic projection areas is reduced, which is assumed to be a key feature of an dysregulated 5-HT system implicated in the pathogenesis of depression (Blier et al. 1987). Pharmacological studies have shown that injection of 5-HT_{1A} receptor agonists in brain areas with a high density of somatodendritic 5-HT_{1A} autoreceptors and also in regions known to express postsynaptic 5-HT_{1A} receptors have anxiolytic effects in rats (De Vry et al. 2004; Li et al. 2006).

Whereas there seems to be a reduction in 5-HT_{1A} binding across limbic regions such as the hippocampus or the ACC, Morley-Fletscher et al. (2004) found an increased level of expressed 5-HT_{1A} receptor mRNA in the frontal cortex of prenatally stressed rats. These somehow conflicting results might be explained by compensatory phenomena. Thus, it is tempting to speculate that the increased

expression of 5-HT_{1A} receptor mRNA in the frontal cortex is a compensatory mechanism aiming to regain top-down control over the hyperactivated limbic regions through overexpression of the inhibitory 5-HT_{1A} receptor which might be reflected as disrupted fronto-limbic connectivity on a system level in MDD.

Post mortem data focussing on the 5-HT_{1A} receptor in depressed patients are basically inconsistent according to the direction of 5-HT_{1A} receptor binding changes. Some studies have reported decreased binding potential in the terminal fields of serotonergic neurotransmission including the medial temporal cortex and the hippocampus (Drevets et al. 1999), whereas others have shown increased binding in the ventrolateral prefrontal cortex (Arango et al. 1995).

The discrepancies across these studies may be explained by differences in factors such as former medication, duration of illness, sample structure, gender differences, post-mortem interval or methodological differences measuring the receptor binding (Boldrini et al. 2008). PET studies have reported elevated 5-HT_{1A} receptor binding potential in almost all terminal fields but also in the raphe nuclei using the 5-HT_{1A} antagonist [^{11}C]WAY-100635 (Parsey et al. 2006; Sullivan et al. 2009).

Focussing on the C(-1019)G polymorphism of the 5-HT_{1A} receptor gene, Lemonde et al. (2003) could show that the polymorphism effects the 5-HT_{1A} receptor gene by derepressing the transcriptional machinery ultimately leading to an enhanced expression frequency of the 5-HT_{1A} receptor in the raphe nuclei and consequently to reduced serotonergic neuron firing. On a systemic level elevated 5-HT_{1A} receptor expression could lead to enhanced reactivity of brain regions known to be involved in emotional processing, especially the amygdala (Le Francois et al. 2008). By that mechanism, the G-allele polymorphism could make the subjects more prone to develop a depressive phenotype highlighting 5-HT dysregulation as a biological trait marker of depression (Neumeister et al. 2004).

Besides, the 5-HT_{1A} receptor, the serotonin transporter has been in focus in neuroimaging studies within the last years. Recent findings demonstrate that variations in the 5-HTT gene are associated with alterations in the neural circuitry involved in emotion evaluation and modulation (Hariri et al. 2002; Caspi et al. 2003; Hariri et al. 2003; Pezawas et al. 2005). Recent studies provide some evidence that neurotrophic factors, most prominently the brain-derived neurotrophic factor (BDNF), modulate 5-HT signalling by promoting development of serotonergic neurons and buffering effects of stress (Nestler et al. 2002; Krishnan et al. 2007; Martinowich et al. 2008). The VAL allele of VAL66MET BDNF has been found to be one potential risk-allele in biasing brain wiring towards susceptibility for depression.

Pezawas et al. (2008) have demonstrated genetic interaction between the 5-HTTPLR polymorphism human serotonin transporter gene (SLC6A4) and BDNF VAL66MET impacting the fronto-limbic circuitry. In the light of recent data indicating that antidepressive drugs may induce neurogenesis or stimulate neurite outgrowth and, by that, counteract neuronal atrophy associated with dysfunction of 5-HT neurotransmission (Malberg et al. 2000), the findings of Pezawas et al. enable a deeper understanding of the mechanisms and effects of interacting neurotransmitter and neurotrophin systems in the pathogenesis of MDD.

1.1.5 Brain Function and Structure in Remitted MDD

Several lines of evidence indicate that remitted depressed patients still show functional and structural changes compared to healthy controls and/or acute depressed patients. Compared to acute depressed patients, remitted MDD patients displayed reduced activity in the anteromedial orbitofrontal cortex as well as in the subgenual prefrontal cortex where antidepressant therapy was associated with attenuated activity (Drevets 2007; Drevets et al. 2008). Other studies also demonstrated decreased activity in the pregenual anterior cingulate and the medial orbitofrontal (Liotti et al. 2002) and the left prefrontal cortex (Okada et al. 2009) in the remitted group compared to healthy controls.

However, while decreases in some regions critically involved in emotion processing have been reported, other findings demonstrate increases in prefrontal regions in response to affective faces interpreted as compensatory mechanism aiming to regain top-down control over an overactivated amygdala (Robinson et al. 2008) and attenuated activity in the cingulate cortex during a working memory task hypothesized as compensatory mechanism to fulfil cognitive tasks on a normal performance level (Schoning et al. 2008).

The notion that persistent miswiring of the fronto-limbic circuitry in the absence of acute depression and its behavioural symptoms might represent a trait-marker of MDD making the patient vulnerable for illness relapse is corroborated by studies showing structural abnormalities in remitted MDD. The orbitofrontal cortex has been reported to have smaller grey matter volume in remitted depressed patients in comparison to depressed patients (Nery et al. 2009). While morphological changes in the orbitofrontal cortex seem to reflect trait-dependent alterations of the depression related regions, corresponding neuropsychological studies indicate no changes on a performance level. Thus, executive impairment as well as impulsive behaviour are not observed in remitted MDD patients, whereas patients suffering from acute episodes of depression show impaired executive and impulsive behaviour indicating neuropsychological alterations as state-dependent (Westheide et al. 2007).

Recent data suggest that structural changes in the cingulate cortex and the hippocampus are associated with MDD. Caetano et al. (2006) have shown that remitted depressed patients have smaller left ACC grey matter volumes compared to healthy controls, whereas acute depressed patients have smaller anterior and posterior cingulate volumes bilaterally compared to healthy subjects. However, patients with first-episode remitted geriatric depression exhibit larger volumes in the left cingulate cortex (Yuan et al. 2008).

In the line with studies showing reduced volume in regions associated with MDD, results on the hippocampus have also identified patterns of volume loss in remitted depressed patients compared to healthy controls (Frodl et al. 2004; Neumeister et al. 2005). However, Frodl et al. (2004) could not detect decreased volume in remitted depressed patients in a 1-year follow-up study, which, could demonstrate volume loss in non-remitted patients. Changes in volume have also been related to treatment response implicating increases in supragenual prefrontal cortex volume as positive indicator of antidepressant therapy efficacy (Yucel et al. 2009).

Miller et al. (2009) demonstrated elevated 5-HT_{1A} receptor binding potential in remitted depressed compared to healthy controls measured by PET. Moreover, they performed genotyping of the C(-1019)G polymorphism of the 5-HT_{1A} receptor gene which is a well characterized G-allele polymorphism associated with increased risk of developing depression. Basically, they found that remitted depressed patients overrepresent the C(-1019)G polymorphism of the 5-HT_{1A} receptor compared to healthy controls. This genetic abnormality could account for the higher distribution of 5-HT_{1A} receptors in the raphe nuclei which might result in increased inhibition of serotonergic neurotransmission within the projection areas throughout the whole cortex caused by an elevated 5-HT_{1A} autoreceptor binding. This inhibition of serotonergic neuronal firing could be accompanied by compensatory up-regulation of 5-HT_{1A} receptors in the terminal fields of serotonergic neurons as indicated by an elevated 5-HT_{1A} receptor binding potential in those areas. This might be one aspect of the molecular basis of system-level alterations in cortico-limbic circuits associated with MDD.

1.2 Morphology and Development of the Human Cerebral Cortex

The evolution of the mammalian brain is characterized by progressive enlargement of the cerebral cortex. However, in contrast to other mammalian species showing a lissencephalic brain morphology without any significant convolution patterns, the human cerebral cortex is strongly convoluted reflecting a gyrencephalic structure made of convex gyri and concave sulci buried deeply within the cortical mantle (Hofman 1985).

The evolutionary transformation from a flat to a strongly convoluted morphology is reflected in ontogenesis during which a smooth, lissencephalic cortex becomes a gyrencephalic, highly folded structure. While the degree of cortical folding during the first phase of development is correlated with the degree of enlargement, the second phase is accompanied by a stop in folding as the folding intensity matches the brain size. In terms of cortical folding, a brief postnatal overshot can be observed, causally related to increased brain size (Armstrong et al. 1995).

One prominent feature of the human cerebral cortex is its inter-individual variability which is reflected in the complex architecture of cortical gyri and sulci. Thus, the vulnerability towards neurodevelopmental and/or neuropsychiatric disorders may be substantially determined by cortical folding processes during intra-urine and/or postnatal development (Dubois et al. 2008).

In general, the cerebral cortex, which is ontogenetically developing out of the dorsal telencephalon, is divided into three regions, the neocortex, the archicortex (midline cortex and hippocampus) and the paleocortex. In contrast to the other regions, the neocortex consists of 6 layers which are radially organized and could be differentiated by distinct morphology and connectivity patterns. Tangentially, the neocortex encompasses a vast number of areas, which can be distinguished by several aspects, such as cyto- and chemoarchitecture, afferents and efferents, neurotransmitter and receptor distribution and patterns of gene expression. Basically, the neocortex can be distinguished in four primary areas, three out of

which are from sensory origin: the primary visual, somatosensory and the auditory area, which receive input from the peripheral sensory organs, such as the eye, ear or the body. The forth primary area is the motor cortex which mediates and modulates voluntary movements. These primary areas are strongly interconnected with higher order areas and subcortical nuclei, particularly the thalamus which receives modality-specific sensory input from the periphery and transmits it to the primary areas (O'Leary et al. 2008).

The hierarchical organization of the human cerebral cortex reflects temporal aspects of development. Whereas the primary areas develop earlier in ontogeny, the higher areas, prominently the prefrontal cortex, develop in later maturation stages which is reflected by levels of synaptogenesis and myelogenesis (Huttenlocher et al. 1997). Neuroimaging studies provide evidence that full maturation of the prefrontal cortex is not finished until young adulthood which is corroborated by neuropsychological findings indicating complex cognitive functions still progressing during adolescent development (Paus et al. 1999; Sowell et al. 1999).

The prefrontal cortex can be divided into orbital, medial and lateral areas with the orbital and medial regions involved in emotion processing, and the lateral regions associated with cognitive, integrative functions. Based on the integrative functions performed by the prefrontal cortex, its complex network of connectivity with other regions of the brain is a mere function of processing complexity.

Briefly, the prefrontal cortex is connected with the brainstem, the basal ganglia, the limbic system and the thalamus while most of the connections are reciprocal. The prefrontal cortex gets strong afferent input from regions, such as the brainstem, the amygdala, the hypothalamus and the hippocampus which provide information about the motivational and emotional status. Moreover, the prefrontal cortex is anatomically defined by efferents originating from thalamic nuclei.

The prefrontal cortex also establishes interconnections with the primary sensory and motor areas. Moreover, information transfer within the prefrontal regions is enabled through corticocortical interconnections some of which are interhemispheric and almost all of which show topological organization (Barbas 2000; Fuster 2001; Krubitzer 2007).

Cortical morphology is mainly driven by mechanical forces and genetical programs (Van Essen 1997; Thompson et al. 2001). Several lines of evidence indicate that arealization, a process during which the area`s functional characteristics and connectivity patterns with other regions are determined, is partly driven by genetic regulation (Krubitzer 2007). The latter is executed by transcription factors expressed by cortical progenitor cells and morphogens originating in specialized regions of the telencephalon (O'Leary et al. 2008). Several studies demonstrated genetical influences on cognitive abilities and also emotional behaviour (Eley et al. 1997; McClearn et al. 1997).

Interestingly, findings suggest heritability of the overall brain volume and certain brain structures, such as the frontal lobe or the corpus callosum (Oppenheim et al. 1989; Tramo et al. 1998; Thompson et al. 2001), whereas cortical gyrification seems to be under less genetic control, although one has to mention that the small variability of gyri and its conservation over generations indicates more or less pronounced genetic control of cortical gyrification (Bartley et al. 1997; Fischl et al. 2008). Particularly, neurodegenerative diseases affecting the frontal cortex and neuropsychiatric disorders, such as schizophrenia have been shown to exhibit remarkable genetic control (Cannon et al. 1998; Thompson et al. 2001).

However, mechanical forces, which may interact with genetic factors, seem to play an important role as well in expanding and folding of the cortical sheet. Several hypotheses have been established tackling the mechanisms by which the human cerebral cortex becomes its characteristic gyrencephalic structure (Hilgetag et al. 2005; Hilgetag et al. 2006). One prominent hypothesis, the mechanical tension hypothesis proposed by van Essen (1997), relates the structure of folding patterns

of the cortex to the specific organization of long-range projecting axons which pull highly interconnected regions tightly together, while weakly interconnected or unconnected regions drift apart potentially affecting migration patterns of neurons and interneurons within the laminar layers of the cortical sheet.

1.3 Cortical Thickness – A Structural Measure of Brain Morphology

As already described before, the human cerebral cortex is a highly convoluted sheet of nerve cells with a surface area of ~2600cm^2 and a cortical thickness between 1 to 4.5 mm, with an average of about 2.5 mm (Mountcastle 1997). Since the cortical thickness reflects the underlying cyto- and myeloarchitecture, such as the structure of the laminar cortical layers, the size, number and density of the neuronal cell bodies as well as synaptogenesis and the myelination of axons, changes in one or some of these cyto- and myeloarchitectural aspects can affect the structure and arrangement of the cortical thickness. Thus, it doesn't seem surprising that regional variations are typical for cortical thickness with sulcal areas normally thinner than gyral regions.

Moreover, the specific thickness each of the six cortical layers isn't uniformly distributed either (Fischl et al. 2000). These differences in laminar thickness may be seen in the context of the mechanical tension hypothesis (Van Essen 1997), where mechanical folding forces within the gyri, would result in tangential pressure creating mechanical resistance in vertical direction avoiding neurons to migrate in the superficial layers of the cortex. Since the cortical layers are characterized by an inside-out pattern, migrating neurons would be arrested within the deep gyral layers of the cortex due to mechanical resistance forces within the intermediate layers. On the other hand, weaker mechanical resistance forces within intermediate layers due to expanded sulci may potentially facilitate neuronal migration. These processes might explain the higher number of neurons and consequently, greater cortical thickness in regions more strongly folded (Hilgetag et al. 2005; Hilgetag et al. 2006).

The mechanisms of neuronal migration in the context of cortical layers have been profoundly conceptualized by the radial unit hypothesis (Rakic 1988) proposing glial guiding of migrating neurons to their target regions. The processes underlying neuronal migration are reflected in the structure, number and organization of cortical layers. According to that, the 1000-fold increase in cortical surface during mammalian evolution without significant increase in the thickness of the cortical mantle might reflect an increase in the number of radial columnar units, also called minicolumns (Mountcastle 1997). Thus, the number of neurons within those minicolumns should be, despite regional differences reflecting different numbers of neurons within cortical minicolumns, highly conserved within mammalian evolution with only little variations (Rakic 1995).

Cortical thickness is a function of volume and surface area, exactly the quotient of the cortical volume divided by the cortical surface area. While the cortical volume is a highly variable measure of cortical morphology enlarging during development by a major increase in pial surface, cortical thickness contributes far less to the enlargement of volume remaining relatively constant during normal ontogeny. Consistently, cortical volume is significantly affected by aging, decreasing by ~10% accompanied by loss of neurons, whereas cortical thickness remains relatively constant. According to that, cortical atrophy and concomitant volume loss observed during normal aging seem to reflect two-dimensional reductions of the pial surface. Thus, the cellular basis of reductions in pial surface area during aging might lie in a reduction of radial cortical minicolumns rather than the number of neurons within these (Pakkenberg et al. 1997).

