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EARLY EFFECTS OF ANTIDEPRESSANTS ON EMOTIONAL PROCESSING

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ABSTRACT

Introduction: The mechanisms of action of antidepressants at the system level remain mainly unresolved. Antidepressants rapidly modulate emotional processing, enhancing processing of positive versus negative information, but this has been mostly demonstrated in healthy subjects and using fairly simple, controlled emotional stimuli such as emotional faces.

Aim of the study: The aim of the studies of this thesis was to shed light on early antidepressant effects on emotional processing both in healthy subjects, avoiding the confounding effect of depressed mood, and in treatment-seeking depressed patients at an early stage of treatment, to elude the confounding effect of improved mood. The studies specifically aimed to reveal antidepressant effects on self-referential processing, a core factor in psychopathology of depression, and to investigate whether/how antidepressants modulate processing of complex, dynamic emotional stimuli resembling daily-life emotional situations.

Methods: In Study 1 (experiments I and II), an open-label study of 30 healthy volunteers, half of the subjects received mirtazapine 15 mg two hours prior to functional magnetic resonance imaging (fMRI), and the other half was scanned without medication as a control group. Study 2 (experiments III and IV) was a double-blind, placebo-controlled study where 32 treatment-seeking depressed patients were randomized to receive escitalopram 10 mg or placebo for one week, after which fMRI was performed. In experiments I and III, neural responses to positive and negative self-referential adjectives as well as a neutral control task were assessed. In experiments II and IV participants listened to spoken emotional narratives and neural responses to the emotional content of the narratives were assessed.

Results: Both mirtazapine in healthy subjects and escitalopram in depressed patients modulated self-referential processing. Mirtazapine attenuated responses to both positive and negative self-referential words in the anterior cortical midline structures (CMS, including the medial prefrontal cortex and the anterior cingulate), whereas escitalopram increased processing of positive relative to negative self-referential words. When comparing the placebo group and the escitalopram group from Study 2 separately with the healthy controls from Study 1, depressed patients receiving

placebo had decreased responses of the anterior CMS to positive versus negative self-referential words, whereas no differences were found between the escitalopram group and healthy controls, implicating normalization of the negative bias in depressed patients receiving escitalopram. Both mirtazapine and escitalopram also modulated brain responses to spoken emotional narratives. Mirtazapine was found to modulate dynamic functional connectivity (measured with seed-based phase synchronization) of large-scale brain circuits, particularly potentiating functional connectivity of the anterior CMS and the limbic regions during positive parts of the narratives. Escitalopram increased synchronization of brain responses (measured with inter-subject correlation, ISC), specifically during positive parts of the narratives.

Conclusions: A single dose of mirtazapine in healthy subjects and a one-week treatment with escitalopram in treatment-seeking depressed patients modulated neural responses to emotional information without any concurrent changes in mood. Both antidepressants modulated self-referential processing, a core psychological process in developing and maintaining depression. Escitalopram normalized the negatively biased self-referential processing of depressed patients in the anterior CMS. Both mirtazapine and escitalopram modulated brain responses to spoken emotional narratives, extending the previous findings of antidepressant effects based on simple emotional stimuli to complex, dynamic, every-day like emotional situations. Specifically, potentiated processing measured with novel methods of dynamic functional connectivity and ISC was found in the anterior CMS among other regions during positive emotional content of the narratives. These results suggest that antidepressants rapidly modulate processing of particularly positive emotional and self-referential information in the anterior CMS. This may be important for their later therapeutic effect.

TIIVISTELMÄ

Johdanto: Masennuslääkkeiden vaikutusmekanismeja systeemitasolla tunnetaan yhä heikosti. Niiden tiedetään vaikuttavan nopeasti tunteiden prosessointiin voimistamalla positiivisen informaation prosessointia negatiiviseen verrattuna. Tämä vaikutus on kuitenkin osoitettu lähinnä terveillä koehenkilöillä sekä käyttäen koeasetelmissa yksinkertaisia ärsykkeitä, kuten emotionaalisia kasvokuvia.

Tavoitteet: Tämän väitöskirjatyön osatutkimusten tavoitteena oli selvittää masennuslääkkeiden varhaisia vaikutuksia tunteiden prosessointiin sekä terveillä koehenkilöillä, välttäen näin masentuneen mielialan sekoittava vaikutus, että masentuneilla potilailla hoidon varhaisessa vaiheessa, välttäen näin korjaantuvan mielialan sekoittava vaikutus. Erityisesti tavoitteena oli tutkia masennuslääkkeiden vaikutusta itseen liittyvään prosessointiin, koska liiallinen keskittyminen omiin, usein negatiivisiin tunteisiin ja ajatuksiin on eräs masennuksen keskeisistä psykologisista ilmiöistä. Lisäksi haluttiin selvittää, kuinka masennuslääkkeet vaikuttavat monimutkaisten, tosielämän emotionaalisia tilanteita muistuttavien ärsykkeiden prosessointiin.

Menetelmät: Osatutkimuksessa 1 (koeasetelmat I ja II) puolet 30 terveestä vapaaehtoisesta sai avoimessa tutkimusasetelmassa 15mg mirtatsapiinia kaksi tuntia ennen toiminnallista magneettikuvausta (fMRI) ja puolet kuvattiin verrokkiryhmänä ilman lääkitystä. Osatutkimuksessa 2 (koeasetelmat III ja IV) 32 hoitoon hakeutunutta masennuspotilasta satunnaistettiin kaksois-sokkoutetussa tutkimusasetelmassa saamaan 10mg essitalopraamia tai lumetta viikon verran, jonka jälkeen suoritettiin fMRI-kuvaus. Koeasetelmissa I ja III mitattiin aivovasteita positiivisille ja negatiivisille itseen liittyville adjektiiveille sekä neutraaleille kontrollisanoille. Koeasetelmissa II ja IV koehenkilöt kuuntelivat kuvauksen aikana tunteita herättäviä tarinoita ja tarinoiden tunnesisällön herättämät aivovasteet mitattiin.

Tulokset: Sekä mirtatsapiini terveillä koehenkilöillä että essitalopraami masennuspotilailla muokkasi aivovasteita itseen liittyviä sanoja prosessoitaessa. Mirtatsapiini vaimensi sekä positiivisten että negatiivisten sanojen herättämiä vasteita odotetuilla alueilla aivojen keskilinjan kortikaalisten alueiden etuosissa (keskimmäinen etuotsalohko ja etummainen pihtipoimu), kun taas essitalopraami voimisti positiivisten

sanojen prosessointia negatiivisiin nähden masennuspotilailla. Kun osatutkimuksen 2 masennuspotilaiden aivovasteita verrattiin lume- ja lääkeryhmässä erikseen osatutkimuksen 1 terveisiin verrokkeihin, havaittiin lumeryhmän reagoivan heikommin positiivisiin sanoihin negatiivisiin nähden, kun taas lääkeryhmän ja terveiden verrokeiden välillä ei ollut eroa. Essitalopraami siis palautti masennuspotilaiden negatiivisesti vääristyneen itseen liittyvän prosessoinnin normaalille, terveelle tasolle. Molemmat masennuslääkkeet muovasivat aivovasteita emotionaalisten tarinoiden tunnesisällölle. Mirtatsapiini vaikutti laaja-alaisesti aivoalueiden välisiin toiminnallisiin yhteyksiin, erityisesti voimistamalla niitä aivojen keskilinja-alueiden etuosassa ja limbisellä alueella tarinoiden positiivisuuden lisääntyessä. Essitalopraami voimisti koehenkilöiden välistä synkroniaa aivovasteissa, erityisesti positiivisen sisällön aikana.

Johtopäätökset: Molemmat tutkitut masennuslääkkeet vaikuttivat tunteiden prosessointiin nopeasti, ilman samanaikaista muutosta mielialassa. Essitalopraami normalisoi masennuspotilaiden negatiivisesti vääristynyttä itseen kohdistuvaa prosessointia, jonka ajatellaan olevan tärkeä tekijä masennustilan kehittymisessä ja jatkumisessa. Molemmat tutkitut masennuslääkkeet myös muokkasivat emotionaalisten tarinoiden herättämiä aivovasteita. Tämä tulos on merkittävä lisä aiempiin löydöksiin, koska se osoittaa masennuslääkkeiden muuttavan myös monimutkaisten ja dynaamisten, lähempänä todellisia arkipäivän tunteita herättäviä tilanteita olevien emotionaalisten ärsykkeiden prosessointia. Todetut muutokset voivat olla merkittävässä roolissa myöhemmän kliinisen lääkevasteen kannalta.