Consistent with these results, showing interindividual differences in cortical grey matter volume as a function of differences in surface area without significant influences of differences in cortical thickness suggesting little covariation between surface area and cortical thickness, a recent genetic study with twins demonstrated that distinct genetic factors might be affecting these two measures of cortical morphology (Panizzon et al. 2009). As a consequence, studies which

only rely on cortical grey matter volume as a measure of morphological changes in the neocortex, may confound the diversity of underlying genetic and cellular forces contributing to normal and pathogenic structural, cortical alterations. Consequently, to consider cortical thickness as a potential endophenotype might provide additional insight in the mechanisms associated with the pathogenesis of neuropsychiatric disorders, such as MDD.

However, focussing on cortical thickness ultimately needs consideration of potentially confounding factors which might obscure the interpretation of neuropathogenic changes in the thickness of the human cerebral cortex. Accordingly, studies have been provided evidence that cortical thickness may be sexually dimorph with a tendency towards larger thickness in healthy female than in healthy male, especially in the temporoparietal regions of the brain (Luders et al. 2006; Sowell et al. 2007). Consistent with this line of research addressing gender differences in measures of cortical morphology, studies have shown sexual dimorphism in cortical thickness in patient groups suffering form several neurodevelopmental or neuropsychiatric disorders, such as schizophrenia (Kuperberg et al. 2003; Narr et al. 2005).

This may have functional implications possibly accounting for gender specific differences in the pathogenesis and –physiology of disorders affecting the cortical mantle. Further confounding factors may lie in aspects concerning MRI measurement technique and instrumental specifications. Han et al. (2006) could demonstrate that the reliability of cortical thickness depends on the type of pulse sequence being used during scan sessions and on data processing parameters whereas scanner upgrade and the number of acquisitions had negligible effects on reliability of cortical thickness measurements. Thus, studies measuring cortical thickness have to be, at least, aware of these potential confounding factors taking them into account in the interpretation of findings, especially when comparing them to data derived from other studies of brain morphology.

1.4 Alterations in Cortical Thickness in Neurological and Neuropsychiatric Disorders

Within the last years, structural neuroimaging studies have put a lot of effort in examining the pathophysiology of neurological diseases on the level of the cerebral cortex morphology. As already described in chapter 1.2, most of these neuroimaging studies have been focussing on the cortical grey matter volume in aiming to delineate structural cortical alterations.

Cortical thickness, as a measure of cortical integrity, has been sparsely used within the neuroimaging community, especially compared to cortical volume, mainly due to software limitations and greater computational cost in data processing. Recent studies on neurological disorders have been addressing alterations of cortical thickness in Alzheimer's disease, where strong thinning of the medial temporal lobe as well as the frontal and the parietal lobes has been demonstrated (Du et al. 2007; Im et al. 2008; Dickerson et al. 2009), frontotemporal dementia accompanied with cortical thinning in bilateral, frontal and temporal regions, inferior parietal regions and the posterior cingulate (Du et al. 2007), schizophrenia associated with a reduction in cortical thickness in paralimbic regions of the ACC, the orbitofrontal cortices, prefrontal and parietal regions (Kuperberg et al. 2003; Goghari et al. 2007; Wang et al. 2007; Fornito et al. 2008; Nesvag et al. 2008; Goldman et al. 2009), attention-deficit/hyperactivity disorder with affected cingulate, prefrontal and inferior parietal regions showing attenuated cortical thickness (Makris et al. 2007), mesial temporal lobe epilepsy with cortical e cingulate during MDD ADDIN EN.CITE (McDonald et al. 2008), autism characterized by cortical thinning of the mirror neuron system (Hadjikhani et al. 2006), specific phobia indicating thickening in cingulate and visual cortical regions (Rauch et al. 2004), Huntington's disease accompanied by cortical thinning in sensomotoric areas (Rosas et al. 2002; Rosas et al. 2008), multiple sclerosis with reductions in cortical thickness in frontal, temporal and motor regions (Sailer et al. 2003) and bipolar disorder associated with strong cortical thinning in prefrontal, sensory and sensory association areas (Lyoo et al. 2006).

In the context of depression, there have only been two studies examining cortical thickness alterations, none of these considering remitted MDD. Walterfang et al. (2009) showed increases in cortical thickness focussing on the corpus callosum in geriatric depression, whereas Peterson et al. (2009) have demonstrated cortical thinning across the lateral surface of the right cerebral hemisphere in persons at high risk for depression, which was deducted from their familial depression history. Moreover, the latter study could provide some evidence that cortical thinning causes cognitive alterations, such as inattention and deficits in visual memory, which, in turn, increased the vulnerability for developing MDD. Thus, it might be reasonable to assume, that functional changes on a behavioural level might mediate the effects of cortical thinning on developing depressive symptoms.

Summarized, there are several lines of evidence indicating that disorders of the brain including neuropsychiatric disorders, might be associated with morphological alterations of the cerebral cortex, measured by cortical thickness. However, it remains unclear, if those cortical alterations reflect trait- or state-dependent changes of the structural integrity of the cerebral cortex. The findings of Peterson et al. (2009), showing reductions in cortical thickness in non-depressive subjects with high risk of developing depression, might be some evidence for thickness changes as trait-related biomarkers of MDD.

1.5 Goal of the Study

The goal of the present diploma thesis is to investigate the pathophysiology of remitted MDD on a systemic, structural level using a mere surface-based approach accounting for individual topological variety. By using cortical thickness as a structural measure potentially altered in remitted MDD, the present study takes some evidence into account indicating cortical thickness having different genetic influences than other structural measures, particularly cortical grey matter volume or surface area (see chapter 1.3). Consequently, different genetic origins might result in different patterns and mechanisms in ontogenetic development.

Thus, it is reasonable to assume that cortical thickness might be uniquely involved in the pathophysiology of MDD which still might be reflected on a structural level in remitted MDD patients.

Moreover, by investigating potential cortical thickness alterations in remitted MDD patients compared to healthy controls, the present study aims to shed light on the pathophysiology of remitted MDD in comparison to acute MDD. Since neuroanatomical changes in acute MDD patients might reflect mainly the current psychopathological state or medication status and hence, represent state markers of MDD, remitted MDD patients might be more appropriate to directly study the vulnerability to depression. Thus, the detection of structural alterations in remitted MDD patients compared to healthy controls might suggest trait-related changes in brain morphology during ontogenetic development associated with the pathophysiology of MDD.

Finally, the present diploma focuses on the influence of particular personality traits on structural alterations measured by cortical thickness aiming to answer the question if potential alterations in cortical thickness really reflect group differences between patients and healthy controls or rather differences in personality traits.

2 Methods

At first, the main advantages of surface-based methods compared to volume-based approaches will be discussed within chapter 2.1. Subsequently, chapters 2.2 – 2.4 contain information about the main methodological parameters, techniques and procedures, such as the sample structure and size, the magnetic resonance imaging acquisition protocol and the preprocessing workflow. Finally, in chapter 2.5, the statistical procedures and methods will be briefly illustrated.

2.1 *Surface-based vs. Volume-based Approaches in Structural MRI*

In contrast to functional magnetic resonance imaging (fMRI) which is regarded as neuroimaging method providing dynamical physiological information about ongoing processes within the brain (Logothetis 2008), structural magnetic resonance imaging (sMRI) provides static anatomical information based on diverse structural measures, such as volume, sulcal depth, gyrification or cortical thickness (Symms et al. 2004).

As already described in chapter 1.2, the human cortex is a highly convoluted two-dimensional sheet consisting of numerous of regions separated by morphological or functional features. The anatomy of the human cortex is a highly variable with brain regions varying in size, orientation and shape. During pathological conditions of the brain, these variations become even more significant. Thus, comparing brains of different subjects in the context of statistical analysis necessitates registration of brains allowing one-to-one comparison so that one particular location in one brain corresponds to the same location in another brain (Rademacher et al. 1993; Roland et al. 1994).

Within the last decade, a lot of effort has been put into developing methods accounting for interindividual variability of the highly variable convoluted two-dimensional human cortex. However, common neuroimaging techniques, such as MRI, display the cortex as a three-dimensional object producing three-dimensional

functional or structural data. Thus, it is not surprising that most of the commonly used methods concerning the minimization of cortical variability rely on volume-based registration techniques normally using 3-D stereotaxic coordinate systems (Van Essen 2004). Several volumetric alignment procedures have been developed using different principles and algorithms (Pantazis et al. 2009). While those alignment approaches provide good results for subcortical regions successfully minimizing interindividual variations, they have clear limitations when applied to the human cerebral cortex typically exhibiting poor correspondence between cortical regions (Makris et al. 2006; Devlin et al. 2007; Pantazis et al. 2009).

The most commonly used registration method compensating for interindividual variability is the so-called Talairach transformation proposed by Talairach and Tournoux (1988). While this method has been proven to be very useful and easy applicable in accounting for interindividual differences in brain size, it doesn't properly account for cortical variability resulting in poor accuracy regarding gyral and sulcal folding patterns. One of the major drawbacks of volume-based alignment approaches, such as Talairach transformation, lies in the incompatibility between the three-dimensional structure of volume representations of the cortex and the natural two-dimensional structure of the cortical sheet resulting in inaccuracies of localization and consequently, in misalignment of cortical regions. Due to the highly folded structure of the human cerebral cortex, anatomical gyral or sulcal landmarks do not occupy the same position in standard volumetric space. On the other hand, anatomical landmarks that may be quite distant in surface space, such as the superior temporal gyrus and the inferior frontal cortex or, more general, the opposite banks of a sulcus, share the same location in volume space. Thus, distances between two points in volume space may not reflect the true distances observed in surface related space causing significant misalignment during Talairach transformation (Fischl et al. 1999; Desai et al. 2005; Argall et al. 2006).

To overcome those limitations of volume-based approaches, surface-based analysis methods of sMRI and fMRI data has been expensively elaborated within the last years resulting in sophisticated registration algorithms in surface space.

Basically, those approaches can be distinguished by their degree of automatization and the surface metrics they are based on. Whereas one approach relies on manually or automatically defined anatomical landmarks and deformation algorithms aligning the individual surface models to the corresponding landmarks on a flattened target surface (e.g. Van Essen et al. 1998; Van Essen 2004; Van Essen 2005), another approach is focussing on automatically constructing surface models based on shape metrics, such as sulcal shape or cortical convexity, which are aligned to a standardized spherical representation of the cortex (e.g. Fischl et al. 1999).

Irrespectively of the surface reconstruction and surface registration method, respectively, used, their reliability and validity depends on implementing adequate surface models accurately representing cortical folding patterns, surface-based atlases as a standardized framework allowing across-subjects statistical analysis of neuroimaging datasets and faithful surface registration algorithms compensating for neuroanatomical differences in cortical shape and folding characteristics (Van Essen 2004; Van Essen 2005). Choosing the right surface-based atlas enabling statistical analysis across subjects for example, is not trivial at all. Whether someone relies on an atlas derived from one individual brain which accurately reflects cortical shape but fails to account for interindividual variability (Van Essen et al. 1997; Geyer et al. 2001), or an atlas based on an averaged template from a population of subjects which reflects shape homologies across subjects but has the disadvantage of blurred cortical convolutions (Mazziotta et al. 2001) strongly depends on the hypothesis and the research questions formulated within the concept of the study.

Several studies have already demonstrated the advantages of surface-based analysis compared to volume-based approaches (Fischl et al. 1999; Andrade et al.

2001; Desai et al. 2005; Anticevic et al. 2008). These advantages mainly include superior cortical alignment precision, spatial preservation of signal after data smoothing and increased statistical power (e.g. Anticevic et al. 2008).

2.2 *Participants*

A sample of 28 remitted major depressive patients without any current drug treatment or psychiatric illness, who did not receive any treatment for at least three months before assessment and 28 age and gender-matched healthy controls, aged from 19 to 43 years, were included in this study. All subjects were recruited in Vienna, Austria, were right-handed and from European ancestry to avoid stratification artifacts.

Inclusion criteria for healthy subjects included: (a) willingness and competence to sign the informed consent form; (b) aged 18 to 45 years; (c) right-handedness; (d) absence of any concurrent or previous psychiatric DSM-IV diagnosis except nicotine dependence; (e) Caucasian subjects of European ancestry. Inclusion criteria for patients included: (a) willingness and competence to sign the informed consent form; (b) aged 18 to 45 years; (c) right-handedness; (d) a DSM-IV diagnosis of remitted MDD; (e) Caucasian subjects of European ancestry.

Exclusion criteria for healthy subjects included: (a) previous or concurrent major medical, neurological or psychiatric illness; (b) clinically significant abnormal values in routine laboratory screening or general physical examination; (c) previous psychopharmacological or psychotherapeutic treatment; (d) current or previous substance abuse except nicotine dependence; (e) current drug treatment except anticontraceptives (f) failure to comply with the study protocol or to follow the instructions of the investigating team. Exclusion criteria for patients included: (a) previous or concurrent major medical or neurological illness; (b) clinically significant abnormal values in routine laboratory screening or general physical

examination; (c) current or previous substance abuse except nicotine dependence; (d) current drug treatment except anticontraceptives (e) failure to comply with the study protocol or to follow the instructions of the investigating team.

Inclusion and exclusion criteria were carefully assessed during neurological examination. Subjects gave written informed consent. The study has been approved by the ethics commission of the Medical University, Vienna.

Psychiatric assessment was conducted using a semi-structured diagnostic interview (Structured Clinical Interview for DSM-IV) (Spitzer et al. 1992) and the Hamilton Depression Rating Scale (Williams 1988) performed by experienced and specially trained staff psychiatrists to exclude the presence of psychiatric illness in the present sample. Moreover, subjects underwent personality assessment including a self-administered personality questionnaire (NEO five factor Inventory) (Costa et al. 1992) and the Temperament and Character Inventory questionnaire (Cloninger et al. 1993).

2.3 *MRI Acquisition*

Three-dimensional structural MRI scans were acquired on a 3T Siemens TIM Trio scanner using a 3D MPRAGE sequence (TR/TE = 2300/4.21ms, flip angle = 9°, inversion time = 900ms, voxel size = 1x1x1.1mm) and preprocessed as being described in chapter 2.4. All MRI measurements were performed at the Centre of Excellence for High-Field Magnetic Resonance, Vienna.

2.4 *Preprocessing*

MRI images were preprocessed using *FreeSurfer* version 4.0.2. (http://surfer.nmr.mgh.harvard.edu) aiming to generate normalized surface models for each participant for further statistical analysis. The whole *FreeSurfer* workflow is described in detail in Dale et al. (1999) as well as Fischl et al. (1999).

Nevertheless, the surface reconstruction workflow architecture should be briefly described herein.

The automated preprocessing workflow started with intensity normalization in order to compensate for magnetic field inhomogeneties during scanning. The intensity normalized image, which is generated from a high resolution anatomical dataset, is further skull stripped to remove extracerebral voxels (Segonne et al. 2004). Next, the resulting image is subcortically segmented by using cutting planes facilitating separation of subcortical structures from cortical regions. Any interior holes within the cortical components were filled in order to create filled white matter masks out of which the full cortical surface models have been generated.

Using a tessellation algorithm, the resulting white matter volume, created for each hemisphere, is covered with triangles in order to produce a triangle-based surface mesh. Simultaneously, the white matter volume is deformed and smoothed resulting in an accurate representation of the grey/white matter boundary and the pial surface (Dale et al. 1999). Using a topology fixer, the defects in the surface models, particularly arising from midbrain structures, were automatically corrected (Segonne et al. 2005).

In order to allow for intersubject comparison of cortical thickness, the surface models, which are still in native space at this step of preprocessing, have to be aligned to a standard template. Intersubject registration in *FreeSurfer* is performed by inflating each of the surfaces to a sphere and consequently registering the spherical surface models to a standard surface-based coordinate system in which cortical thickness comparisons can be made on a node-to-node basis (Fischl et al. 1999; Fischl et al. 1999). The main advantage of a spherical representation of the cortex is its simplicity in mathematical terms and its topological accuracy which allows the preservation of the cortical anatomy of the original surface model (Fischl et al. 1999; Desai et al. 2005).

Cortical thickness estimates were obtained by measuring the distance between the grey/white and the pial surfaces. Due to the intersubject registration, mean cortical thickness measurements could be compared between subjects at each point/node on the cortical surface.

2.5 *Statistical Analysis*

2.5.1 Demographic and Psychometric Data

In order to assess group differences in age and psychometric scores unpaired, two-tailed t-tests using *SPSS* version 15.0 (http://www.spss.com) were performed. Three psychometric variables were used, two of them (neuroticism and extraversion) derived from a personality questionnaire (NEO Five Factor Inventory) and one (harm avoidance) from the Temperament and Character Inventory questionnaire (TCI).

2.5.2 Region-of-Interest Analysis

Based on the literature reviewed in chapter one showing functional and structural alterations in subjects with both, acute MDD and remitted MDD, five, manually drawn regions of interest (ROI`s) were a priori selected, namely the three subparts of the cingulate cortex (i.e. the anterior cingulate, the midcingulate and the posterior cingulate cortex) according to Vogt (2005), the dorsolateral prefrontal cortex and the orbitofrontal cortex.

To calculate group differences in mean cortical thickness within these ROI`s, thickness data was mapped on a average surface, generated from the healthy subjects and smoothed using a 10 mm full-width-at-half-maximum Gaussian filter. Statistical cortical thickness difference maps for each hemisphere were constructed using a general linear model assessing the main effect of group on

cortical thickness on a node-to-node basis using the statistical software and graphical interface *qdec* provided by *FreeSurfer*.

To compensate for multiple comparisons, cortical thickness differences were false discovery rate (FDR) corrected at a region-based $P < .05$ significance level for each hemisphere (Genovese et al. 2002). For illustrating purposes, statistical difference maps were imported into *SUMA* (Saad et al. 2004) and projected onto an average healthy subjects` surface.

Further statistical analysis focussing on the main effects of the three psychometric variables separately and the interaction effects between the group variable and each of the psychometric variables on cortical thickness were conducted using *SPSS* and the free statistical software *R* (http://www.r-project.org). This was done by extracting the peak node showing the strongest group difference with respect to cortical thickness and performing an ANCOVA for each of the psychometric variables consistently including the group variable.

2.5.3 Whole Cortex Analysis

In order to assure that the ROI approach did not overlook significant group differences in cortical thickness in other areas than the a priori hypothesized, whole cortex analysis was performed. This was done by using a general linear model assessing the main effect of group on cortical thickness on a node-to-node basis using the statistical software and graphical interface *qdec* provided by *FreeSurfer*. To compensate for multiple comparisons, results, as in the ROI analysis, were false discovery rate (FDR) corrected at a surface-wide $P < .05$ significance level for each hemisphere. Psychometric variables were not included in the whole cortex analysis.

3 Results

3.1 Demographic and Psychometric Data

There were no significant group differences in age between remitted MDD patients and healthy controls (see table 1). However, there were significant group differences in all three psychometric variables (see table 1 and figure 1). With respect to neuroticism, the patient group showed significantly higher scores than the healthy control group ($t = -4.9$; $df = 54$; $p < 0.001$). Concerning the psychometric variable extraversion, remitted MDD patient demonstrated lower scores compared to healthy controls ($t = 3.3$; $df = 54$; $p < 0.01$). Analyzing group differences in harm avoidance scores also revealed higher values in the patient group ($t = -2.3$; $df = 49$; $p < 0.05$).

Table 1
Demographic and psychometric data

	Patients (n = 28)	Healthy subjects (n = 28)
Age (years)[a]	25.7 (4.9)	24.2 (4.2)
Sex (male), n (%)	14 (50)	14 (50)
Neuroticism[b]	2 (0.6)	1.3 (0.5)
Extraversion[c]	2.2 (0.5)	2.6 (0.4)
Harm avoidance[d]	12.4 (3.6)	9.9 (3.9)

Note: Values are mean and standard deviation unless otherwise noted.
[a]t-test showed no significant group difference.
[b]t-test showed significant group difference ($p < 0.001$).
[c]t-test showed significant group difference ($p < 0.01$).
[d]Data available for 26 patients and 25 healthy controls. t-test showed significant group difference ($p < 0.05$).

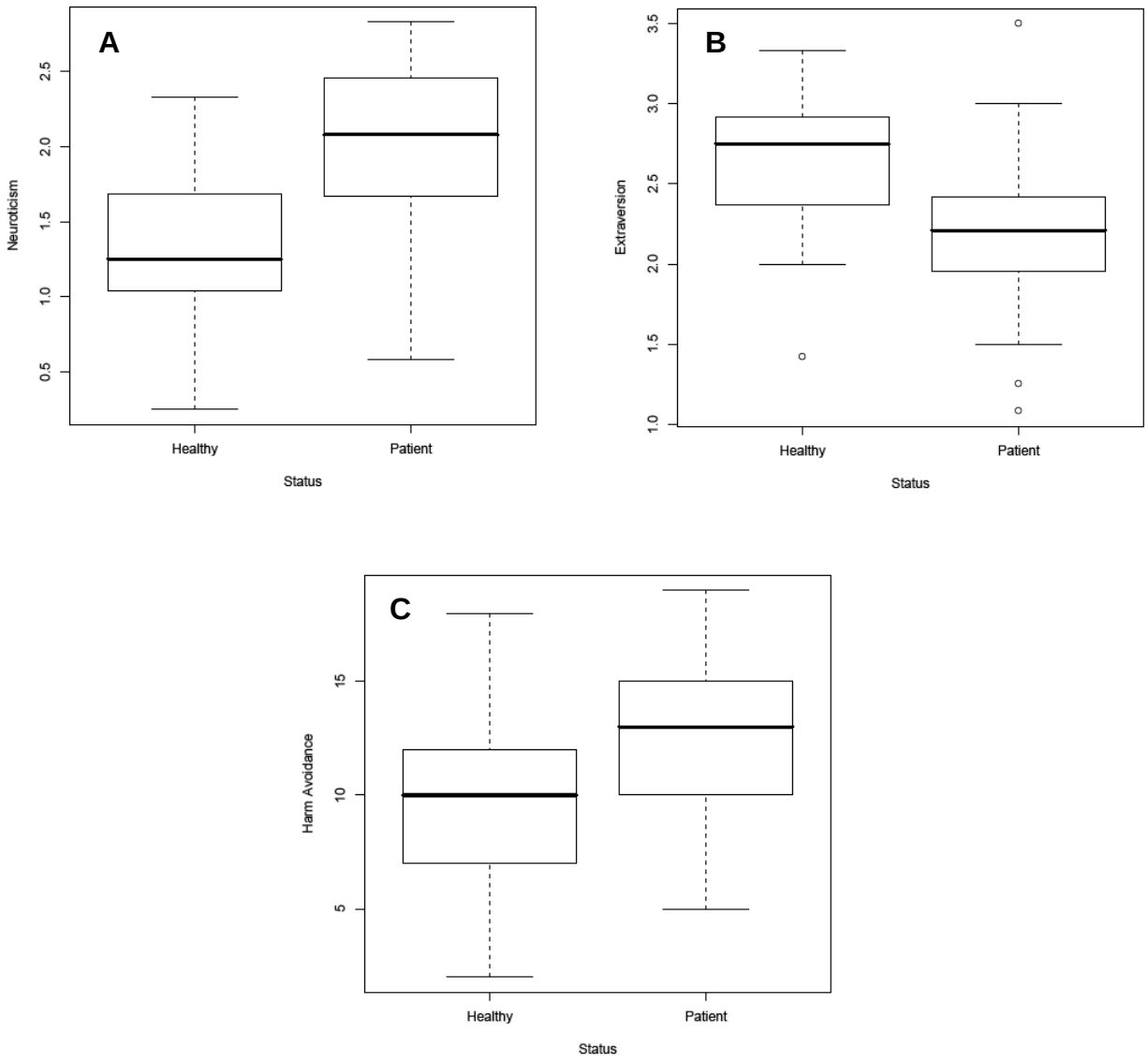


Figure 1. Differences in psychometric scores between remitted MDD patients and healthy controls. A. Boxplot illustrating higher neuroticism scores in patients compared to healthy controls (mean (SD) neuroticism score: healthy = 1.3mm (0.5); patients = 2 (0.6)). B. Boxplot illustrating lower extraversion scores in patients compared to healthy controls (mean (SD) extraversion score: healthy = 2.6 (0.4); patients = 2.2 (0.5)). C. Boxplot illustrating higher harm avoidance scores in patients compared to healthy controls (mean (SD) harm avoidance score: healthy = 9.9 (3.9); patients = 12.4 (3.6)).

3.2 Region-of-Interest Analysis

A statistical cortical thickness difference map for the left hemisphere is shown in figure 2. This map shows a pattern of reduced cortical thickness in the left midcingulate cortex, localized more within the anterior portion, in remitted MDD patients compared to healthy controls (corrected p = 0.004). The group difference within this region remained significant even after FDR correction. The other to parts of the cingulate cortex (see chapter 2.5.2) as well as the dorsolateral prefrontal cortex and the orbitofrontal cortex, which have been, based on results from recent structural MRI depression research literature, a priori selected as ROI`s, displayed no statistically significant group differences after controlling for multiple comparisons by means of FDR correction.

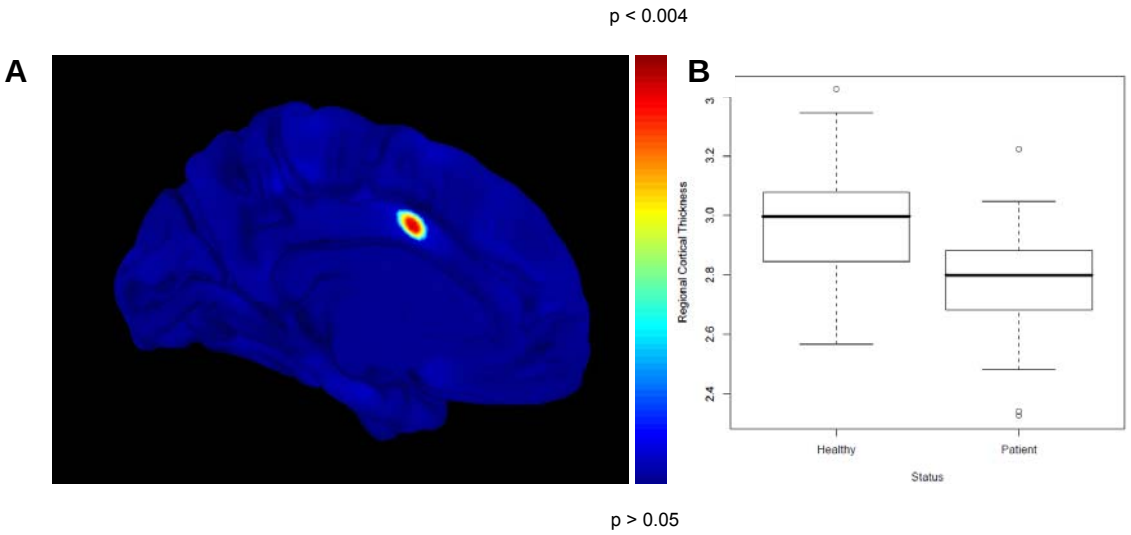


Figure 2. Differences in cortical thickness between remitted MDD patients and healthy controls. A. Statistical cortical thickness difference map showing reduced cortical thickness in the midcingulate cortex in remitted MDD patients compared to healthy controls ($p < 0.004$). Colorbar represents FDR corrected p-values. B. Boxplot illustrating lower mean cortical thickness (mm) in patients compared to healthy controls (mean (SD) cortical thickness: patients = 2.8mm (0.2); healthy = 3mm (0.2)). Mean cortical thickness has been extracted from the peak node showing the largest group difference lying within the anterior portion of the midcingulate cortex.

Further analyses focussing of putative effects of the three psychometric scores neuroticism, extraversion and harm-avoidance on cortical thickness didn't show any significant main effects. Moreover, analysis displayed no significant interaction effects between group and each of the psychometric variables (see figure 3).

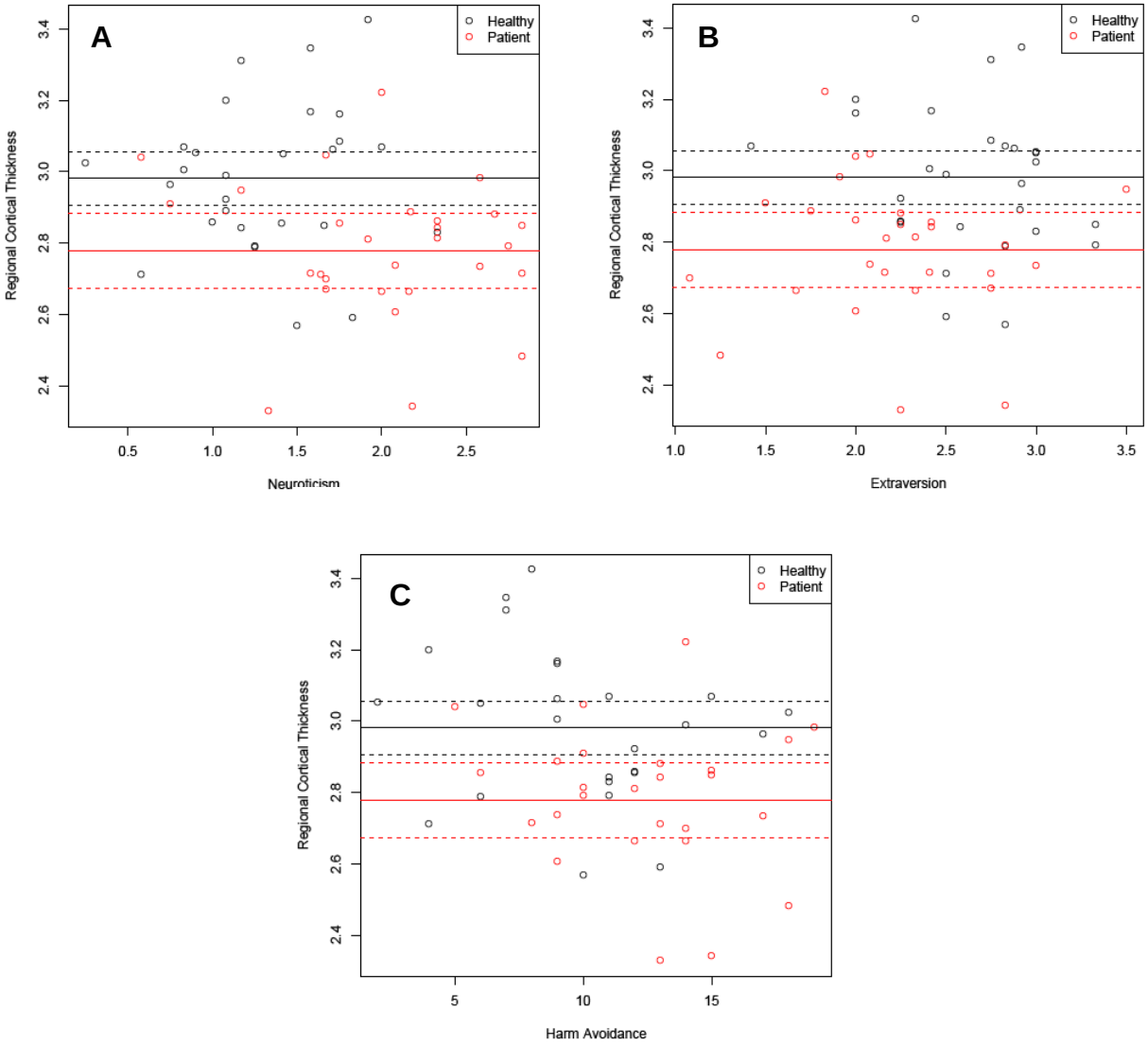


Figure 3. Correlation of psychometric scores and cortical thickness compared between remitted MDD patients and healthy controls. A. Scatterplot illustrating no correlation between neuroticism and cortical thickness. B. Scatterplot illustrating no correlation between extraversion and cortical thickness. C. Scatterplot illustrating no correlation between harm avoidance and cortical thickness. Mean regional cortical thickness has been extracted from the peak node showing the largest group difference lying within the anterior portion of the midcingulate cortex (see figure 2).