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Helsinki, February 2019

Emma Komulainen

CONTENT

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals:

I. Emma Komulainen, Roope Heikkilä, Katarina Meskanen, Tuukka T. Raij, Lauri Nummenmaa, Pekka Jylhä, Tarja Melartin, Catherine J. Harmer, Erkki Isometsä and Jesper Ekelund. A single dose of mirtazapine attenuates neural responses to self-referential processing. Journal of Psychopharmacology 2016 Jan;30(1):23-32.

II. Emma Komulainen, Enrico Glerean, Katarina Meskanen, Roope Heikkilä, Lauri Nummenmaa, Tuukka T. Raij, Jari Lahti, Pekka Jylhä, Tarja Melartin, Erkki Isometsä and Jesper Ekelund. Single dose of mirtazapine modulates whole-brain functional connectivity during emotional narrative processing. Psychiatry Research: Neuroimaging 2017 May;30(263):61-69.

III. Emma Komulainen, Roope Heikkilä, Lauri Nummenmaa, Tuukka T. Raij, Catherine J. Harmer, Erkki Isometsä and Jesper Ekelund. Short-term escitalopram treatment normalizes aberrant self-referential processing in major depressive disorder. Journal of Affective Disorders 2018 Aug;15(236):222-229.

IV. Emma Komulainen, Enrico Glerean, Roope Heikkilä, Lauri Nummenmaa, Tuukka T. Raij, Erkki Isometsä and Jesper Ekelund. Escitalopram enhances synchrony of brain responses during emotional narratives. Submitted in Neuroimage.

ABBREVIATIONS

ACC	Anterior cingulate cortex
ANOVA	Analysis of variance
ATD	Acute tryptophan depletion
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BDNF	Brain-derived neurotrophic factor
BOLD	Blood oxygen level dependent
CBT	Cognitive behavioural therapy
CMS	Cortical midline structures
CRH	Corticotropin-releasing hormone
DLPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
DSM	Diagnostic and Statistical Manual of Mental Disorders
EPI	Echo planar imaging
FDR	False discovery rate
fMRI	Functional magnetic resonance imaging
FWE	Family-wise error
FWER	Family-wise error rate
GLM	General linear model
GWAS	Genome-wide association study
HA	High arousal
HDR	Haemodynamic response

HPA	Hypothalamus-pituitary-adrenal-axis
5HTTLPR	Serotonin transporter-linked polymorphic region
IFG	Inferior frontal gyrus
IPC	Inferior parietal cortex
ISC	Inter-subject correlation
LA	Low arousal
MADRS	Montgomery-Åsberg Depression Rating Scale
MCC	Middle cingulate cortex
MDD	Major depressive disorder
MFG	Medial frontal gyrus
MNI	Montreal Neurological Institute
MPFC	Medial prefrontal cortex
MTC	Middle temporal cortex
NA	Negative affect
NA-HA	Negative affect, high arousal
NA-LA	Negative affect, low arousal
NICE	National Institute for Health and Care Excellence
OFC	Orbitofrontal cortex
PA	Positive affect
PA-HA	Positive affect, high arousal
PCC	Posterior cingulate cortex
PFC	Prefrontal cortex
pgACC	Perigenual anterior cingulate cortex

PSSS-R	Perceived Social Support Scale Revised
ROI	Region of interest
SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex
SBPS	Seed-based phase synchronization
sgACC	Subgenual anterior cingulate cortex
SMA	Supplementary motor area
SNRI	Serotonin and noradrenaline reuptake inhibitor
SPC	Superior parietal cortex
SSRI	Selective serotonin reuptake inhibitor
STC	Superior temporal cortex
VLPFC	Ventrolateral prefrontal cortex
VMPFC	Ventromedial prefrontal cortex

1 INTRODUCTION

Major depressive disorder (MDD) is a common mental disorder causing substantial suffering, disability, and costs (Druss, Rosenheck, & Sledge, 2000; Vos et al., 2017). Prevalence of MDD remains high although treatment coverage has increased (Jorm, Patten, Brugha, & Mojtabai, 2017). Developments in treatment outcomes and mortality rates of mental disorders have not been as favourable as in many other fields of medicine in the last decades (Cuthbert & Insel, 2013). A likely reason for this is the complex and largely unknown pathogenesis of mental disorders and the lack of a neuroscience-based diagnostic system (Cuthbert & Insel, 2013). MDD is currently viewed as a disorder of brain circuits, with abnormal functioning particularly in the emotion circuits of the brain (Williams, 2017). Advancements in neuroimaging techniques have enabled investigation of these circuits as well as antidepressant effects on them. Based on the findings of the ability of antidepressants to modulate emotional processing rapidly in healthy subjects, a cognitive neuropsychological theory of antidepressant action, suggesting this shift in emotional processing to be crucial for their later therapeutic effect, has been formulated (Harmer, Duman, & Cowen, 2017). If the early changes in emotional processing prove to be a necessary factor in the mechanism of action across different antidepressants and other treatment modalities, better understanding of these changes can significantly improve efforts to find early predictive markers to guide treatment choices and improve treatment outcomes. The studies of this thesis were designed to test the cognitive neuropsychological theory by investigating the early effects of two different antidepressants in two different populations, namely healthy subjects and depressed patients. The present studies add to previous findings from simple and controlled experimental settings with mostly healthy subjects, by investigating antidepressant effects on emotional processing in treatment-seeking depressed patients and using novel methods to assess neural responses to complex, natural emotional stimuli.

2 BACKGROUND

2.1 PUBLIC HEALTH IMPACT OF DEPRESSION

Major depressive disorder (MDD) is one of the leading contributors to the global disease burden. In the latest Global Burden of Disease Study of the World Health Organization, MDD was the fifth leading cause of non-fatal disease burden (Vos et al., 2017). When using disability-adjusted life-years as a summary method, summing years lived with a disability and years of life lost due to premature mortality, MDD ranked in the top twenty disease burden globally and in the top ten in high-income countries (Hay et al., 2017). MDD is a common, long-term, and recurrent condition (Hardeveld et al., 2013; Vuorilehto, Melartin, & Isometsä, 2009). In the World Health Organization World Mental Health Survey, conducted in 18 countries, the one-year prevalence of MDD was 5.5% in high-income countries and 5.9% in low-income countries, and the life-time prevalence was 14.6% in high-income countries and 11.1% in low-income countries (Bromet et al., 2011). Women have about a twofold higher risk for MDD than men (Bromet et al., 2011). Approximately 10% of men and 20% of women suffer from a major depressive episode in their lifetime (Bijl, Ravelli, & van Zessen, 1998). In Finland, in the national Health 2011 Survey, the one-year prevalence of MDD was 7.4% (10% for women, 4.4% for men) (Markkula et al., 2015). About one-third of depressed patients suffer a recurrence of MDD within a follow-up of a few years (Hardeveld et al., 2013; Vuorilehto et al., 2009). Furthermore, in a sample of Finnish primary care depressive patients, one-quarter of the patients persisted in a full major depressive episode for the entire 18-month follow-up (Vuorilehto et al., 2009). With longer follow-up period and broader diagnostic perspective, the prognosis of MDD gets even less favourable. The amount of patients with full and sustained recovery decreased from 60% to 30% in 2-year and 6-year follow-up, respectively (Verduijn et al., 2017). When broadening the diagnostic conceptualization towards “real world” patients by including comorbid dysthymia, anxiety disorders and (hypo)manic symptoms, less than 20% were recovered and more than 50% suffered from chronic episodes at 6-year follow-up.

Prevalence of depression has not significantly changed globally during the last decades, even though the use of treatment interventions has grown (Jorm et al., 2017). Mortality rates also remain high: depressed patients have a mortality almost twice as

high as that of the general population (Cuijpers & Smit, 2002). Alarmingly, the gap in mortality between people with mental disorders, including depression, and the general population is increasing (Cuijpers & Smit, 2002; Walker, McGee, & Druss, 2015). Depressed patients have a high risk for suicide attempts. Suicide is the second leading cause of death of young adults, and more than half of the people who die by suicide meet the criteria for current depressive disorder (Bolton, Gunnell, & Turecki, 2015; Isometsä, 2014).