3.3 Whole Cortex Analysis

In order to assure that the ROI approach did not overlook significant group differences in cortical thickness in other areas than the a priori hypothesized, additional whole cortex analysis was performed. After correcting for multiple comparisons no further significant group differences in cortical thickness along the cortex have been found. Figure 4 shows uncorrected statistical difference maps also showing a tendency of cortical thinning within some parietal and frontal regions of the cortex bilaterally in the patient group, but also tendencies of cortical thickening in other parts of the parietal cortex bilaterally and the temporal cortex more pronounced within the right hemisphere.

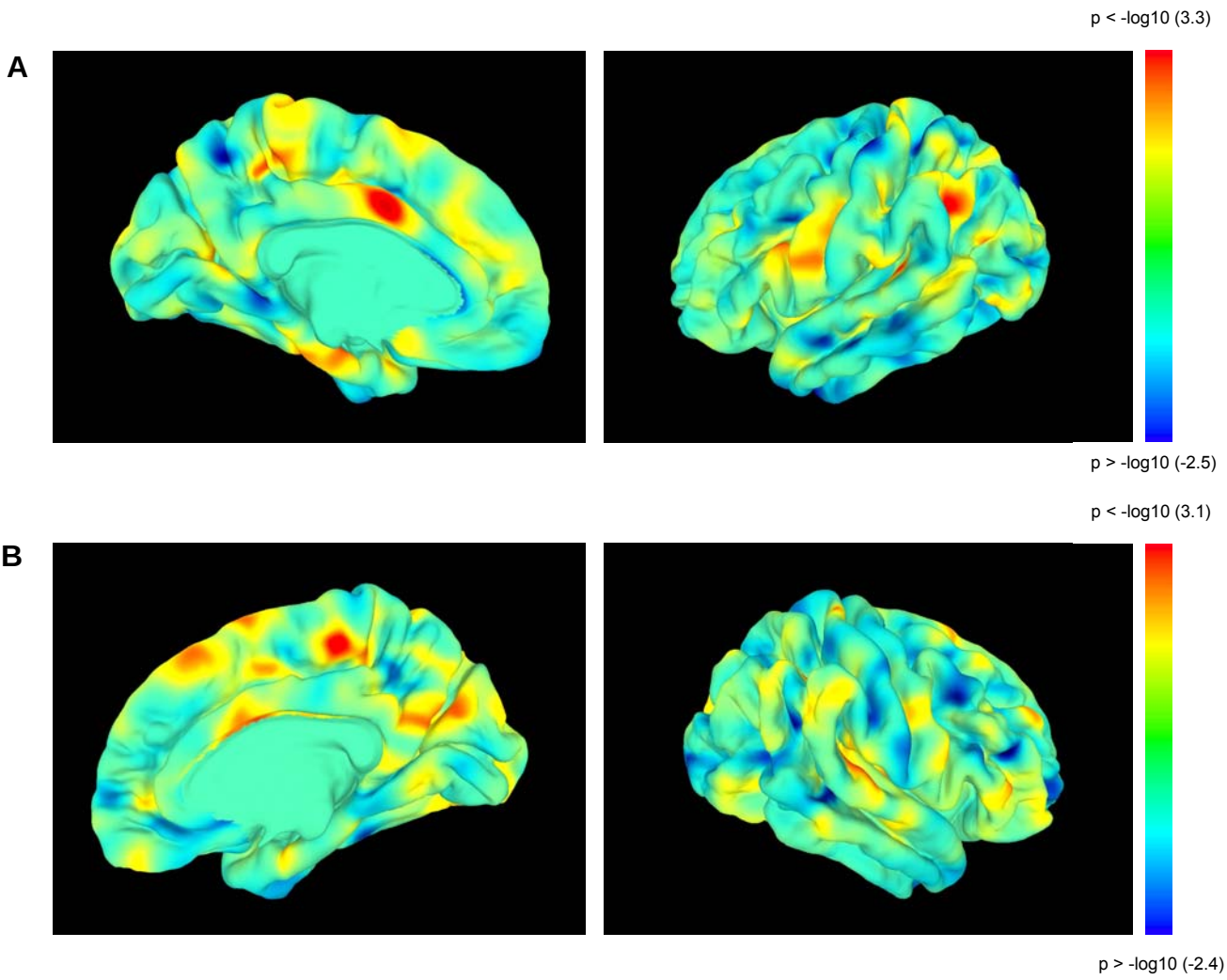
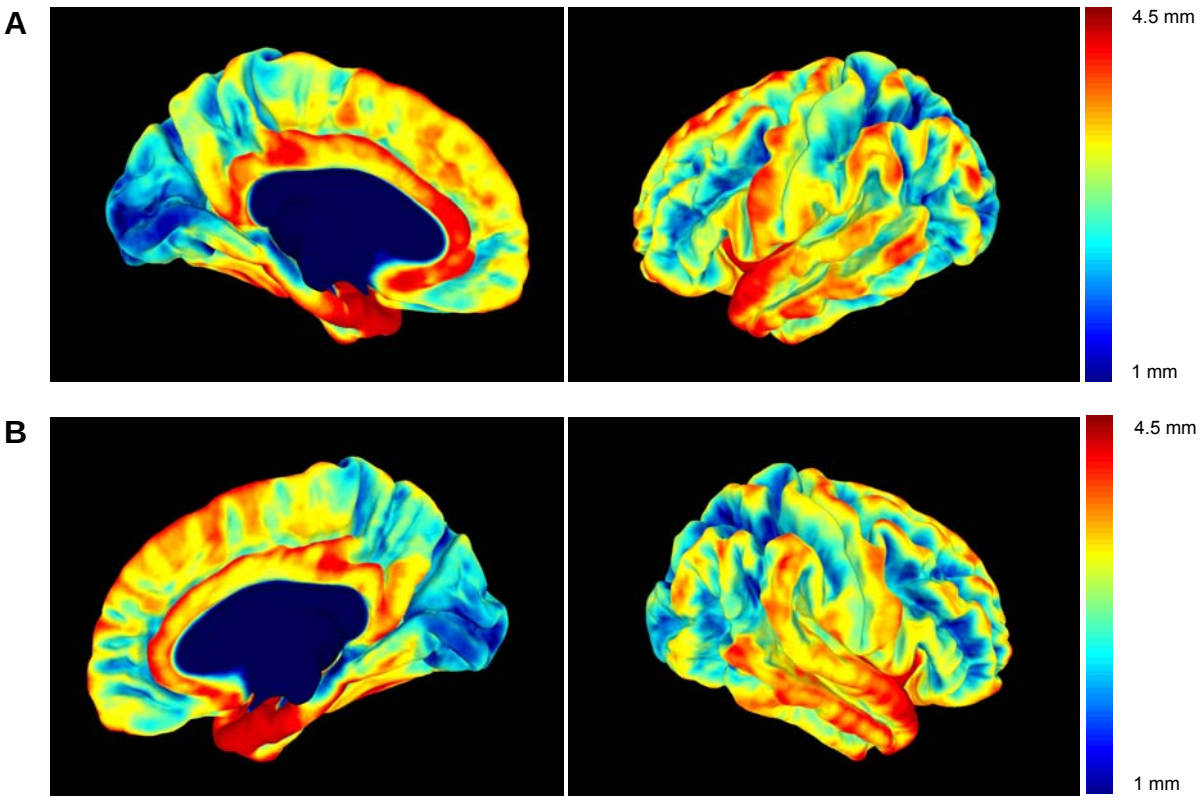


Figure 4. Whole cortex statistical difference cortical thickness maps of the patient and healthy group based on -log(10)p values used for illustration purposes (i.e. a logarithmized p value of 1.3, for example, means a straight p value of 0.05). A. Statistical difference cortical thickness map of medial and lateral left hemisphere. B. Statistical difference cortical thickness map of medial and lateral right hemisphere. Color bars representing uncorrected logarithmized p values ranging between -2.5 (dark blue representing higher cortical thickness in the patient group compared to healthy controls) and 3.3 (dark red representing lower cortical thickness in the patient group compared to healthy controls) for the left hemisphere and between -2.4 and 3.1 for the right hemisphere. Results in the corpus callosum and the midbrain are not meaningful.

Average thickness maps of remitted MDD patients and healthy controls, as illustrated in figure 5, display reductions in cortical thickness in the patient group especially within the whole cingulate cortex bilaterally, but more pronounced on the left hemisphere, as well within the temporal cortex. However, none of these regions, except the already mentioned midcingulate cortex, with reduced cortical thickness in the patient group compared to healthy controls remained significant after FDR correction.



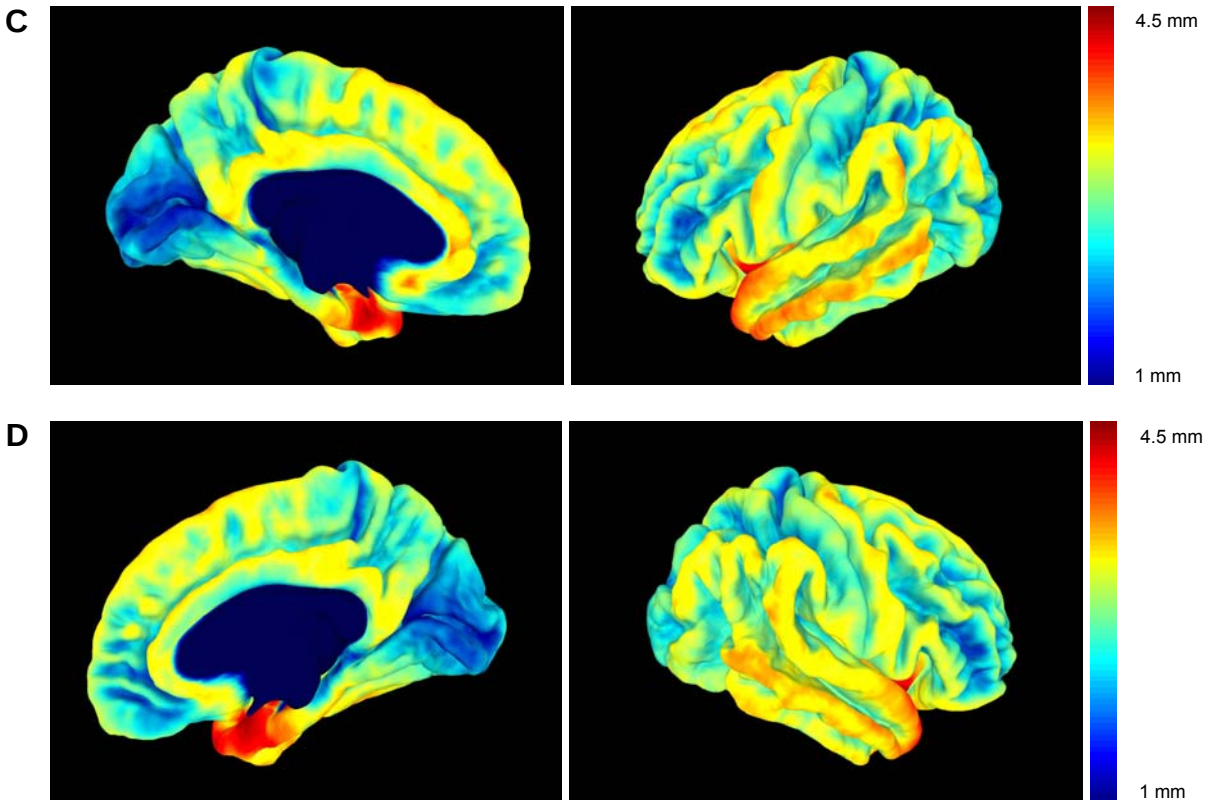


Figure 5. Mean cortical thickness maps (mm) of the patient and healthy group (mean cortical thickness in both groups for each hemisphere = 2.6mm). A. Whole cortex mean cortical thickness maps of medial and lateral left hemisphere of healthy controls. B. Whole cortex mean cortical thickness maps of medial and lateral right hemisphere of healthy controls. C. Whole cortex mean cortical thickness maps of medial and lateral left hemisphere of patients. D. Whole cortex mean cortical thickness maps of medial and lateral right hemisphere of patients. Color bars representing mean cortical thickness values in mm ranging between 1mm (dark blue) and 4.5mm (dark red). Results in the corpus callosum and the midbrain are not meaningful. t-tests showed no group differences in whole cortex mean cortical thickness in the left as well as in the right hemisphere between patients and healthy controls.

4 Discussion

The present diploma thesis showed reduced cortical thickness in the anterior midcingulate cortex in remitted MDD patients compared to healthy controls. To our knowledge, this is the first study demonstrating cortical thickness alterations in MDD patients indicating structural changes still present even after full remission.

The anterior midcingulate cortex is involved in several integrative processes such as attention-for-action/target selection (Posner et al. 1988), motivational valence assignment/reward assessment (Mesulam 1990; Knutson et al. 2000; Bush et al. 2002; Kirsch et al. 2003), novelty detection (Raichle et al. 1994; Clark et al. 2000), motor response selection (Pardo et al. 1990; Bush et al. 1999; Williams et al. 2004), error detection/monitoring (Gehring et al. 2000), reward-based decision making (Bush et al. 2002) and working memory (Petit et al. 1998). Moreover several lines of evidence indicate involvement of the anterior midcingulate cortex in fear processing (Vogt et al. 2003), social pain perception (Eisenberger et al. 2004), pain anticipation (Ploghaus et al. 1999; Bermpohl et al. 2006), and in visceral stimulation (Svensson et al. 1997; Strigo et al. 2003).

Through recruitment of the rostral cingulate motor area, which is a part of the anterior midcingulate cortex, projecting to the spinal cord and motor cortices (Dum et al. 1991), the anterior midcingulate cortex mediates behavioural responses, such as avoidance behaviours (Vogt 2005). Thus, through integration of motivational, reward- and pain-related information, the anterior midcingulate cortex plays a key role in multiinformational decision making directly modulating areas known to be responsible for motor, cognitive and behavioural responses by recruitment of the rostral cingulate motor area and areas such as the dorsolateral prefrontal cortex, the parietal cortex, the striatum and thalamus.

Thus, the anterior midcingulate cortex is assumed to be a motivational and attentional control centre preparing and monitoring adequate behavioural responses to incoming emotional, reward- and pain-related information (Whalen et al. 1998; Bush et al. 2000). Drevets et al. (2008) suggest the anterior midcingulate cortex as part of a highly interconnected visceromotor network particularly involved in introspective functions and visceral reactions to emotional information. Interestingly, the visceromotor network is lacking substantial direct sensory connections, but interacts with limbic regions as well as the hypothalamus. By that, it mediates visceral reactions to emotional stimuli which seem to be impaired in MDD (Drevets et al. 2008).

Studies focussing on functional alterations affecting the anterior midcingulate cortex in the pathophysiology of MDD demonstrated reduced activity in this brain region at rest as well as a reaction to emotional stimuli (Mayberg et al. 1999; Drevets et al. 2002). Fitzgerald et al. (2008) corroborated these findings showing decreased activity to negative emotion induction and increased activity after selective serotonin reuptake inhibitor treatment.

Besides functional changes in the anterior midcingulate cortex associated with the pathophysiology of MDD, several studies also could demonstrate reductions in grey matter volume in MDD patients (Sassi et al. 2004; Caetano et al. 2006). Those structural changes, together with functional alterations, might suggest impaired emotional and executive functioning in patients with acute MDD, mainly affecting selective attention, planning and the effortful regulation of affective states. This might explain symptoms of depressed mood and anhedonia with patients identifying and experiencing emotional stimuli primarily within a negative context (Phillips et al. 2003).

Reduced cortical thickness in the left anterior midcingulate cortex could be interpreted within the framework of impaired executive functioning and regulation of affective states. Since the present diploma thesis found reduced cortical thickness in remitted MDD patient, it is reasonable that cognitive, integrative

processing is still abnormal when mood is restored which might be evidence for trait-related structural changes associated with MDD. This interpretation is corroborated by findings showing functional changes in euthymic MDD patients in the cingulate cortex (Schoning et al. 2008) and reduced left anterior cingulate grey matter volume reductions in remitted MDD patients (Caetano et al. 2006). Interestingly, Caetano et al (2006) only found structural changes in the left anterior cingulate cortex in remitted MDD patients compared to healthy controls, whereas in the right hemisphere as well as in other regions, which displayed reduced volumes in acute MDD patients, the authors did not find any structural abnormalities in remitted MDD patients.

Since the anterior midcingulate cortex mediates fear processing in the context of visceromotor reactions, one might also argue that cortical thickness reductions within this region might provoke impaired fear processing and subsequent behavioural responses. The pattern of reduced cortical thickness in remitted MDD patients might, therefore, indicate that these functions are still impaired explaining the tendency of interpreting emotional stimuli primarily within a negative context as a typical behavioural abnormality observed in acute MDD patients. Less control over visceral stress responses induced by negative stimuli, in turn, makes remitted MDD patients more vulnerable developing recurrent depression.

Moreover, cortical thickness reductions in the cingulate cortex have also been observed in subjects with attention-deficit/hyperactivity disorder (Makris et al. 2007) demonstrating dysfunctional attentional control associated with reduced cortical thickness which might be still present in remitted MDD patients. Interestingly, Chen et al. (2007) reported a negative correlation between baseline symptom severity in MDD and anterior midcingulate cortex grey matter volume. The authors interpreted this result as attenuated protective power of the structurally impaired anterior midcingulate cortex in regulating affective-attentional processes which might predispose people to greater severity of depressive symptoms. Reduced cortical thickness in the anterior midcingulate cortex might have similar implications, predisposing remitted MDD patients for relapsing.

The notion that cortical thickness reductions might affect cognitive functioning which, in turn, increases the vulnerability developing MDD, is strengthened by results of Peterson et al. (2009) showing cortical thinning on persons high risk for depression, deducted from their familial depression history, causing cognitive alterations, such as inattention and deficits in visual memory. This causal relationship has been inferred with a special statistical mediator analysis. Within the context of the present study, the observed cortical thickness reductions in remitted MDD patients might lead to impaired fear processing, allocation of attentional resources and subsequent deficits in decision making and behavioural responses in response to emotional stimuli in the anterior midcingulate cortex increasing the probability developing MDD.

Since the cortical thickness reflects the underlying cyto- and myeloarchitecture, such as the structure of the laminar cortical layers, the size, number and density of the neuronal cell bodies as well as synaptogenesis and the myelination of axons (Mountcastle 1997), theses factors might be involved in cortical thickness reductions. Several studies provided evidence of neuronal and glial atrophy resulting in cortical thickness reductions in regions such as the pregenual cingulate cortex, orbitofrontal cortex or the DLPFC (Ongur et al. 1998; Rajkowska et al. 1999; Rajkowska et al. 2001). Interestingly, laminar analysis of cortical thickness reductions revealed layers III and V mostly affected by glial loss (Ongur et al. 1998; Rajkowska et al. 1999; Rajkowska et al. 2001).

Studies on rats have shown that prolonged stress leads to dendritic atrophy and glia loss within the prefrontal cortex, including the anterior midcingulate cortex, which is assumed to have a key regulatory role in stress-related homeostatic mechanisms, particularly by modulating HPA axis function and by that, cortical secretion (Liu et al. 2008), through increased, stress-induced HPA activity (Radley et al. 2006; Banasr et al. 2007). In rats increased stress-induced HPA activity and concomitant dendritic, neuronal and/or glial atrophy was associated with impaired regulation of fear processing of conditioned stimuli (Izquierdo et al. 2006). In the light of the herein reported structural changes in cortical thickness in the anterior

midcingulate cortex putatively associated with functional impairments on cognitive modulation level involved in emotional processing, these results from rat experiments and additional findings in human post-mortem studies reporting increased cortisol levels (Gold et al. 2002; Carroll et al. 2007), might be one possible explanation mechanism for the cellular processes underlying cortical thickness reductions in remitted MDD patients.

The origins of weakened protective power of the anterior midcingulate cortex with respect to stress-inducing emotional stimuli from the environment might lie in attenuated inhibition via gabaergic neurotransmission. Studies provide some evidence that MDD patients display reduced GABA concentrations in the plasma and cerebrospinal fluid resulting in blunted inhibition of hypothalamic-pituitary-adrenal activity (Hasler et al. 2007), which, in turn, leads to increased cortisol secretion provoking perpetuated and thereby even greater impairments in anterior midcingulate cortex functioning associated with structural changes, such as reductions in cortical thickness. Indeed, studies have demonstrated gabaergic neuron atrophy in the medial prefrontal cortex including the anterior midcingulate cortex resulting in weakened inhibitory control over the HPA axis (Radley et al. 2009). Based on these results it is reasonable to assume that abnormal gabaergic neurotransmission arising from and affecting the anterior midcingulate cortex via reciprocal feedback processes between the latter and the HPA axis, still occur when mood is restored making remitted MDD patients more vulnerable towards stress-inducing, environmental stimuli and ultimately, MDD itself.

Impaired top-down control over limbic regions has also been reported in studies applying functional connectivity approaches showing reduced functional connectivity between the anterior midcingulate cortex and the amygdala (Anand et al. 2005; Chen et al. 2008). Attenuated functional connectivity might reflect impaired regulatory power of the anterior midcingulate cortex over limbic regions, such as the amygdala or the hypothalamus, ultimately leading to emotional dysregulation for which weakened gabaergic control might be symptomatic on a neuromolecular level. Reduced cortical thickness in the anterior midcingulate

cortex in remitted MDD patients might be a structural marker of impaired top-down control as a trait-marker of MDD.

One might assume that impaired fear processing through weakened inhibitory control of the anterior midcingulate cortex over limbic regions predisposing MDD patients to avoidance behaviour might be reflected on a personality level including higher harm avoidance scores. Statistical analysis in the context of this study revealed higher harm avoidance scores in remitted MDD patients compared to healthy controls, but could not detect any significant effects of these differences on cortical thickness. One possible explanation of these findings could be that pronounced harm avoidance behaviour might be simply not reflected in alterations of cortical thickness or, as an epiphenomenon of MDD, could not explain cortical thickness alterations as much as the psychiatric disorder itself. However, there is some evidence that, at least, neuroticism and extraversion are reflected on the structural level of cortical thickness with more neurotic and extraverted persons displaying thinner cortex in several cortical regions (Wright et al. 2006). Although the results of this study show differences in these personality scores between remitted MDD patients and healthy controls, the psychiatric disorder may explain cortical thickness differences to a much greater extent than personality differences which could be confirmed by statistical analysis performed in the course of the present diploma thesis.

Besides increased cortisol levels and decreased gabaergic neurotransmission, several studies also demonstrate decreased postsynaptic 5-HT_{1A} receptor binding and mRNA expression in the cingulate during MDD (Drevets et al. 2007) reflecting blunted serotonin neurotransmission as a hallmark of depression. Several lines of indicate that there is a strong interaction between the serotonin and the cortisol system particularly highlighting the influence of the cortisol on 5-HT_{1A} receptor binding and mRNA expression which is both reduced under persistent cortisol hypersecretion (Lopez et al. 1998) which might explain attenuated postsynaptic 5-HT_{1A} receptor binding and mRNA expression in MDD patients (Drevets et al. 2007).

These results have to be examined within the context of genetic variations in the serotonin receptor and/or transporter genes. For example, recent findings demonstrated that variations in the serotonin transporter gene (SLC6A4) are associated with alterations in the neural circuitry involved in emotion evaluation and modulation (Hariri et al. 2002; Caspi et al. 2003; Hariri et al. 2003; Pezawas et al. 2005). Especially carriers of the s allele of the 5-HTTLPR polymorphism of the serotonin transporter display increased risk for depression when exposed to stressful life events (Hariri et al. 2002; Caspi et al. 2003).

Moreover, recent studies provide some evidence that neurotrophic factors, most prominently the brain-derived neurotrophic factor (BDNF), modulate 5-HT signalling by promoting development of serotonergic neurons and buffering effects of stress (Nestler et al. 2002; Krishnan et al. 2007; Martinowich et al. 2008). The VAL allele of VAL66MET BDNF has been found to be one potential risk-allele in biasing brain wiring towards susceptibility for depression. Taking its protective effects into account, failures within the genetic architecture would lead to reduced neurogenesis and/or neurite outgrowth which could be counteracted by antidepressant therapy (Malberg et al. 2000). Interestingly, Pezawas et al. (2008) have demonstrated genetic interaction between the 5-HTTPLR polymorphism human serotonin transporter gene (SLC6A4) and BDNF VAL66MET impacting the fronto-limbic circuitry.

Taking all together, reduced cortical thickness of the anterior midcingulate cortex in remitted MDD patients and concomitant impairments in cognitive control and emotional regulation might be partially explained by a hypoactivated gabaergic and serotonergic neurotransmission, an impaired neurotrophic system and a hyperactivated cortisol secretion promoting glial, dendritic and neuronal atrophy which exerts its detrimental effects especially in the context of stressful live events or adverse environmental stimuli predisposing remitted MDD patients to develop depression.

Limitations of the study lie in the sample size and potential inhomogenities within the sample. Since differences in cortical thickness between remitted MDD patients and healthy controls are expected to be smaller compared to acute depressed patients, possible structural alterations in additional cortical regions might be masked through the relatively small sample size of 28 patients. Moreover, the patient group displays some inhomogenities, for example with respect to the distribution and patterns of personality variables, maybe influencing the interpretation of results. Thus, future studies should control for factors being inhomogeneous within the patient group and if necessary and meaningful, perform advanced statistical analysis with carefully built subgroups based on clinical and/or psychometric variables.

5 Conclusion

For the first time, the present study was able to show cortical thickness alterations in remitted MDD patients indicating that structural changes in special regions of the cortical mantle still exist when mood is restored. These results might provide evidence that cortical thickness reductions, particularly in the anterior midcingulate cortex, might represent a trait marker reflecting vulnerability to depression. On a functional level, changes in cortical thickness might be associated with dysfunctional emotional processing in terms of impaired top-down control over limbic circuits and/or the neuroendocrine system, especially the HPA axis, regulating stress responses to emotional stimuli. These results may enhance the understanding of the neurobiology of remitted MDD and provide a putative structural disease marker reflecting vulnerability to depression.

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List of Tables

List of Figures

References

Anand, A., Y. Li, Y. Wang, J. Wu, S. Gao, L. Bukhari, V. P. Mathews, A. Kalnin and M. J. Lowe (2005). "Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study." Biol Psychiatry **57**(10): 1079-88.

Andrade, A., F. Kherif, J. F. Mangin, K. J. Worsley, A. L. Paradis, O. Simon, S. Dehaene, D. Le Bihan and J. B. Poline (2001). "Detection of fMRI activation using cortical surface mapping." Hum Brain Mapp **12**(2): 79-93.

Anticevic, A., D. L. Dierker, S. K. Gillespie, G. Repovs, J. G. Csernansky, D. C. Van Essen and D. M. Barch (2008). "Comparing surface-based and volume-based analyses of functional neuroimaging data in patients with schizophrenia." Neuroimage **41**(3): 835-48.

Arango, V., M. D. Underwood, A. V. Gubbi and J. J. Mann (1995). "Localized alterations in pre- and postsynaptic serotonin binding sites in the ventrolateral prefrontal cortex of suicide victims." Brain Res **688**(1-2): 121-33.

Argall, B. D., Z. S. Saad and M. S. Beauchamp (2006). "Simplified intersubject averaging on the cortical surface using SUMA." Hum Brain Mapp **27**(1): 14-27.

Armstrong, E., A. Schleicher, H. Omran, M. Curtis and K. Zilles (1995). "The ontogeny of human gyrification." Cereb Cortex **5**(1): 56-63.

Banasr, M. and R. S. Duman (2007). "Regulation of neurogenesis and gliogenesis by stress and antidepressant treatment." CNS Neurol Disord Drug Targets **6**(5): 311-20.

Bao, A. M., G. Meynen and D. F. Swaab (2008). "The stress system in depression and neurodegeneration: focus on the human hypothalamus." Brain Res Rev **57**(2): 531-53.

Barbas, H. (2000). "Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices." Brain Res Bull **52**(5): 319-30.

Barch, D. M., Y. I. Sheline, J. G. Csernansky and A. Z. Snyder (2003). "Working memory and prefrontal cortex dysfunction: specificity to schizophrenia compared with major depression." Biol Psychiatry **53**(5): 376-84.

Bartley, A. J., D. W. Jones and D. R. Weinberger (1997). "Genetic variability of human brain size and cortical gyral patterns." Brain **120 (Pt 2)**: 257-69.

Bermpohl, F., A. Pascual-Leone, A. Amedi, L. B. Merabet, F. Fregni, N. Gaab, D. Alsop, G. Schlaug and G. Northoff (2006). "Dissociable networks for the expectancy and perception of emotional stimuli in the human brain." Neuroimage **30**(2): 588-600.

Berton, O. and E. J. Nestler (2006). "New approaches to antidepressant drug discovery: beyond monoamines." Nat Rev Neurosci **7**(2): 137-51.

Blier, P. and C. de Montigny (1987). "Modification of 5-HT neuron properties by sustained administration of the 5-HT1A agonist gepirone: electrophysiological studies in the rat brain." Synapse **1**(5): 470-80.

Boldrini, M., M. D. Underwood, J. J. Mann and V. Arango (2008). "Serotonin-1A autoreceptor binding in the dorsal raphe nucleus of depressed suicides." J Psychiatr Res **42**(6): 433-42.

Bush, G., J. A. Frazier, S. L. Rauch, L. J. Seidman, P. J. Whalen, M. A. Jenike, B. R. Rosen and J. Biederman (1999). "Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the Counting Stroop." Biol Psychiatry **45**(12): 1542-52.

Bush, G., P. Luu and M. I. Posner (2000). "Cognitive and emotional influences in anterior cingulate cortex." Trends Cogn Sci **4**(6): 215-222.

Bush, G., B. A. Vogt, J. Holmes, A. M. Dale, D. Greve, M. A. Jenike and B. R. Rosen (2002). "Dorsal anterior cingulate cortex: a role in reward-based decision making." Proc Natl Acad Sci U S A **99**(1): 523-8.

Caetano, S. C., S. Kaur, P. Brambilla, M. Nicoletti, J. P. Hatch, R. B. Sassi, A. G. Mallinger, M. S. Keshavan, D. J. Kupfer, E. Frank and J. C. Soares (2006). "Smaller cingulate volumes in unipolar depressed patients." Biol Psychiatry **59**(8): 702-6.

Cannon, T. D., T. G. van Erp, M. Huttunen, J. Lonnqvist, O. Salonen, L. Valanne, V. P. Poutanen, C. G. Standertskjold-Nordenstam, R. E. Gur and M. Yan (1998). "Regional gray matter, white matter, and cerebrospinal fluid distributions in schizophrenic patients, their siblings, and controls." Arch Gen Psychiatry **55**(12): 1084-91.