MDD causes substantial impairment in performance of normal activities (Bromet et al., 2011). Furthermore, MDD causes disability particularly in young adults, i.e. individuals who are beginning to bring significant economic and social contributions to their families and societies (Kessler et al., 2005). Indeed, indirect costs from depression, especially from loss of work days, are as great or greater than those from other common disorders such as heart diseases, diabetes, and back problems (Druss et al., 2000).

2.2 DEFINITION OF DEPRESSION

Depression is characterized by persistently low mood and/or loss of interest and ability to experience daily life pleasures. These core symptoms are accompanied by vegetative and psychomotor disturbances such as sleeping disturbances, altered appetite, slowing of movement and thought, and impaired concentration. Melancholia was already described by the ancient Greeks and Romans. Hippocrates postulated that melancholia, a state of “aversion to food, despondency, sleeplessness, irritability and restlessness”, was caused by the influence of “black bile” on the brain, often together with melancholic temperament (Sadock, Sadock, & Ruiz, 2009). Emil Kraepelin later placed all pathological alterations of mood, including melancholia, mania, and mixed episodes, into one entity (manic-depressive insanity), separating it from dementia praecox, which later became schizophrenia (Greene, 2007; Mondimore, 2005). Diagnosis of depression in the current classification systems, the International Classification of Diseases and the Diagnostic and Statistical Manual of Mental Disorders (DSM), is based on manifesting a certain amount of common descriptive features, i.e. observed and expressed signs and symptoms (APA, 1994; World Health Organization, 1992). The diagnostic criteria of MDD according to the DSM-IV, the classification used in this thesis, are presented in Table 1.

Table 1. *Diagnostic criteria of MDD in DSM-IV. Criteria A-E must be met.*

A.	At least five of the symptoms 1-9 are present during a same two-week period. Symptoms represent a change from previous functioning. At least one of them is either symptom 1 or 2.
1.	Depressed mood.
2.	Markedly diminished interest or pleasure in all, or almost all, activities. Symptoms 1-2 are present most of the day, nearly every day.
3.	Significant weight loss or weight gain or decrease/increase in appetite.
4.	Insomnia or hypersomnia.
5.	Psychomotor agitation or retardation.
6.	Fatigue or loss of energy.
7.	Feelings of worthlessness or excessive or inappropriate guilt.
8.	Diminished ability to think or concentrate or indecisiveness.
9.	Recurrent thought of death, recurrent suicidal ideation without a specific plan or a suicide attempt or a specific plan for committing a suicide. Symptoms 3-8 are present nearly every day.
B.	No life-time hypomanic, manic or mixed episode.
C.	The symptoms cause clinically significant distress or impairment in functioning.
D.	The symptoms are not due to direct physiological effects, a substance, or a general medical condition.
E.	The symptoms are not better accounted for by bereavement.

Depression is a heterogeneous group of illness manifestations, constituting numerous combinations of symptoms. In fact, two patients diagnosed with MDD may share only one common symptom, and there are 227 theoretical ways to meet the diagnostic criteria (theoretical, because symptoms do not co-occur randomly and some combinations are more common than others (Zimmerman, Ellison, Young, Chelminski and Dalrymple 2015)). A leading thought of any medical classification system is that grouping illness manifestations or disorders together should be based on shared aetiology and underlying pathophysiology (Spitzer, 2001). This ideal serves the ultimate purpose of diagnosis, namely optimizing treatment, and it has been a goal also throughout the history of DSM, starting from the 3rd edition in 1980. However, as the pathophysiology of mental illnesses was largely unknown at the time of creating

the DSM-III in the 1970s, it was decided that the diagnostic categories ought to arise from shared descriptive features (Hyman, 2007; Spitzer, 2001). Despite substantial advances in neuroscience in the last decades, the pathogenesis of depression remains poorly understood and there are no biological markers ready to be used for diagnosis (Kapur, Phillips, & Insel, 2012). Thus, the classification of psychiatric disorders and the diagnosis of MDD currently remain descriptive. This likely weakens the outcome of treatment and hampers the development of new treatment options, as will be discussed later.

2.3 AETIOLOGY OF DEPRESSION

Aetiology of MDD is multifactorial, arising from both genetic and environmental factors. It is understood in the diathesis/stress model, which considers separately the influence of vulnerability (diathesis) and exposure to stress (Monroe, Slavich, Torres, & Gotlib, 2007; Willner, Scheel-Kruger, & Belzung, 2013). This means that for an individual with increased vulnerability even milder stress may trigger MDD, whereas an individual with low vulnerability may survive a major stressful life event without falling into clinical depression. Differential-susceptibility theory is related to diathesis/stress model but instead of emphasizing vulnerability to stressing conditions predisposing to maladaptive development and psychopathology, it postulates that neurobiological sensitivity to environmental conditions may also be protective in positive, development-enhancing conditions (Boyce, 2016). Thus, a sensitive child in negative social environment has a high risk for maladaptive development and psychopathology but in positive social environment may show stronger outcome than a more resilient peer.

Vulnerability can arise from genetic or environmental factors. Based on twin studies, heritability of MDD is approximately 30-40% (Kendler, Gatz, Gardner, & Pedersen, 2006b; Sullivan, Neale, & Kendler, 2000). Severe forms of depression seem to have higher heritability whereas in more moderate forms environmental factors play a bigger role (Rusby, Tasker & Cherkas, 2016). The most widely researched candidate gene for MDD is the human serotonin transporter gene, but other candidate genes include serotonin receptor 2A gene, brain-derived neurotrophic factor (BDNF) gene, tryptophane hydroxylase gene, catechol-o-methyltransferase gene, and many others (Levinson, 2006; Lohoff, 2010). However, no gene finding has been consistently replicated and meta-analyses yield mixed results (Lohoff, 2010). Most of the genome-

wide association studies (GWAS) have also not presented clear conclusions about the genetic variants associated with depression (Hek et al., 2013; Lohoff, 2010). However, a recent and thus far the largest GWAS meta-analysis, including over 135 000 cases, found 44 significant gene loci with 30 new regions that had not been described in previous studies (Wray et al., 2018). The genes in these regions included genes with a reported association with presynaptic differentiation and neuroinflammation as well as obesity and body mass index, and multiple genes affecting known targets of antidepressant drugs such as dopaminergic and glutamine neurotransmission and neuronal calcium signalling.

The personality trait of neuroticism, representing a tendency for negative emotionality and emotional reactivity (Jacobs et al., 2011), is one of the strongest risk factors of MDD (Kendler, Gardner, & Prescott, 2006; Kotov, Gamez, Schmidt, & Watson, 2010). It is not independent of genetic factors, but part of the risk of MDD arising from genetic factors is explained by neuroticism, as MDD and neuroticism share almost 50% of the genetic risk factors (Hettema , Neale , Myers , Prescott , & Kendler 2006; Kendler, Gatz, Gardner, & Pedersen, 2006a). Genetic factors also contribute to childhood adversity and low parental warmth, which are known environmental vulnerability factors of depression (Kendler, Gardner, et al., 2006), highlighting the difficulty in disentangling environmental vulnerability from genetic vulnerability (Colodro-Conde et al., 2018).

According to the diathesis/stress model, vulnerability alone is insufficient to cause MDD; a stressor is also needed. Most commonly, in depression the stressors are external events, a major adverse life event or a chronic minor stress, but they can also be internal events such as hormonal change or head injury (Willner et al., 2013). Evidence supporting the diathesis/stress model arises from several studies linking stressful life events to subsequent depression, twin studies linking genetic vulnerability to depression combined with a stressful life event to depression, and studies investigating the influence of cognitive vulnerability to depression on sensitivity to stressful life events (Monroe et al., 2007; Willner et al., 2013). Caspi et al. (2003) reported in their seminal paper, which provided direct evidence for the gene-environment interaction, that the risk for depression was increased in individuals carrying a short (s) allele of the serotonin transporter-linked polymorphic region (5HTTLPR) after experiencing childhood adversity or more recent stressful life events.

Since then, there has been an ongoing debate about this topic, with many studies and meta-analyses replicating the finding and others reporting no significant gene-by-environment interaction (Karg, Burmeister, Shedden, & Sen, 2011; Risch et al., 2009). A recent and the largest collaborative meta-analysis found no evidence of an increasing risk of the 5HTTLPR s allele for depression in individuals exposed to stress (Culverhouse et al., 2017). However, as the genetic risk for MDD arises from multiple risk variants, the studies of genetic stress sensitivity have also moved from a candidate gene approach to a genome-wide approach using a polygenic risk score, calculated as a weighted sum of the number of risk alleles (detected by GWAS studies) carried by an individual (Torkamani, Wineinger, & Topol, 2018), to test for a gene-by-environment interaction. A recent study found a significant interaction of the polygenic risk score and personal stressful life events, directly supporting the diathesis-stress model of depression (Colodro-Conde et al., 2018).

2.4 NEUROBIOLOGY OF DEPRESSION

What are the pathophysiological processes that take place when an individual falls into depression? Although substantial progress in understanding the neurobiology of depression has occurred in the last decades, much remains unresolved.

2.4.1 Monoamines

The monoamine hypothesis of depression originates from the late 1950s, when the first antidepressants were found (Hillhouse & Porter 2015). Iproniazid (the first monoamine oxidase inhibitor) was developed for treatment of tuberculosis but was found to also have antidepressant effect. Imipramine (the first tricyclic antidepressant) was developed as an antipsychotic agent but instead was found to be effective for treatment of severe depression. These compounds were shown to potentiate serotonin or noradrenaline transmission, and thus, depression was postulated to be explained by deficiency in monoamine (serotonin, noradrenaline or dopamine) transmission (Ruhe, Mason, & Schene, 2007). All current drugs licensed for use in treating depression enhance monoamine transmission acutely. However, even though the drugs influence monoamine transmission immediately, the clinical effect takes weeks to achieve. Thus, changes in neurochemistry alone cannot explain the antidepressant action and pathophysiology of depression. This is supported by studies using manipulation of monoamine levels by experimental depletion. Serotonin depletion is

achieved by rapidly lowering the level of tryptophan, an amino acid essential for serotonin formation that cannot be synthesized by the body but must be ingested (so-called acute tryptophan depletion, ATD) (Ruhe et al., 2007). ATD does not cause depression in healthy individuals and causes only a moderate decrease in mood of patients in remission from depression and not currently on antidepressant medication, but consistently causes relapse of depression symptoms in remitted depression patients currently using serotonergic antidepressant medication (Ruhe et al., 2007; Willner et al., 2013). Depletion of noradrenaline has similar effects on patients using noradrenergic antidepressants (Willner et al., 2013). In healthy controls with a family history of depression, monoamine depletion seems to cause a slight decrease in mood (Ruhe et al., 2007). Thus, experimental depletion may reveal a biological vulnerability to depression. Another view is that ATD does not really cause a relapse of depression symptoms, but mimics an abrupt discontinuation of an antidepressant, which often leads to mood effects that are considered to be different from the actual depression symptoms (Ruhe et al., 2007). What seems to be clear is that levels of monoamines in the brain are not direct correlates to mood. However, currently used antidepressants, effective in treatment of depression, enhance monoamine action, suggesting it has some role in the neurobiology of depression, even though enhanced monoamine action *per se* does not seem to be responsible for the clinical effect of antidepressants or the pathophysiology of depression.

Positron emission tomography (PET) imaging studies have also revealed abnormal functioning of serotonin system in depression. However, the evidence do not unambiguously support the association of decreased serotonergic transmission with depression. For example, some studies have found decreased postsynaptic serotonin 1A-receptor binding whereas others report increased receptor binding in both presynaptic and postsynaptic serotonin 1A-receptors. Evidence for serotonin transported binding also remain mixed (Savitz & Drevets, 2013).

2.4.2 Stress and neuroendocrinology

Stress response is a normal, adaptive reaction that has the goal of restoring balance, i.e. homeostasis. This response includes a shift of attention towards the threat, altered reward responses, mild anxiety and dysphoria, activation of the hypothalamic-pituitary-adrenal (HPA) axis, and mild inflammation (Gold, 2015). In depression, the stress

response is thought to be dysregulated, e.g. via increased activation from amygdala and decreased inhibition from hippocampus and subgenual prefrontal cortex (PFC), leading to over activation of HPA-axis (Gold, 2015). This over activation increases noradrenaline release, which promotes global alarm state and further potentiates amygdala activation, and increases glutamate release which may lead to excitotoxicity. Peripherally hypercortisolemia increases insulin resistance and changes blood coagulation and immune systems, possibly predisposing to cardiovascular diseases (Gold, 2015). In animal models, chronic administration of glucocorticoids leads to anhedonia, whereas antagonizing corticotropin-releasing hormone (CRH) signalling has an anxiolytic effect (Krishnan & Nestler, 2010). However, all depressed patients do not have increased cortisol levels (Krishnan & Nestler, 2010; Vreeburg et al., 2009). It has been suggested that dysregulation of the HPA feedback system may play a role particularly in the most severe and psychotic forms of depression (Vreeburg et al., 2009). Reactivity of the HPA axis may also reflect vulnerability to depression (Willner et al., 2013).

2.4.3 Neurogenesis and neuroplasticity

Neurogenesis was for long thought to occur only during embryonic development but is now known to continue also in the adult brain. However, adult neurogenesis only occurs in two specific places which can be seen as remnants of the embryonic proliferation centres, namely in the supraventricular zone and the dentate gyrus of the hippocampus (Urban & Guillemot, 2014). Adult neurogenesis is essential in normal stress response. If neurogenesis is inhibited, return to baseline after glucocorticoid release in response to stress is delayed (Gold, 2015). However, chronic stress and cortisol secretion suppress neurogenesis (Gold, 2015). Particularly unpredictable stress is a powerful inhibitor of neurogenesis in animal models (Willner et al., 2013). Depression is associated with decreased volume of the hippocampus, one of the two specific regions in the brain where adult neurogenesis occurs (Urban & Guillemot, 2014). Repeated depression episodes seem to be associated with a larger volume reduction (Koolschijn, van Haren, Lensvelt-Mulders, Hulshoff Pol, & Kahn, 2009; Videbech & Ravnkilde, 2004). Furthermore, suppressed neurogenesis has been observed post-mortem in elderly depression patients (Willner et al., 2013). The role of decreased neurogenesis in depression remains poorly understood, but it is thought to be involved in impaired ability to introduce new, adaptive cognitions and behaviour to

support coping (Willner et al., 2013). Importantly, however, blockage of hippocampal neurogenesis alone is not enough to produce depressive behaviour in rodents (Krishnan & Nestler, 2008).

Brain-derived neurotrophic factor (BDNF) supports appropriate function of neural networks by promoting neuronal plasticity. Neuronal plasticity includes a variety of adaptive changes in function and structure of the brain in response to internal and external milieu, such as growth or elimination of axonal and dendritic branches, survival or apoptosis of neurons, synaptogenesis and regulation of synaptic strength (Castrén & Hen, 2013). Prolonged, un-controllable stress and hypercortisolemia are associated with decreased levels of BDNF together with depressive phenotype in animals. Decreased BDNF levels as well as synaptic loss in hippocampus and PFC have been observed in depressed individuals (Gold, 2015). Decreased BDNF levels together with neurotoxic effects of glucocorticoids during prolonged exposure to stress may lead to atrophy of dendrites and cell death (Willner et al., 2013), resulting in volume reductions seen in hippocampus and PFC (Koolschijn et al., 2009), and possibly also impaired limbic-cortical connectivity related to depression (Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015).

2.4.4 Inflammation

Inflammation is thought to play a role in the neurobiology of depression. Depression is more prevalent in individuals with illnesses associated with chronic inflammation, such as cardiovascular diseases, type 2 diabetes, or rheumatoid arthritis, than in healthy individuals. Interestingly, approximately one-third of patients treated with recombinant human cytokine interleukin-2 or interferon alpha develop depression. Cytokines are known to influence serotonin intake, decrease expression of serotonin-1A receptors, increase CRH level, and regulate synaptic plasticity (Abdallah, Sanacora, Duman, & Krystal, 2015). On the other hand, CRH increases cytokine production via increased noradrenaline release and via a cortisol-induced increase of visceral fat, which is an active pro-inflammatory tissue (Gold, 2015). A dysregulated stress system, including an over-active HPA axis, cytokines, and oxidative stress, may lead to accelerated cellular ageing (Gold, 2015; Verhoeven et al., 2014). This is supported by the finding of telomere shortening, indicating 7-10 years of accelerated ageing for MDD patients with the most severe and long-lasting symptoms compared with healthy controls

(Verhoeven et al., 2014). Interestingly, this converges with epidemiological findings of about 7-10 years of loss in life expectancy in MDD (Chang et al., 2011; Walker et al., 2015).