Carroll, B. J., F. Cassidy, D. Naftolowitz, N. E. Tatham, W. H. Wilson, A. Iranmanesh, P. Y. Liu and J. D. Veldhuis (2007). "Pathophysiology of hypercortisolism in depression." Acta Psychiatr Scand Suppl(433): 90-103.

Caspi, A., K. Sugden, T. E. Moffitt, A. Taylor, I. W. Craig, H. Harrington, J. McClay, J. Mill, J. Martin, A. Braithwaite and R. Poulton (2003). "Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene." Science **301**(5631): 386-9.

Chen, C. H., K. Ridler, J. Suckling, S. Williams, C. H. Fu, E. Merlo-Pich and E. Bullmore (2007). "Brain imaging correlates of depressive symptom severity and predictors of symptom improvement after antidepressant treatment." Biol Psychiatry **62**(5): 407-14.

Chen, C. H., J. Suckling, C. Ooi, C. H. Fu, S. C. Williams, N. D. Walsh, M. T. Mitterschiffthaler, E. M. Pich and E. Bullmore (2008). "Functional coupling of the amygdala in depressed patients treated with antidepressant medication." Neuropsychopharmacology **33**(8): 1909-18.

Clark, V. P., S. Fannon, S. Lai, R. Benson and L. Bauer (2000). "Responses to rare visual target and distractor stimuli using event-related fMRI." J Neurophysiol **83**(5): 3133-9.

Cloninger, C. R., D. M. Svrakic and T. R. Przybeck (1993). "A psychobiological model of temperament and character." Arch Gen Psychiatry **50**(12): 975-90.

Costa, P. T. and R. R. McCrae (1992). "Revised NEO Personality Inventory (NEO-PI-R) and NEO Five-Factor Inventory (NEO-FFI) professional manual." Psychological Assessment Resources, Odessa

Czeh, B. and P. J. Lucassen (2007). "What causes the hippocampal volume decrease in depression? Are neurogenesis, glial changes and apoptosis implicated?" Eur Arch Psychiatry Clin Neurosci **257**(5): 250-60.

Dale, A. M., B. Fischl and M. I. Sereno (1999). "Cortical surface-based analysis. I. Segmentation and surface reconstruction." Neuroimage **9**(2): 179-94.

De Vry, J., R. Schreiber, C. Melon, M. Dalmus and K. R. Jentzsch (2004). "5-HT1A receptors are differentially involved in the anxiolytic- and antidepressant-like effects of 8-OH-DPAT and fluoxetine in the rat." Eur Neuropsychopharmacol **14**(6): 487-95.

Desai, R., E. Liebenthal, E. T. Possing, E. Waldron and J. R. Binder (2005). "Volumetric vs. surface-based alignment for localization of auditory cortex activation." Neuroimage **26**(4): 1019-29.

Devlin, J. T. and R. A. Poldrack (2007). "In praise of tedious anatomy." Neuroimage **37**(4): 1033-41; discussion 1050-8.

Dickerson, B. C., E. Feczko, J. C. Augustinack, J. Pacheco, J. C. Morris, B. Fischl and R. L. Buckner (2009). "Differential effects of aging and Alzheimer's disease on medial temporal lobe cortical thickness and surface area." Neurobiol Aging **30**(3): 432-40.

Drevets, W. C. (2007). "Orbitofrontal cortex function and structure in depression." Ann N Y Acad Sci **1121**: 499-527.

Drevets, W. C., W. Bogers and M. E. Raichle (2002). "Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism." Eur Neuropsychopharmacol **12**(6): 527-44.

Drevets, W. C., E. Frank, J. C. Price, D. J. Kupfer, D. Holt, P. J. Greer, Y. Huang, C. Gautier and C. Mathis (1999). "PET imaging of serotonin 1A receptor binding in depression." Biol Psychiatry **46**(10): 1375-87.

Drevets, W. C., J. L. Price and M. L. Furey (2008). "Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression." Brain Struct Funct **213**(1-2): 93-118.

Drevets, W. C., J. Savitz and M. Trimble (2008). "The subgenual anterior cingulate cortex in mood disorders." CNS Spectr **13**(8): 663-81.

Drevets, W. C., M. E. Thase, E. L. Moses-Kolko, J. Price, E. Frank, D. J. Kupfer and C. Mathis (2007). "Serotonin-1A receptor imaging in recurrent depression: replication and literature review." Nucl Med Biol **34**(7): 865-77.

Du, A. T., N. Schuff, J. H. Kramer, H. J. Rosen, M. L. Gorno-Tempini, K. Rankin, B. L. Miller and M. W. Weiner (2007). "Different regional patterns of cortical thinning in Alzheimer's disease and frontotemporal dementia." Brain **130**(Pt 4): 1159-66.

Dubois, J., M. Benders, C. Borradori-Tolsa, A. Cachia, F. Lazeyras, R. Ha-Vinh Leuchter, S. V. Sizonenko, S. K. Warfield, J. F. Mangin and P. S. Huppi (2008). "Primary cortical folding in the human newborn: an early marker of later functional development." Brain **131**(Pt 8): 2028-41.

Dum, R. P. and P. L. Strick (1991). "The origin of corticospinal projections from the premotor areas in the frontal lobe." J Neurosci **11**(3): 667-89.

Duman, R. S., G. R. Heninger and E. J. Nestler (1997). "A molecular and cellular theory of depression." Arch Gen Psychiatry **54**(7): 597-606.

Eisenberger, N. I. and M. D. Lieberman (2004). "Why rejection hurts: a common neural alarm system for physical and social pain." Trends Cogn Sci **8**(7): 294-300.

Eley, T. C. and R. Plomin (1997). "Genetic analyses of emotionality." Curr Opin Neurobiol **7**(2): 279-84.

Evans, D. L., D. S. Charney, L. Lewis, R. N. Golden, J. M. Gorman, K. R. Krishnan, C. B. Nemeroff, J. D. Bremner, R. M. Carney, J. C. Coyne, M. R. Delong, N. Frasure-Smith, A. H. Glassman, P. W. Gold, I. Grant, L. Gwyther, G. Ironson, R. L. Johnson, A. M. Kanner, W. J. Katon, P. G. Kaufmann, F. J. Keefe, T. Ketter, T. P. Laughren, J. Leserman, C. G. Lyketsos, W. M. McDonald, B. S. McEwen, A. H. Miller, D. Musselman, C. O'Connor, J. M. Petitto, B. G. Pollock, R. G. Robinson, S. P. Roose, J. Rowland, Y. Sheline, D. S. Sheps, G. Simon, D. Spiegel, A. Stunkard, T. Sunderland, P. Tibbits, Jr. and W. J. Valvo (2005). "Mood disorders in

the medically ill: scientific review and recommendations." Biol Psychiatry **58**(3): 175-89.
Fischl, B. and A. M. Dale (2000). "Measuring the thickness of the human cerebral cortex from magnetic resonance images." Proc Natl Acad Sci U S A **97**(20): 11050-5.
Fischl, B., N. Rajendran, E. Busa, J. Augustinack, O. Hinds, B. T. Yeo, H. Mohlberg, K. Amunts and K. Zilles (2008). "Cortical folding patterns and predicting cytoarchitecture." Cereb Cortex **18**(8): 1973-80.
Fischl, B., M. I. Sereno and A. M. Dale (1999). "Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system." Neuroimage **9**(2): 195-207.
Fischl, B., M. I. Sereno, R. B. Tootell and A. M. Dale (1999). "High-resolution intersubject averaging and a coordinate system for the cortical surface." Hum Brain Mapp **8**(4): 272-84.
Fitzgerald, P. B., A. R. Laird, J. Maller and Z. J. Daskalakis (2008). "A meta-analytic study of changes in brain activation in depression." Hum Brain Mapp **29**(6): 683-95.
Fornito, A., M. Yucel, S. J. Wood, C. Adamson, D. Velakoulis, M. M. Saling, P. D. McGorry and C. Pantelis (2008). "Surface-based morphometry of the anterior cingulate cortex in first episode schizophrenia." Hum Brain Mapp **29**(4): 478-89.
Frodl, T., E. M. Meisenzahl, T. Zetzsche, T. Hohne, S. Banac, C. Schorr, M. Jager, G. Leinsinger, R. Bottlender, M. Reiser and H. J. Moller (2004). "Hippocampal and amygdala changes in patients with major depressive disorder and healthy controls during a 1-year follow-up." J Clin Psychiatry **65**(4): 492-9.
Fuster, J. M. (2001). "The prefrontal cortex--an update: time is of the essence." Neuron **30**(2): 319-33.
Gaspar, P., O. Cases and L. Maroteaux (2003). "The developmental role of serotonin: news from mouse molecular genetics." Nat Rev Neurosci **4**(12): 1002-12.
Gehring, W. J. and R. T. Knight (2000). "Prefrontal-cingulate interactions in action monitoring." Nat Neurosci **3**(5): 516-20.
Genovese, C. R., N. A. Lazar and T. Nichols (2002). "Thresholding of statistical maps in functional neuroimaging using the false discovery rate." Neuroimage **15**(4): 870-8.
Geyer, S., A. Schleicher, T. Schormann, H. Mohlberg, A. Bodegard, P. E. Roland and K. Zilles (2001). "Integration of microstructural and functional aspects of human somatosensory areas 3a, 3b, and 1 on the basis of a computerized brain atlas." Anat Embryol (Berl) **204**(4): 351-66.
Goghari, V. M., K. Rehm, C. S. Carter and A. W. MacDonald, 3rd (2007). "Regionally specific cortical thinning and gray matter abnormalities in the healthy relatives of schizophrenia patients." Cereb Cortex **17**(2): 415-24.
Gold, P. W. and G. P. Chrousos (2002). "Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states." Mol Psychiatry **7**(3): 254-75.
Goldman, A. L., L. Pezawas, V. S. Mattay, B. Fischl, B. A. Verchinski, Q. Chen, D. R. Weinberger and A. Meyer-Lindenberg (2009). "Widespread reductions of cortical thickness in schizophrenia and spectrum disorders and evidence of heritability." Arch Gen Psychiatry **66**(5): 467-77.
Gross, C. and R. Hen (2004). "The developmental origins of anxiety." Nat Rev Neurosci **5**(7): 545-52.

Hadjikhani, N., R. M. Joseph, J. Snyder and H. Tager-Flusberg (2006). "Anatomical differences in the mirror neuron system and social cognition network in autism." Cereb Cortex **16**(9): 1276-82.

Hamidi, M., W. C. Drevets and J. L. Price (2004). "Glial reduction in amygdala in major depressive disorder is due to oligodendrocytes." Biol Psychiatry **55**(6): 563-9.

Han, X., J. Jovicich, D. Salat, A. van der Kouwe, B. Quinn, S. Czanner, E. Busa, J. Pacheco, M. Albert, R. Killiany, P. Maguire, D. Rosas, N. Makris, A. Dale, B. Dickerson and B. Fischl (2006). "Reliability of MRI-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade and manufacturer." Neuroimage **32**(1): 180-94.

Hariri, A. R., V. S. Mattay, A. Tessitore, B. Kolachana, F. Fera, D. Goldman, M. F. Egan and D. R. Weinberger (2002). "Serotonin transporter genetic variation and the response of the human amygdala." Science **297**(5580): 400-3.

Hariri, A. R. and D. R. Weinberger (2003). "Functional neuroimaging of genetic variation in serotonergic neurotransmission." Genes Brain Behav **2**(6): 341-9.

Harvey, P. O., P. Fossati, J. B. Pochon, R. Levy, G. Lebastard, S. Lehericy, J. F. Allilaire and B. Dubois (2005). "Cognitive control and brain resources in major depression: an fMRI study using the n-back task." Neuroimage **26**(3): 860-9.

Hasler, G., J. W. van der Veen, T. Tumonis, N. Meyers, J. Shen and W. C. Drevets (2007). "Reduced prefrontal glutamate/glutamine and gamma-aminobutyric acid levels in major depression determined using proton magnetic resonance spectroscopy." Arch Gen Psychiatry **64**(2): 193-200.

Hilgetag, C. C. and H. Barbas (2005). "Developmental mechanics of the primate cerebral cortex." Anat Embryol (Berl) **210**(5-6): 411-7.

Hilgetag, C. C. and H. Barbas (2006). "Role of mechanical factors in the morphology of the primate cerebral cortex." PLoS Comput Biol **2**(3): e22.

Hofman, M. A. (1985). "Size and shape of the cerebral cortex in mammals. I. The cortical surface." Brain Behav Evol **27**(1): 28-40.

Hoyer, D., J. P. Hannon and G. R. Martin (2002). "Molecular, pharmacological and functional diversity of 5-HT receptors." Pharmacol Biochem Behav **71**(4): 533-54.

Huttenlocher, P. R. and A. S. Dabholkar (1997). "Regional differences in synaptogenesis in human cerebral cortex." J Comp Neurol **387**(2): 167-78.

Im, K., J. M. Lee, S. Won Seo, S. Hyung Kim, S. I. Kim and D. L. Na (2008). "Sulcal morphology changes and their relationship with cortical thickness and gyral white matter volume in mild cognitive impairment and Alzheimer's disease." Neuroimage **43**(1): 103-13.

Izquierdo, A., C. L. Wellman and A. Holmes (2006). "Brief uncontrollable stress causes dendritic retraction in infralimbic cortex and resistance to fear extinction in mice." J Neurosci **26**(21): 5733-8.

Kirsch, P., A. Schienle, R. Stark, G. Sammer, C. Blecker, B. Walter, U. Ott, J. Burkart and D. Vaitl (2003). "Anticipation of reward in a nonaversive differential conditioning paradigm and the brain reward system: an event-related fMRI study." Neuroimage **20**(2): 1086-95.

Knutson, B., A. Westdorp, E. Kaiser and D. Hommer (2000). "FMRI visualization of brain activity during a monetary incentive delay task." Neuroimage **12**(1): 20-7.

Konarski, J. Z., R. S. McIntyre, S. H. Kennedy, S. Rafi-Tari, J. K. Soczynska and T. A. Ketter (2008). "Volumetric neuroimaging investigations in mood disorders: bipolar disorder versus major depressive disorder." Bipolar Disord **10**(1): 1-37.

Koolschijn, P. C., N. E. van Haren, G. J. Lensvelt-Mulders, H. E. Hulshoff Pol and R. S. Kahn (2009). "Brain volume abnormalities in major depressive disorder: A meta-analysis of magnetic resonance imaging studies." Hum Brain Mapp.

Krishnan, K. R., P. M. Doraiswamy, S. N. Lurie, G. S. Figiel, M. M. Husain, O. B. Boyko, E. H. Ellinwood, Jr. and C. B. Nemeroff (1991). "Pituitary size in depression." J Clin Endocrinol Metab **72**(2): 256-9.

Krishnan, V., M. H. Han, D. L. Graham, O. Berton, W. Renthal, S. J. Russo, Q. Laplant, A. Graham, M. Lutter, D. C. Lagace, S. Ghose, R. Reister, P. Tannous, T. A. Green, R. L. Neve, S. Chakravarty, A. Kumar, A. J. Eisch, D. W. Self, F. S. Lee, C. A. Tamminga, D. C. Cooper, H. K. Gershenfeld and E. J. Nestler (2007). "Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions." Cell **131**(2): 391-404.

Krishnan, V. and E. J. Nestler (2008). "The molecular neurobiology of depression." Nature **455**(7215): 894-902.

Krubitzer, L. (2007). "The magnificent compromise: cortical field evolution in mammals." Neuron **56**(2): 201-8.

Kuperberg, G. R., M. R. Broome, P. K. McGuire, A. S. David, M. Eddy, F. Ozawa, D. Goff, W. C. West, S. C. Williams, A. J. van der Kouwe, D. H. Salat, A. M. Dale and B. Fischl (2003). "Regionally localized thinning of the cerebral cortex in schizophrenia." Arch Gen Psychiatry **60**(9): 878-88.

Le Francois, B., M. Czesak, D. Steubl and P. R. Albert (2008). "Transcriptional regulation at a HTR1A polymorphism associated with mental illness." Neuropharmacology **55**(6): 977-85.