2.4.5 Other mechanisms

Chronic stress can up- or downregulate gene expression in the brain via epigenetic changes, i.e. regulating the transcriptional potential of the genes without changing the DNA sequence (Vialou, Feng, Robison, & Nestler, 2013). For example, in mice susceptible to sustained social defeat stress, decreased DNA methylation of the promoter of the CRH gene has been observed together with upregulation of CRH and depressive phenotype (Vialou et al., 2013).

Changes in reward processing are thought to have a role particularly in the pathophysiology of anhedonia, a core characteristic of depression. The activity and volume of the nucleus accumbens, a key region in reward processing, are reduced in depression and there is a negative correlation between nucleus accumbens responses to reward and anhedonia symptoms in depressed patients (Gold, 2015). In animal models, stress increases activity of the nucleus accumbens, thus potentiating reward processing (Nestler & Carlezon, 2006). However, severe stress exposure has been shown to abolish this activation and switch the behavioural response from appetitive to aversive (Lemos et al., 2012).

Recently, the role of glutamate in depression has gained increasing interest. Stress and glucocorticoid administration increase glutamate release. This is normally adaptive, but excessive or prolonged glutamate release may lead to cellular damage, loss of neurogenesis, and decreased plasticity (Gold, 2015; Popoli, Yan, McEwen, & Sanacora, 2012). Ketamine, an antagonist of the glutamate NMDA receptor, has rapid and robust antidepressant and antisuicidal effect in treatment-resistant depression: response rates of 70% after a single intravenous infusion have been reported (Zarate Jr & Machado-Vieira, 2017). Ketamine causes a glutamate surge in the PFC, which seems to activate complex plasticity signalling pathways (Zarate Jr & Machado-Vieira, 2017). This may lead to rapidly increased synaptic plasticity and improved connectivity in the PFC.

2.5 PSYCHOPATHOLOGY OF DEPRESSION

What are the psychopathological processes leading to depression? What kind of changes in information processing may predispose to and maintain depression?

2.5.1 Cognitive model of depression

"Self is worthless, life is pointless, future is hopeless". This is how Aaron Beck, the creator of the cognitive model of depression, encapsulates the triad of biased cognitions of depression. The cognitive model postulates that dysfunctional attitudes of self that arise from early life experiences and are embedded within cognitive structures, *schemas*, fundamentally influence information processing (Beck 2008). Schemas represent cognitive vulnerability to depression and are latent until activated by a stressor (Scher, Ingram, & Segal, 2005). When activated, the schemas bias information processing, e.g. shifting attention towards negative information, and cause mild depressive symptoms. Repeated activation of negative schemas leads to a depressive mode, which can be formulated as a network of cognitive, behavioural, affective, motivational, and physiological schemas. Repeated minor stressing events or a major depressogenic event strengthen and lock the connections of the network of negatively oriented schemas, resulting in production of the various signs and symptoms of depression. The depressive mode takes control of information processing, which becomes automatic and less reactive to positive events of the environment. Attention is shifted towards negative internal experiences, away from the external environment. At the same time, cognitive control is attenuated, disabling coping mechanisms such as reappraisal. When schemas are repeatedly activated, they may become rigid and resilient to change (Crick & Dodge, 1994), compatibly with sensitization seen in recurrent depression (Beck, 2008).

Cognitive vulnerability/biases are linked to neurophysiological changes implicated in the neurobiology of depression. For example, presence of the 5-HTTLPR short allele, representing genetic vulnerability to depression, is associated with both increased amygdala reactivity and negatively biased information processing (e.g. attention, recall, interpretation) (Beck 2008). Beck has suggested that genetic vulnerability leads to repeated negative cognitive processing via increased limbic reactivity, and this may contribute to the formation of maladaptive schemas. Biased appraisal of stress has been linked to increased cortisol response; experimental manipulation appraised as

social defeat evoked an increased cortisol response (Beck 2008). There is also a link between cognitive control of emotion and the HPA axis; successful voluntary downregulation of negative affect is associated with decreased amygdala and increased PFC activity, and with adaptive diurnal rhythm of cortisol secretion (Urry et al., 2006). Thus, cognitive and neurobiological approaches to depression may be not only parallel, but also interactive with each other (Beck, 2008).

2.5.2 Cognitive bias in depression

Abundant empirical studies have demonstrated biased cognitive processes, i.e. preferential processing of negative versus positive material in depression. Strong evidence exists for negatively biased memory; depressed patients remember more negative than positive material (Gaddy & Ingram, 2014; Gotlib & Joormann, 2010). For attentional and perception bias, the empirical findings are more inconsistent. There is a general consensus about altered facial expression recognition in depression (Demenescu, Kortekaas, den Boer, & Aleman, 2010). Some studies have described decreased recognition of subtle happy expressions (Harmer et al., 2009; Surguladze et al., 2004) and a tendency to label neutral expressions as sad (Leppänen, 2006). However, other studies have found no evidence of decreased recognition of particularly happy expression (Anderson et al., 2011; Mikhailova, Vladimirova, Iznak, Tsusulkovskaya, & Sushko, 1996), instead reporting less accurate emotional recognition in general (Anderson et al., 2011; Mikhailova et al., 1996; Surguladze et al., 2004). This generally decreased discrimination of emotions may reflect withdrawal of depressed patients from the emotions of others (Anderson et al., 2011). As discussed later in this section, depressed patients seem to be excessively engaged in their own negative emotions. Interestingly, one recent study found a specific deficit in recognition of disgusted facial expressions only (Douglas, Porter, Knight, & Maruff, 2018).

Most of the studies investigating automatic allocation of attention towards negative stimuli have not provided evidence of biased processing in depression (Gotlib & Joormann, 2010). However, some studies using longer exposure times have demonstrated bias towards negative, particularly sad or self-relevant stimuli (instead of threating stimuli, e.g. fearful facial expression) (Joormann & Gotlib, 2007; Mogg & Bradley, 2005). This has been interpreted to mean that early, automatic orienting of

attention might not be biased in depression. However, during longer exposure, when attention has been shifted to negative material, depressed patients may have difficulties in disengaging from it (Gotlib & Joormann, 2010). This may be related to impairments in inhibitory control observed in depression. For example, depressed patients have a reduced ability to inhibit negative material (e.g. negative words or sad faces) in a so-called negative affective priming task (Gotlib & Joormann, 2010; Joormann & Gotlib, 2010). Furthermore, impaired inhibition of negative material is associated with increased rumination and inability to use adaptive emotional regulation strategies such as reappraisal (Joormann & Gotlib, 2010). Depressed patients also have difficulties in removing irrelevant negative material from their working memory (Gotlib & Joormann, 2010).

Taken together, depressed patients seem to have difficulties in shifting attention away from negative material and using appropriate regulation strategies to enable recovery from negative affect. Instead, they keep processing negative, particularly self-related, material. Indeed, depression is also associated with increased self-focus and negatively biased self-referential processing, i.e. excessive attribution of negative emotions to self (Gaddy & Ingram, 2014; Northoff, 2007). Self-related cognitive bias is a defining characteristic of depression, as it is included in the diagnostic criteria of MDD (i.e. “feelings of worthlessness or excessive or inappropriate guilt”). The importance of biased self-referential processing in developing and maintaining MDD is supported by empirical evidence (Wisco, 2009), including a meta-analysis that found negative self-referential cognitions to predict current and future depression, negative self-beliefs and interpretation being the strongest predictors (Phillips, Hine, & Thorsteinsson, 2010).

2.6 NEURAL UNDERPINNINGS OF THE COGNITIVE BIAS OF DEPRESSION

Functional magnetic resonance imaging (fMRI) offers a means to investigate neural impairments behind biased emotional processing in depression. How is the function of the emotion circuits of the brain altered in depression?

2.6.1 Regional perspective

Several studies have shown that depressed patients have increased amygdala reactivity to negative facial expressions (Fu, Williams, Cleare, Brammer, Walsh, Kim, et al., 2004; Godlewska, Norbury, Selvaraj, Cowen, & Harmer, 2012; Ruhe, Booij,

Veltman, Michel, & Schene, 2012; Sheline et al., 2001b; Stuhrmann, Suslow, & Dannlowski, 2011; Surguladze et al., 2005) as well as to other aversive visual stimuli (Siegle, Steinhauer, Thase, Stenger, & Carter, 2002) relative to healthy subjects, although not all studies have yielded the same result (Gotlib et al., 2005; Keedwell, Andrew, Williams, Brammer, & Phillips, 2005). Correspondingly, depressed patients have been reported to have decreased amygdala reactivity to positive facial expressions (Stuhrmann et al., 2013; Victor, Furey, Fromm, Ohman, & Drevets, 2010) as well as decreased striatal responses to reward-related processing (Zhang, Chang, Guo, Zhang, & Wang, 2013). However, inconsistencies remain: two meta-analyses of brain activity alterations in depression found increased amygdala responses to negative stimuli (Fitzgerald, Laird, Maller, & Daskalakis, 2008; Hamilton et al., 2012), whereas two meta-analyses found no evidence of consistently increased amygdala reactivity (Diener et al., 2012; Muller et al., 2017). The inconsistencies may be related to a variety of emotional and cognitive tasks used in the studies, in addition to other sources of heterogeneity (Muller et al., 2017). In a systematic review, including only studies using facial expression tasks, half of the studies found altered amygdala reactivity, predominantly showing hyperactivity to negative and hypoactivity to positive facial expressions (Stuhrmann et al., 2011). Abnormal amygdala activity may reflect altered salience and perception, and (together with hippocampus) also memory, of emotional material (Disner, Beevers, Haigh, & Beck, 2011). Amygdala, together with ventromedial prefrontal cortex (VMPFC) and subgenual anterior cingulate cortex (sgACC), projects to brainstem, basal forebrain nuclei and hypothalamus (Duncan & Barrett, 2007), controlling for visceromotor responses to emotional stimuli. Thus amygdala may also have a role in endocrine, vegetative and psychomotor disturbances seen in depression, such as increased CRH-release (via hypothalamus), autonomic over-reactivity, arousal and insomnia (via locus coeruleus and basal forebrain), gastrointestinal symptoms (via vagus nerve) and decreased reward-directed behavior (via nucleus accumbens) (Drevets, 2001).

The thalamus, a brain region connected to amygdala, also shows increased reactivity to negative material (Anand, Li, Wang, Wu, Gao, Bukhari, et al., 2005; Fu, Williams, Cleare, Brammer, Walsh, Kim, et al., 2004) as well as increased baseline (resting state) activity (Hamilton et al., 2012) in depressed patients. The thalamus is a known “hub of information”, relaying sensory signals from the environment and modulating

cortico-cortical information flow. It has been suggested that increased activity of the thalamus in depression leads to increased relay of negative emotional information to the amygdala, which further projects via sgACC to higher cortical regions, resulting in an increased awareness of and responses to negative information (Disner et al., 2011). The dorsal striatum (caudatum and putamen) plays a role in cortico-thalamic pathways, receiving projections from the cortex, projecting further to the thalamus, and back again to the cortex. The dorsal striatum is coupled with both motor (dorsal putamen) and cognitive (putamen and caudate) functional networks (Choi, Yeo, & Buckner, 2012), thus contributing to processing of and response to emotional information. Increased responses of the dorsal striatum and globus pallidum to negative emotional stimuli and decreased responses to positive emotional stimuli have been reported in depressed patients (Diener et al., 2012; Fu, Williams, Cleare, Brammer, Walsh, Kim, et al., 2004; Surguladze et al., 2005), although one meta-analysis found decreased caudate responses to negative stimuli (Hamilton et al., 2012). The insula is interconnected to the thalamus and amygdala and has a role in tracking salience of internal and external events and in awareness of interoceptive states (Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004; Hamilton et al., 2012). Increased reactivity of the insula to negative emotional information has been reported in several studies, including a meta-analysis (Fu, Williams, Cleare, Brammer, Walsh, Kim, et al., 2004; Godlewska et al., 2012; Hamilton et al., 2012), but another meta-analysis reported decreased responses (Diener et al., 2012). Reduced insula responses have been argued to reflect anhedonia related to depression as well as impaired cognitive-emotional integration (Diener et al., 2012), whereas increased responses have been interpreted to mirror increased salience to negative material (Hamilton et al., 2012).

Alterations in the PFC and anterior cingulate cortex (ACC) activity seem to have a crucial role in cognitive and emotional impairments associated with depression. Decreased dorsolateral prefrontal cortex (DLPFC) activity in response to emotional (particularly negative) or cognitive tasks is a frequently reported finding in depressed patients (Beevers, Clasen, Stice, & Schnyer, 2010; Disner et al., 2011; Hamilton et al., 2012; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007), although increased responses have been reported as well (Fitzgerald et al., 2006; Keedwell et al., 2005). Decreased activity of the DLPFC (and VLPFC) is commonly related to impaired cognitive control of overactive limbic responses, such as directing and shifting

attention, inhibiting irrelevant material, and reappraising and contextualizing emotional information (Beevers et al., 2010; Disner et al., 2011; Hamilton et al., 2012). Thus, increased bottom-up signalling from the thalamus and amygdala via sgACC, together with decreased top-down control from the DLPFC via dorsal ACC, has been suggested to result in biased processing of negative stimuli (Disner et al., 2011).

Medial PFC (MPFC), tightly linked to the ACC, has conventionally been thought to mediate inhibitory control from the lateral PFC to limbic regions (Duncan & Barrett, 2007). In addition, the anterior/medial frontal regions (MPFC, orbitofrontal cortex (OFC), and ACC) seem to have an important role in integrating exteroceptive and interoceptive information to guide appropriate motor and visceral responses, thus fundamentally participating in emotion generation and regulation (Duncan & Barrett, 2007; Phillips, Ladouceur, & Drevets, 2008; Rive et al., 2013). This integrative role is enabled by the widespread connections of these regions to the thalamus, striatum and limbic structures, insula and sensory cortices (particularly from the OFC), and hypothalamus and brainstem (particularly from the VMPFC and sgACC) (Duncan & Barrett, 2007; Ongur & Price, 2000). Depressed patients have mostly increased MPFC and ACC responses to negative emotional stimuli and in emotional regulation tasks, involving particularly automatic regulation strategies (Grimm, Boesiger, et al., 2009; Hamilton et al., 2012; Rive et al., 2013; Rosenblau et al., 2012; Sheline et al., 2009), and this has been suggested to mirror increased salience to negative material or increased need for automatic emotional regulation (Hamilton et al., 2012; Rive et al., 2013).

These anterior cortical midline structures (CMS), however, together with the posterior cingulate cortex (PCC) and precuneus, also have a key role in processing self-referential material (Northoff et al., 2006). The ventral ACC (together with the amygdala) has been shown to activate particularly during self-referential processing of negative emotional information (Yoshimura et al., 2009). Increased responses of the MPFC and ACC to rumination task (Cooney, Joormann, Eugène, Dennis, & Gotlib, 2010), negative self-referential words (Yoshimura et al., 2010), or negative and positive self-referential words (Lemogne et al., 2009) have been reported in depressed patients – although some studies describe decreased responses (Davidson, Irwin, Anderle, & Kalin, 2003; Diener et al., 2012; Grimm, Ernst, et al., 2009) – suggesting that abnormal functioning of these regions could be behind the increased self-focus associated with

depression. An imbalance of subcortical signalling from the amygdala and ventral striatum, together with abnormal functioning of the anterior CMS and reduced cognitive control from the lateral PFC, has been proposed as a theoretical model to explain the negative bias in self-processing of depressed patients (Northoff, 2007) (Figure 1).