Lemonde, S., G. Turecki, D. Bakish, L. Du, P. D. Hrdina, C. D. Bown, A. Sequeira, N. Kushwaha, S. J. Morris, A. Basak, X. M. Ou and P. R. Albert (2003). "Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide." J Neurosci **23**(25): 8788-99.

Li, X., T. Inoue, T. Abekawa, S. Weng, S. Nakagawa, T. Izumi and T. Koyama (2006). "5-HT1A receptor agonist affects fear conditioning through stimulations of the postsynaptic 5-HT1A receptors in the hippocampus and amygdala." Eur J Pharmacol **532**(1-2): 74-80.

Liotti, M., H. S. Mayberg, S. McGinnis, S. L. Brannan and P. Jerabek (2002). "Unmasking disease-specific cerebral blood flow abnormalities: mood challenge in patients with remitted unipolar depression." Am J Psychiatry **159**(11): 1830-40.

Liu, R. J. and G. K. Aghajanian (2008). "Stress blunts serotonin- and hypocretin-evoked EPSCs in prefrontal cortex: role of corticosterone-mediated apical dendritic atrophy." Proc Natl Acad Sci U S A **105**(1): 359-64.

Logothetis, N. K. (2008). "What we can do and what we cannot do with fMRI." Nature **453**(7197): 869-78.

Lopez, J. F., D. T. Chalmers, K. Y. Little and S. J. Watson (1998). "A.E. Bennett Research Award. Regulation of serotonin1A, glucocorticoid, and mineralocorticoid receptor in rat and human hippocampus: implications for the neurobiology of depression." Biol Psychiatry **43**(8): 547-73.

Luders, E., K. L. Narr, P. M. Thompson, D. E. Rex, R. P. Woods, H. Deluca, L. Jancke and A. W. Toga (2006). "Gender effects on cortical thickness and the influence of scaling." Hum Brain Mapp **27**(4): 314-24.

Lyoo, I. K., Y. H. Sung, S. R. Dager, S. D. Friedman, J. Y. Lee, S. J. Kim, N. Kim, D. L. Dunner and P. F. Renshaw (2006). "Regional cerebral cortical thinning in bipolar disorder." Bipolar Disord **8**(1): 65-74.

Makris, N., J. Biederman, E. M. Valera, G. Bush, J. Kaiser, D. N. Kennedy, V. S. Caviness, S. V. Faraone and L. J. Seidman (2007). "Cortical thinning of the attention and executive function networks in adults with attention-deficit/hyperactivity disorder." Cereb Cortex **17**(6): 1364-75.

Makris, N., J. Kaiser, C. Haselgrove, L. J. Seidman, J. Biederman, D. Boriel, E. M. Valera, G. M. Papadimitriou, B. Fischl, V. S. Caviness, Jr. and D. N. Kennedy (2006). "Human cerebral cortex: a system for the integration of volume- and surface-based representations." Neuroimage **33**(1): 139-53.

Malberg, J. E., A. J. Eisch, E. J. Nestler and R. S. Duman (2000). "Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus." J Neurosci **20**(24): 9104-10.

Martinowich, K. and B. Lu (2008). "Interaction between BDNF and serotonin: role in mood disorders." Neuropsychopharmacology **33**(1): 73-83.

Matsuo, K., D. C. Glahn, M. A. Peluso, J. P. Hatch, E. S. Monkul, P. Najt, M. Sanches, F. Zamarripa, J. Li, J. L. Lancaster, P. T. Fox, J. H. Gao and J. C. Soares (2007). "Prefrontal hyperactivation during working memory task in untreated individuals with major depressive disorder." Mol Psychiatry **12**(2): 158-66.

Mayberg, H. S. (1997). "Limbic-cortical dysregulation: a proposed model of depression." J Neuropsychiatry Clin Neurosci **9**(3): 471-81.

Mayberg, H. S., M. Liotti, S. K. Brannan, S. McGinnis, R. K. Mahurin, P. A. Jerabek, J. A. Silva, J. L. Tekell, C. C. Martin, J. L. Lancaster and P. T. Fox (1999). "Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness." Am J Psychiatry **156**(5): 675-82.

Mayberg, H. S., A. M. Lozano, V. Voon, H. E. McNeely, D. Seminowicz, C. Hamani, J. M. Schwalb and S. H. Kennedy (2005). "Deep brain stimulation for treatment-resistant depression." Neuron **45**(5): 651-60.

Mazziotta, J., A. Toga, A. Evans, P. Fox, J. Lancaster, K. Zilles, R. Woods, T. Paus, G. Simpson, B. Pike, C. Holmes, L. Collins, P. Thompson, D. MacDonald, M. Iacoboni, T. Schormann, K. Amunts, N. Palomero-Gallagher, S. Geyer, L. Parsons, K. Narr, N. Kabani, G. Le Goualher, D. Boomsma, T. Cannon, R. Kawashima and B. Mazoyer (2001). "A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM)." Philos Trans R Soc Lond B Biol Sci **356**(1412): 1293-322.

McClearn, G. E., B. Johansson, S. Berg, N. L. Pedersen, F. Ahern, S. A. Petrill and R. Plomin (1997). "Substantial genetic influence on cognitive abilities in twins 80 or more years old." Science **276**(5318): 1560-3.

McDonald, C. R., D. J. Hagler, Jr., M. E. Ahmadi, E. Tecoma, V. Iragui, L. Gharapetian, A. M. Dale and E. Halgren (2008). "Regional neocortical thinning in mesial temporal lobe epilepsy." Epilepsia **49**(5): 794-803.

Mesulam, M. M. (1990). "Large-scale neurocognitive networks and distributed processing for attention, language, and memory." Ann Neurol **28**(5): 597-613.

Miller, J. M., K. G. Brennan, T. R. Ogden, M. A. Oquendo, G. M. Sullivan, J. J. Mann and R. V. Parsey (2009). "Elevated serotonin 1A binding in remitted major depressive disorder: evidence for a trait biological abnormality." Neuropsychopharmacology **34**(10): 2275-84.

Morley-Fletcher, S., M. Darnaudery, E. Mocaer, N. Froger, L. Lanfumey, G. Laviola, P. Casolini, A. R. Zuena, L. Marzano, M. Hamon and S. Maccari (2004). "Chronic treatment with imipramine reverses immobility behaviour, hippocampal corticosteroid receptors and cortical 5-HT(1A) receptor mRNA in prenatally stressed rats." Neuropharmacology **47**(6): 841-7.

Mountcastle, V. B. (1997). "The columnar organization of the neocortex." Brain **120 (Pt 4)**: 701-22.

Mulert, C., G. Leicht, O. Pogarell, R. Mergl, S. Karch, G. Juckel, H. J. Moller and U. Hegerl (2007). "Auditory cortex and anterior cingulate cortex sources of the early evoked gamma-band response: relationship to task difficulty and mental effort." Neuropsychologia **45**(10): 2294-306.

Narr, K. L., R. M. Bilder, A. W. Toga, R. P. Woods, D. E. Rex, P. R. Szeszko, D. Robinson, S. Sevy, H. Gunduz-Bruce, Y. P. Wang, H. DeLuca and P. M. Thompson (2005). "Mapping cortical thickness and gray matter concentration in first episode schizophrenia." Cereb Cortex **15**(6): 708-19.

Nemeroff, C. B. and M. J. Owens (2002). "Treatment of mood disorders." Nat Neurosci **5 Suppl**: 1068-70.

Nery, F. G., H. H. Chen, J. P. Hatch, M. A. Nicoletti, P. Brambilla, R. B. Sassi, A. G. Mallinger, M. S. Keshavan and J. C. Soares (2009). "Orbitofrontal cortex gray matter volumes in bipolar disorder patients: a region-of-interest MRI study." Bipolar Disord **11**(2): 145-53.

Nestler, E. J., M. Barrot, R. J. DiLeone, A. J. Eisch, S. J. Gold and L. M. Monteggia (2002). "Neurobiology of depression." Neuron **34**(1): 13-25.

Nesvag, R., G. Lawyer, K. Varnas, A. M. Fjell, K. B. Walhovd, A. Frigessi, E. G. Jonsson and I. Agartz (2008). "Regional thinning of the cerebral cortex in schizophrenia: effects of diagnosis, age and antipsychotic medication." Schizophr Res **98**(1-3): 16-28.

Neumeister, A., S. Wood, O. Bonne, A. C. Nugent, D. A. Luckenbaugh, T. Young, E. E. Bain, D. S. Charney and W. C. Drevets (2005). "Reduced hippocampal volume in unmedicated, remitted patients with major depression versus control subjects." Biol Psychiatry **57**(8): 935-7.

Neumeister, A., T. Young and J. Stastny (2004). "Implications of genetic research on the role of the serotonin in depression: emphasis on the serotonin type 1A receptor and the serotonin transporter." Psychopharmacology (Berl) **174**(4): 512-24.

O'Leary, D. D. and S. Sahara (2008). "Genetic regulation of arealization of the neocortex." Curr Opin Neurobiol **18**(1): 90-100.

Okada, G., Y. Okamoto, S. Morinobu, S. Yamawaki and N. Yokota (2003). "Attenuated left prefrontal activation during a verbal fluency task in patients with depression." Neuropsychobiology **47**(1): 21-6.

Okada, G., Y. Okamoto, H. Yamashita, K. Ueda, H. Takami and S. Yamawaki (2009). "Attenuated prefrontal activation during a verbal fluency task in remitted major depression." Psychiatry Clin Neurosci **63**(3): 423-5.

Ongur, D., W. C. Drevets and J. L. Price (1998). "Glial reduction in the subgenual prefrontal cortex in mood disorders." Proc Natl Acad Sci U S A **95**(22): 13290-5.

Ongur, D., A. T. Ferry and J. L. Price (2003). "Architectonic subdivision of the human orbital and medial prefrontal cortex." J Comp Neurol **460**(3): 425-49.

Oppenheim, J. S., J. E. Skerry, M. J. Tramo and M. S. Gazzaniga (1989). "Magnetic resonance imaging morphology of the corpus callosum in monozygotic twins." Ann Neurol **26**(1): 100-4.

Pakkenberg, B. and H. J. Gundersen (1997). "Neocortical neuron number in humans: effect of sex and age." J Comp Neurol **384**(2): 312-20.

Panizzon, M. S., C. Fennema-Notestine, L. T. Eyler, T. L. Jernigan, E. Prom-Wormley, M. Neale, K. Jacobson, M. J. Lyons, M. D. Grant, C. E. Franz, H. Xian, M. Tsuang, B. Fischl, L. Seidman, A. Dale and W. S. Kremen (2009). "Distinct Genetic Influences on Cortical Surface Area and Cortical Thickness." Cereb Cortex.

Pantazis, D., A. Joshi, J. Jiang, D. W. Shattuck, L. E. Bernstein, H. Damasio and R. M. Leahy (2009). "Comparison of landmark-based and automatic methods for cortical surface registration." Neuroimage.

Pardo, J. V., P. J. Pardo, K. W. Janer and M. E. Raichle (1990). "The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm." Proc Natl Acad Sci U S A **87**(1): 256-9.

Parsey, R. V., M. A. Oquendo, R. T. Ogden, D. M. Olvet, N. Simpson, Y. Y. Huang, R. L. Van Heertum, V. Arango and J. J. Mann (2006). "Altered serotonin 1A binding in major depression: a [carbonyl-C-11]WAY100635 positron emission tomography study." Biol Psychiatry **59**(2): 106-13.

Paus, T., A. Zijdenbos, K. Worsley, D. L. Collins, J. Blumenthal, J. N. Giedd, J. L. Rapoport and A. C. Evans (1999). "Structural maturation of neural pathways in children and adolescents: in vivo study." Science **283**(5409): 1908-11.

Peterson, B. S., V. Warner, R. Bansal, H. Zhu, X. Hao, J. Liu, K. Durkin, P. B. Adams, P. Wickramaratne and M. M. Weissman (2009). "Cortical thinning in persons at increased familial risk for major depression." Proc Natl Acad Sci U S A **106**(15): 6273-8.

Petit, L., S. M. Courtney, L. G. Ungerleider and J. V. Haxby (1998). "Sustained activity in the medial wall during working memory delays." J Neurosci **18**(22): 9429-37.

Pezawas, L., A. Meyer-Lindenberg, E. M. Drabant, B. A. Verchinski, K. E. Munoz, B. S. Kolachana, M. F. Egan, V. S. Mattay, A. R. Hariri and D. R. Weinberger (2005). "5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression." Nat Neurosci **8**(6): 828-34.

Pezawas, L., A. Meyer-Lindenberg, A. L. Goldman, B. A. Verchinski, G. Chen, B. S. Kolachana, M. F. Egan, V. S. Mattay, A. R. Hariri and D. R. Weinberger (2008). "Evidence of biologic epistasis between BDNF and SLC6A4 and implications for depression." Mol Psychiatry **13**(7): 709-16.

Phillips, M. L., W. C. Drevets, S. L. Rauch and R. Lane (2003). "Neurobiology of emotion perception II: Implications for major psychiatric disorders." Biol Psychiatry **54**(5): 515-28.

Pittenger, C. and R. S. Duman (2008). "Stress, depression, and neuroplasticity: a convergence of mechanisms." Neuropsychopharmacology **33**(1): 88-109.

Ploghaus, A., I. Tracey, J. S. Gati, S. Clare, R. S. Menon, P. M. Matthews and J. N. Rawlins (1999). "Dissociating pain from its anticipation in the human brain." Science **284**(5422): 1979-81.

Posner, M. I., S. E. Petersen, P. T. Fox and M. E. Raichle (1988). "Localization of cognitive operations in the human brain." Science **240**(4859): 1627-31.

Rademacher, J., V. S. Caviness, Jr., H. Steinmetz and A. M. Galaburda (1993). "Topographical variation of the human primary cortices: implications for neuroimaging, brain mapping, and neurobiology." Cereb Cortex **3**(4): 313-29.

Radley, J. J., K. L. Gosselink and P. E. Sawchenko (2009). "A discrete GABAergic relay mediates medial prefrontal cortical inhibition of the neuroendocrine stress response." J Neurosci **29**(22): 7330-40.

Radley, J. J., A. B. Rocher, M. Miller, W. G. Janssen, C. Liston, P. R. Hof, B. S. McEwen and J. H. Morrison (2006). "Repeated stress induces dendritic spine loss in the rat medial prefrontal cortex." Cereb Cortex **16**(3): 313-20.

Raichle, M. E., J. A. Fiez, T. O. Videen, A. M. MacLeod, J. V. Pardo, P. T. Fox and S. E. Petersen (1994). "Practice-related changes in human brain functional anatomy during nonmotor learning." Cereb Cortex **4**(1): 8-26.

Rajkowska, G., A. Halaris and L. D. Selemon (2001). "Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder." Biol Psychiatry **49**(9): 741-52.

Rajkowska, G., J. J. Miguel-Hidalgo, J. Wei, G. Dilley, S. D. Pittman, H. Y. Meltzer, J. C. Overholser, B. L. Roth and C. A. Stockmeier (1999). "Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression." Biol Psychiatry **45**(9): 1085-98.

Rakic, P. (1988). "Specification of cerebral cortical areas." Science **241**(4862): 170-6.

Rakic, P. (1995). "A small step for the cell, a giant leap for mankind: a hypothesis of neocortical expansion during evolution." Trends Neurosci **18**(9): 383-8.

Rauch, S. L., C. I. Wright, B. Martis, E. Busa, K. G. McMullin, L. M. Shin, A. M. Dale and B. Fischl (2004). "A magnetic resonance imaging study of cortical thickness in animal phobia." Biol Psychiatry **55**(9): 946-52.

Robinson, J. L., E. S. Monkul, D. Tordesillas-Gutierrez, C. Franklin, C. E. Bearden, P. T. Fox and D. C. Glahn (2008). "Fronto-limbic circuitry in euthymic bipolar disorder: evidence for prefrontal hyperactivation." Psychiatry Res **164**(2): 106-13.