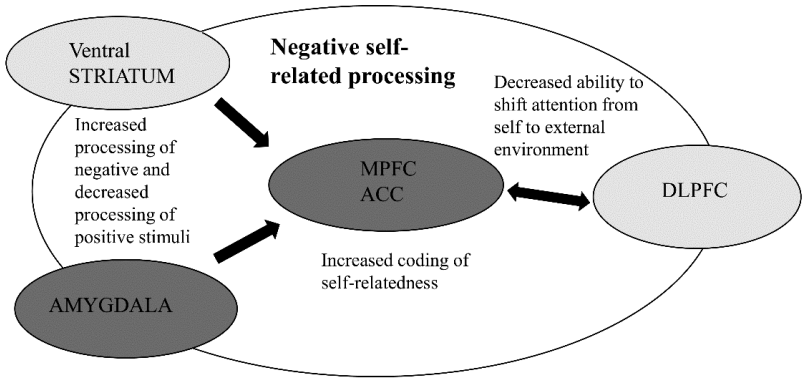

Figure 1. *A schematic visualization of negatively biased self-referential processing in depression (modulated from Northoff, 2007). Light gray represents decreased activity and dark grey increased activity. Self-relatedness is excessively tagged to sensory information in the MPFC/ACC. Biased processing of emotional stimuli in the limbic regions leads to increased attribution of negative emotions to self. Decreased cognitive control from the DLPFC and abnormal emotional-cognitive interaction lead to increased self-focus and difficulties in focusing on the external environment.*

To summarize, even though some fairly consistent findings have emerged, such as increased limbic and decreased lateral PFC responses to negative stimuli, many inconsistencies remain. Accordingly, a recent meta-analysis could not find any brain region with consistently altered activity in depression (Muller et al., 2017). This is likely at least partly due to heterogeneity of the tasks and patient populations (e.g. medicated/non-medicated, heterogeneity of illness manifestations), but may also reflect the complicated nature of the neural impairments underlying the depression. It is plausible that hyperactivation or hypoactivation of a single brain region in depression depends on the task and the functional network it is involved in at that moment.

2.6.2 Network perspective

As it seems evident that abnormal function of any single brain region cannot explain the wide spectrum of symptoms of depression, recently the neurobiological research

on depression has increasingly shifted towards investigation of large-scale functional brain networks. Functional brain networks implicated in depression include the default mode network (DMN), which activates during rest and is involved particularly in internally oriented attention (Raichle, 2015), the (dorsal) attention network involved in control of externally oriented attention (Corbetta & Shulman, 2002), the fronto-parietal cognitive control network involved in top-down regulation of attention and emotion (Vincent, Kahn, Snyder, Raichle, & Buckner, 2008), the affective or limbic network involved in emotional processing (sometimes divided into positive/reward and negative/threat networks), and the salience network (overlapping with the affective network, extending to ventral attention regions such as the fronto-insular cortex, dorsal ACC, and temporal pole) (Seeley et al., 2007; Williams, 2017; Yeo et al., 2011) (Figure 2).

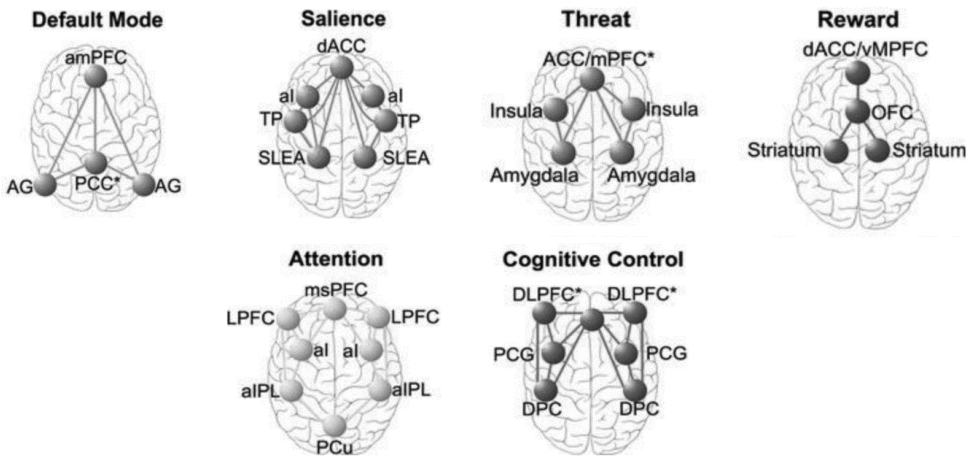

Figure 2. *Functional networks implicated in depression. amPFC=anterior medial prefrontal cortex, AG=angular gyrus, aI=anterior insula, aIPL=anterior inferior parietal lobule, DLPFC=dorsolateral prefrontal cortex+anterior prefrontal cortex+inferior frontal cortex, DPC=dorsal parietal cortex , LPFC=lateral prefrontal cortex, msPFC=medial superior prefrontal cortex, PCG=precentral gyrus, , PCu=precuneus, SLEA=sublenticular extended amygdala. With permission of Williams et al. 2017. Depression and Anxiety. Jan;34(1):9-24.*

Resting-state fMRI studies have found abnormal connectivity particularly in the DMN in depressed patients. Increased connectivity of the DMN (Greicius et al., 2007; Kaiser

et al., 2015) has been reported, but opposite findings exist as well (Wang, Hermens, Hickie, & Lagopoulos, 2012). Specifically, Kaiser et al. (2015) found in their meta-analysis of resting-state studies depression to be associated with increased connectivity between the cognitive control network and the DMN and decreased connectivity between the cognitive control network and the attention network, plausibly reflecting a bias towards increased ruminative, internal attention and reduced attention to the external environment. Indeed, dominance of the DMN over the attention network is associated with increased rumination in depressed patients (Hamilton et al., 2011). A smaller meta-analysis of six studies assessing functional connectivity in the DMN of depressed patients found consistently increased connectivity in this network, and concluded that increased connectivity of the DMN and the sgPFC is associated with rumination (Hamilton, Farmer, Fogelman, & Gotlib, 2015). Guo et al. (2016) noted that while healthy subjects showed a switch from high to low connectivity in the DMN between resting-state and natural viewing of film conditions, in depressed patients (with melancholic features) this switch was minimal, implicating attenuated reactivity of the DMN. They also found diminished connectivity of the attention network regions in depressed patients during the free viewing condition, particularly during the positive film clip in the DMPFC.

Another somewhat consistent finding in depressed patients is decreased connectivity between the limbic regions (affective network) and the MPFC/ACC, mediating the top-down control of the cognitive control network, in rest or during negative emotional tasks, plausibly reflecting impaired emotional regulation (Anand, Li, Wang, Wu, Gao, Bukhari, et al., 2005; Carballedo et al., 2011; Kaiser et al., 2015; Matthews, Strigo, Simmons, Yang, & Paulus, 2008; Wang et al., 2012). The meta-analysis of Kaiser et al. (2015) found decreased connectivity of the cognitive control network in depressed patients. The MPFC may have a key role in abnormal functioning of the core brain networks in depression. Sheline et al. (2010) reported that all three major brain networks implicated in depression – the DMN, cognitive control, and affective network – showed increased connectivity to the same region of the DMPFC. The same region was found to have increased local connectivity (regional homogeneity) in depressed patients in the meta-analysis of Iwabuchi et al. (2015).

In conclusion, depression is associated with dysfunctions in the large-scale brain networks involved in processing of emotion and salience, internally and externally

focused attention, and higher order regulation of these functions. Although inconsistencies remain, abundant evidence exists for limbic over-responsiveness to negative material (and under-responsiveness to positive material) with impaired capacity for cognitive control, together with elevated functioning of the networks involved in internally focused attention and attenuated functioning of the networks involved in externally focused attention. Recently, it has been suggested that information about the functional networks could be used to group patients with depressive and anxiety symptoms into neural circuit biotypes outside the descriptive diagnostic categories of mood and anxiety disorders (e.g. “rumination type” defined by hyperconnectivity of the DMN, or “threat dysregulation type” defined by abnormal affective network connectivity) to better direct treatment choice and development of new treatments (Williams, 2017).

2.7 TREATMENT OF DEPRESSION

National and international guidelines recommend antidepressant medication, normally selective serotonin reuptake inhibitors (SSRIs), as a first-line or second-line treatment for most patients with MDD. Another first-line option is psychotherapy or a combination of antidepressant medication and psychotherapy. Other interventions, usually third-line options and reserved for treatment-resistant depression, include combination pharmacotherapy, electroconvulsive therapy, transcranial magnetic stimulation, and neuromodulation therapies (vagal nerve stimulation, deep brain stimulation) (Bauer et al., 2007; Depression: Current Care Guidelines, 2016, www.kaypahoito.fi ; The National Institute of Health and Care Excellence (NICE) guideline: https://www.nice.org.uk/guidance/cg90).