Roland, P. E. and K. Zilles (1994). "Brain atlases--a new research tool." Trends Neurosci **17**(11): 458-67.

Rosas, H. D., A. K. Liu, S. Hersch, M. Glessner, R. J. Ferrante, D. H. Salat, A. van der Kouwe, B. G. Jenkins, A. M. Dale and B. Fischl (2002). "Regional and progressive thinning of the cortical ribbon in Huntington's disease." Neurology **58**(5): 695-701.

Rosas, H. D., D. H. Salat, S. Y. Lee, A. K. Zaleta, V. Pappu, B. Fischl, D. Greve, N. Hevelone and S. M. Hersch (2008). "Cerebral cortex and the clinical expression of Huntington's disease: complexity and heterogeneity." Brain **131**(Pt 4): 1057-68.

Rose, E. J. and K. P. Ebmeier (2006). "Pattern of impaired working memory during major depression." J Affect Disord **90**(2-3): 149-61.

Saad, Z. S., R. C. Reynolds, B. Argall, S. Japee and R. W. Cox (2004). "SUMA: An interface for subject-based intra- and inter-subject analysis with AFNI." Proceedings of the 2004 IEEE International Symposium on Biomedical Imaging, Arlington, VA. New York: IEEE: 1510-1513.

Sailer, M., B. Fischl, D. Salat, C. Tempelmann, M. A. Schonfeld, E. Busa, N. Bodammer, H. J. Heinze and A. Dale (2003). "Focal thinning of the cerebral cortex in multiple sclerosis." Brain **126**(Pt 8): 1734-44.

Saleem, K. S., H. Kondo and J. L. Price (2008). "Complementary circuits connecting the orbital and medial prefrontal networks with the temporal, insular, and opercular cortex in the macaque monkey." J Comp Neurol **506**(4): 659-93.

Sapolsky, R. M. (2000). "Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders." Arch Gen Psychiatry **57**(10): 925-35.

Sassi, R. B., P. Brambilla, J. P. Hatch, M. A. Nicoletti, A. G. Mallinger, E. Frank, D. J. Kupfer, M. S. Keshavan and J. C. Soares (2004). "Reduced left anterior cingulate volumes in untreated bipolar patients." Biol Psychiatry **56**(7): 467-75.

Schoning, S., P. Zwitserlood, A. Engelien, A. Behnken, H. Kugel, H. Schiffbauer, K. Lipina, C. Pachur, A. Kersting, U. Dannlowski, B. T. Baune, P. Zwanzger, T. Reker, W. Heindel, V. Arolt and C. Konrad (2008). "Working-memory fMRI reveals cingulate hyperactivation in euthymic major depression." Hum Brain Mapp.

Segonne, F., A. M. Dale, E. Busa, M. Glessner, D. Salat, H. K. Hahn and B. Fischl (2004). "A hybrid approach to the skull stripping problem in MRI." Neuroimage **22**(3): 1060-75.

Segonne, F., E. Grimson and B. Fischl (2005). "A genetic algorithm for the topology correction of cortical surfaces." Inf Process Med Imaging **19**: 393-405.

Sheline, Y. I. (2003). "Neuroimaging studies of mood disorder effects on the brain." Biol Psychiatry **54**(3): 338-52.

Sheline, Y. I., D. M. Barch, J. M. Donnelly, J. M. Ollinger, A. Z. Snyder and M. A. Mintun (2001). "Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study." Biol Psychiatry **50**(9): 651-8.

Soares, J. C. and J. J. Mann (1997). "The functional neuroanatomy of mood disorders." J Psychiatr Res **31**(4): 393-432.

Sohn, M. H., M. V. Albert, K. Jung, C. S. Carter and J. R. Anderson (2007). "Anticipation of conflict monitoring in the anterior cingulate cortex and the prefrontal cortex." Proc Natl Acad Sci U S A **104**(25): 10330-4.

Sowell, E. R., B. S. Peterson, E. Kan, R. P. Woods, J. Yoshii, R. Bansal, D. Xu, H. Zhu, P. M. Thompson and A. W. Toga (2007). "Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age." Cereb Cortex **17**(7): 1550-60.

Sowell, E. R., P. M. Thompson, C. J. Holmes, T. L. Jernigan and A. W. Toga (1999). "In vivo evidence for post-adolescent brain maturation in frontal and striatal regions." Nat Neurosci **2**(10): 859-61.

Spitzer, R. L., J. B. Williams, M. Gibbon and M. B. First (1992). "The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description." Arch Gen Psychiatry **49**(8): 624-9.

Staley, J. K., R. T. Malison and R. B. Innis (1998). "Imaging of the serotonergic system: interactions of neuroanatomical and functional abnormalities of depression." Biol Psychiatry **44**(7): 534-49.

Strigo, I. A., G. H. Duncan, M. Boivin and M. C. Bushnell (2003). "Differentiation of visceral and cutaneous pain in the human brain." J Neurophysiol **89**(6): 3294-303.

Sullivan, G. M., R. T. Ogden, M. A. Oquendo, J. S. Kumar, N. Simpson, Y. Y. Huang, J. J. Mann and R. V. Parsey (2009). "Positron emission tomography quantification of serotonin-1A receptor binding in medication-free bipolar depression." Biol Psychiatry **66**(3): 223-30.

Svensson, P., S. Minoshima, A. Beydoun, T. J. Morrow and K. L. Casey (1997). "Cerebral processing of acute skin and muscle pain in humans." J Neurophysiol **78**(1): 450-60.

Symms, M., H. R. Jager, K. Schmierer and T. A. Yousry (2004). "A review of structural magnetic resonance neuroimaging." J Neurol Neurosurg Psychiatry **75**(9): 1235-44.
Talairach, J. and P. Tournoux (1988). "Co-planar Stereotaxic Atlas of the Human Brain." Thieme Medical, New York.
Thompson, P. M., T. D. Cannon, K. L. Narr, T. van Erp, V. P. Poutanen, M. Huttunen, J. Lonnqvist, C. G. Standertskjold-Nordenstam, J. Kaprio, M. Khaledy, R. Dail, C. I. Zoumalan and A. W. Toga (2001). "Genetic influences on brain structure." Nat Neurosci **4**(12): 1253-8.
Tramo, M. J., W. C. Loftus, T. A. Stukel, R. L. Green, J. B. Weaver and M. S. Gazzaniga (1998). "Brain size, head size, and intelligence quotient in monozygotic twins." Neurology **50**(5): 1246-52.
Van Essen, D. C. (1997). "A tension-based theory of morphogenesis and compact wiring in the central nervous system." Nature **385**(6614): 313-8.
Van Essen, D. C. (2004). "Surface-based approaches to spatial localization and registration in primate cerebral cortex." Neuroimage **23 Suppl 1**: S97-107.
Van Essen, D. C. (2005). "A Population-Average, Landmark- and Surface-based (PALS) atlas of human cerebral cortex." Neuroimage **28**(3): 635-62.
Van Essen, D. C. and H. A. Drury (1997). "Structural and functional analyses of human cerebral cortex using a surface-based atlas." J Neurosci **17**(18): 7079-102.
Van Essen, D. C., H. A. Drury, S. Joshi and M. I. Miller (1998). "Functional and structural mapping of human cerebral cortex: solutions are in the surfaces." Proc Natl Acad Sci U S A **95**(3): 788-95.
Vogt, B. A. (2005). "Pain and emotion interactions in subregions of the cingulate gyrus." Nat Rev Neurosci **6**(7): 533-44.
Vogt, B. A., G. R. Berger and S. W. Derbyshire (2003). "Structural and functional dichotomy of human midcingulate cortex." Eur J Neurosci **18**(11): 3134-44.
Vogt, B. A., L. Vogt and S. Laureys (2006). "Cytology and functionally correlated circuits of human posterior cingulate areas." Neuroimage **29**(2): 452-66.
Walterfang, M., M. Yucel, S. Barton, D. C. Reutens, A. G. Wood, J. Chen, V. Lorenzetti, D. Velakoulis, C. Pantelis and N. B. Allen (2009). "Corpus callosum size and shape in individuals with current and past depression." J Affect Disord **115**(3): 411-20.
Wang, L., M. Hosakere, J. C. Trein, A. Miller, J. T. Ratnanather, D. M. Barch, P. A. Thompson, A. Qiu, M. H. Gado, M. I. Miller and J. G. Csernansky (2007). "Abnormalities of cingulate gyrus neuroanatomy in schizophrenia." Schizophr Res **93**(1-3): 66-78.
Westheide, J., M. Wagner, B. B. Quednow, C. Hoppe, D. Cooper-Mahkorn, B. Strater, W. Maier and K. U. Kuhn (2007). "Neuropsychological performance in partly remitted unipolar depressive patients: focus on executive functioning." Eur Arch Psychiatry Clin Neurosci **257**(7): 389-95.
Whalen, P. J., G. Bush, R. J. McNally, S. Wilhelm, S. C. McInerney, M. A. Jenike and S. L. Rauch (1998). "The emotional counting Stroop paradigm: a functional magnetic resonance imaging probe of the anterior cingulate affective division." Biol Psychiatry **44**(12): 1219-28.
Williams, J. B. (1988). "A structured interview guide for the Hamilton Depression Rating Scale." Arch Gen Psychiatry **45**(8): 742-7.
Williams, Z. M., G. Bush, S. L. Rauch, G. R. Cosgrove and E. N. Eskandar (2004). "Human anterior cingulate neurons and the integration of monetary reward with motor responses." Nat Neurosci **7**(12): 1370-5.

Wright, C. I., D. Williams, E. Feczko, L. F. Barrett, B. C. Dickerson, C. E. Schwartz and M. M. Wedig (2006). "Neuroanatomical correlates of extraversion and neuroticism." Cereb Cortex **16**(12): 1809-19.

Yuan, Y., W. Zhu, Z. Zhang, F. Bai, H. Yu, Y. Shi, Y. Qian, W. Liu, T. Jiang, J. You and Z. Liu (2008). "Regional gray matter changes are associated with cognitive deficits in remitted geriatric depression: an optimized voxel-based morphometry study." Biol Psychiatry **64**(6): 541-4.

Yucel, K., M. C. K. M, R. Chahal, V. Taylor, K. Macdonald, R. Joffe and G. Macqueen (2009). "Increased subgenual prefrontal cortex size in remitted patients with major depressive disorder." Psychiatry Res **173**(1): 71-6.

Zakzanis, K. K., L. Leach and E. Kaplan (1998). "On the nature and pattern of neurocognitive function in major depressive disorder." Neuropsychiatry Neuropsychol Behav Neurol **11**(3): 111-9.

Abstract

Major depressive disorder (MDD) is among the four leading causes of disease burden throughout the world and is associated with medical morbidity and mortality across the lifespan. It is characterized by functional and structural alterations of the brain reflecting dysfunctional brain circuits of emotion processing and cognitive control. A vast number of studies have focussed on alterations in the acute state of depression which may primarily represent state-dependent pathophysiological changes thereby masking those neurobiological changes mainly associated with genetic susceptibility to depression. Thus, the present diploma thesis focuses on the remitted state of MDD aiming to reveal trait markers of MDD by using cortical thickness as a measure of morphological integrity.

Structural magnetic resonance imaging scans of 28 remitted major depressive patients without any current drug treatment or psychiatric illness, who did not receive any treatment for at least three months before assessment and 28 age and gender-matched healthy controls, were obtained. Structural images were analyzed using a mere surface-based approach, which, in contrast to standard volumetric methods, preserves the topological folding patterns of the cortex, and, by that, reduces anatomical variability thereby increasing statistical power. After standard preprocessing the data were analyzed within a general linear model assessing the effects of group differences between patients and healthy controls. Additionally, psychometric variables were included in statistical analysis aiming to investigate potential influences of personality traits.

Analysis revealed cortical thickness alterations in remitted MDD patients compared to healthy controls localized within the anterior midcingulate cortex. Since the anterior midcingulate cortex is mainly implicated in emotional control and regulation, these results might suggest impaired top-down control over limbic circuits on a functional level indicating increased stress responsiveness even when mood is restored on a behavioural level. These findings may enhance the

understanding of the neurobiology of remitted MDD and provide a putative structural disease marker reflecting vulnerability to depression.

Zusammenfassung

Depression gehört zu den weltweit vier häufigsten Ursachen von Krankheitslast und ist assoziiert mit medizinischer Morbidität und Mortalität. Charakteristisch für Depression sind funktionelle und strukturelle Veränderungen des Gehirns als Zeichen dysfunktionaler Gehirnschaltkreise der Emotionsverarbeitung sowie der kognitiven Kontrolle. Viele Studien haben sich hauptsächlich mit der akuten Phase von Depression beschäftigt, in der sich in erster Linie vermutlich zustandsabhängige pathophysiologische Veränderungen zeigen, wodurch die eigentlichen neurobiologischen Veränderungen, die im Zusammenhang mit genetischer Vulnerabilität für Depression stehen, verschleiert werden. Um tatsächliche Merkmals-Marker zu finden, setzt die vorliegende Diplomarbeit den Schwerpunkt auf remittierte Depression unter Verwendung der kortikalen Dicke als Maß für die morphologische Integrität.

Strukturelle Magnetresonanztomographie-Scans wurden an 28 remittiert Depressiven, die keine Form von Behandlung innerhalb der letzten drei Monate erhalten haben und ohne aktuelle medikamentöse Behandlung bzw. psychiatrische Erkrankung waren, sowie an 28, in Bezug auf Alter und Geschlecht abgestimmte, Gesunden durchgeführt. Die erhobenen, strukturellen Bilder wurden mittels eines oberflächen-basierten Verfahrens, welches im Kontrast zu reinen volumetrischen Ansätzen, die topologischen Faltungsmuster des Kortex realitätsgetreu abbildet, wodurch die anatomische Variabilität reduziert und die statistische Power erhöht werden, ausgewertet. Mit dem Ziel mögliche Gruppenunterschiede zwischen Depressiven und Gesunden ausfindig zu machen, wurden die Daten im Anschluss an die Präprozessierung mittels eines ‚Allgemeinen linearen Modells' statistisch analysiert. Um mögliche Einflüsse von Persönlichkeitsmerkmalen zu untersuchen, wurden zusätzlich psychometrische Variablen in das Modell integriert.

Die statistische Analyse konnte Unterschiede in der kortikalen Dicke zwischen Depressiven und Gesunden zeigen, die im anterioren midzingulären Kortex

lokalisiert sind. In Anbetracht dessen dass der anteriore midzinguläre Kortex eine wichtige Rolle bei der Emotionskontrolle bzw. –regulation spielt, deuten die Ergebnisse auf eine beeinträchtigte Top-Down-Kontrolle von Emotionshirnschaltkreisen hin, was sich auf der Verhaltensebene vermutlich in Form eine erhöhten Empfindlichkeit gegenüber Stresseinflüssen äußert. Die vorliegenden Ergebnisse können hoffentlich zu einem vertieften Verständnis der neurobiologischen Grundlagen von Depression beitragen und legen womöglich einen potentiellen, strukturellen Krankheitsmarker, der die Vulnerabilität für Depression widerspiegelt, nahe.

Curriculum Vitae

Personal Information

Name:	Manuel Nagl
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Education

Since 2007	Academic studies in *Human Integrative Neurosciences*, University of Vienna
2000 - 2004	Academic studies in *Communication Science*, University of Vienna
1999 - 2000	Civilian service (Oö. Nervenheilanstalt Wagner-Jauregg Linz)
1991 - 1999	Gymnasium Kollegium Petrinum Linz
1990 - 1991	BG und BRG Peuerbachstraße Linz
1986 - 1990	Volksschule Karlhof Linz

Scientific Experience

Since 2008	Project work in the *Clinical Neuroimaging Group*, Medical University
Since 2005	Research assistant at the *Department of Communication*, Faculty of Social Sciences, University of Vienna