All currently licensed antidepressants enhance monoamine transmission. The first antidepressants, so called tricyclic antidepressants such as amitriptyline and clomipramine, are at least equally effective for severe depression as SSRIs, but less well tolerated due to their side-effect profile and cardiovascular toxicity (Anderson, 2000). Thus, they are usually not a first-line option. The newer antidepressants are traditionally grouped into SSRIs, selective noradrenaline reuptake inhibitors (reboxetine), selective serotonin and noradrenaline reuptake inhibitors (SNRIs; duloxetine and venlafaxine), and others such as mirtazapine (alpha2-adrenoceptor

antagonist), bupropion (inhibiting noradrenaline and dopamine reuptake), and agomelatine (melatonin agonist) (Bauer et al., 2007). Antidepressants have been shown to be effective compared with placebo in randomized placebo-controlled trials and meta-analysis (Cipriani et al., 2018; Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008; Undurraga & Baldessarini, 2012). Typically 50-60% of patients in the studies respond to antidepressant treatment (Stahl, Entsuah, & Rudolph, 2002; Trivedi et al., 2006; Undurraga & Baldessarini, 2012). Different antidepressants are generally considered equally effective and treatment guidelines typically recommend SSRIs as a first-line option due to their favourable risk-benefit ratio (Depression: Current Care Guidelines, 2016, www.kaypahoito.fi ; The NICE guideline: https://www.nice.org.uk/guidance/cg90). However, some differences in efficacy between antidepressants have been more recently found in large network meta-analyses, suggesting superior efficacy of agomelatine, amitriptyline, mirtazapine, escitalopram, venlafaxine, paroxetine, and vortioxetine (vs. poorer efficacy for fluoxetine, fluvoxamine, reboxetine, and trazodone), and particularly good acceptability of agomelatine, citalopram, escitalopram, fluoxetine, sertraline, and vortioxetine (vs. poorer acceptability for amitriptyline, clomipramine, duloxetine, fluvoxamine, reboxetine, trazodone, and venlafaxine) (Cipriani et al., 2018).

2.7.1 Antidepressants: mechanism of action

SSRIs enhance serotonin transmission by blocking serotonin reuptake into presynaptic serotonergic neurons via inhibition of the serotonin transporter. SNRIs inhibit both serotonin and noradrenaline reuptake. Mirtazapine does not have effect on monoamine reuptake, but it blocks alfa2 –autoreceptors and thus enhances noradrenaline release in locus coeruleus and cortex, and serotonin release in cortex. Additionally, increased noradrenaline release in the brainstem stimulates more serotonin release in cortex via alfa 1 –receptors of serotonin neurons. Mirtazapine is also an antagonist of 5HT2A- and 5HT2C –receptors, further increasing noradrenalin and dopamine release in cortical regions. (Stahl, 2013) A newer antidepressant vortioxetine blocks several subtypes of serotonin receptors (Harmer et al., 2017).

There is a well-known delay between the rapid changes in neurotransmission, occurring immediately after antidepressant administration, and the clinical effect typically emerging several weeks later. It is believed that acute increases in

neurotransmitter levels are followed by adaptive changes, explaining this delay in clinical action (Harmer et al., 2017). The classic neurochemical theory suggests that desensitization of serotonin-1A autoreceptors is the key adaptive change. These autoreceptors normally inhibit serotonin release, but as repeated SSRI treatment decreases their sensitivity, serotonin availability in the synapses consequently increases (Stahl, 2013). More recently research has proceeded from neurotransmitters to post-synaptic mechanisms following the initial increase in monoamine concentration, with focus on the role of neuroplasticity and neurogenesis in antidepressant action (Harmer et al., 2017). As synaptic concentration of monoamines increases, they bind to G-protein coupled receptors, triggering changes in intracellular second messengers and protein kinases. This leads to increased expression of CREB (cAMP response element-binding), which then eventually enhances expression of BDNF, resulting in increased neurogenesis and neuroplasticity (Willner et al., 2013). Chronic, but not acute, use of an antidepressant increases expression of BDNF and its receptor, as well as hippocampal neurogenesis and synaptic plasticity, in rodents. These changes are associated with behavioural responses to antidepressants (Harmer et al., 2017; Willner et al., 2013). Furthermore, in mice with impairment in the BDNF receptor, the behavioural responses to antidepressants as well as their effects on cell survival and proliferation are suppressed.

2.7.2 From molecular-level to system-level actions

How do these adaptive changes at the molecular level translate into system-level changes, i.e. changes in functioning of brain circuits, cognitive processes, subjective experiences, and ultimately depressive symptoms? This question remains mainly unresolved. Cognitive behavioural therapy targets the biased cognitions and maladaptive beliefs maintaining depression, and thus, among psychological approaches in studying depression, processing of emotional information has long been a core focus. Biological approaches in studying depression and antidepressant action instead have mostly focused on the molecular level, and the changes in emotional processing have been thought to be a result of recovery, occurring after improved mood (Harmer et al., 2017). However, recently, the effects of antidepressants on emotional processing at both behavioural and neural levels have received more attention, as Harmer et al. showed that a single dose of reboxetine improved processing of positive emotional stimuli in healthy volunteers and depressed patients

(Harmer, Hill, Taylor, Cowen, & Goodwin, 2003; Harmer et al., 2009). These findings evoked a cognitive neuropsychological theory of antidepressant action, postulating that an early shift towards positive material in information processing may be essential for antidepressants' mechanism of action, rather than a consequence of improved mood (Harmer et al., 2017).

2.7.3 Towards predictive markers

Understanding the mechanism of action of antidepressants is essential for developing new treatment interventions. Also, and importantly, it may help to identify biological or neuropsychological markers to predict treatment response. There is currently very limited evidence to guide treatment choice based on individual characteristics of the patient or subtype of depression. The choice between different antidepressants or between antidepressants and other treatment options is typically made considering the medical risk factors of the patient (such as somatic illnesses and other medication), availability of treatments, and wishes and expectations of the patient (Depression: Current Care Guidelines, 2016, www.kaypahoito.fi ; NICE guideline: https://www.nice.org.uk/guidance/cg90). No clinically useful predictive markers exist to direct treatment choice. As discussed before, since the pathophysiology of depression is largely unknown, there are also no diagnostic tests for depression, but instead the diagnosis is made based on common descriptive features. This means that a very heterogeneous group of patients, likely with different pathophysiological processes underlying their symptoms, is treated with the same intervention. Diagnosis based on the known pathophysiology guiding the treatment is expected to improve treatment outcome, as has been seen in, for instance, infectious diseases, heart diseases, and cancer (Cuthbert & Insel, 2013). However, mostly because depression is a heterogeneous syndrome with abnormal functioning in widespread brain circuits instead of discrete brain regions, its pathophysiology is not likely to be rapidly resolved. Instead, efforts could be targeted to investigate possible biological or neuropsychological markers guiding the treatment choice within and even across the heterogeneous diagnostic categories. Other fields of medicine already use the "stratified medicine" or "precision medicine" approach, i.e. stratifying broad illness groups into treatment-relevant subgroups based on a biological marker, to better target treatments. For example, in oncology the treatment can be successfully targeted based on overexpression of human epidermal growth factor 2 in the cancer tissue not only in

breast cancer but across several cancer types (Kapur et al., 2012). Promising results exist to support the altered brain responses to emotional processing, and their early changes during antidepressant treatment, as possible predictive markers in depression.

2.8 EFFECT OF ANTIDEPRESSANTS ON EMOTIONAL PROCESSING

2.8.1 Behavioural level

2.8.1.1 Facial expression recognition

Harmer et al. (2003) first found that healthy volunteers recognized ambiguous happy facial expressions more accurately only 2 h after a single dose of noradrenergic antidepressant reboxetine compared with a placebo. Importantly, this was observed without any change in subjective mood and affective state, or in processing of non-emotional information.

A single dose of SSRI citalopram has shown a similar improving effect on happy facial expression recognition in many (Harmer, Bhagwagar, et al., 2003; Murphy, Norbury, O'Sullivan, Cowen, & Harmer, 2009), but not all studies (Bhagwagar, Cowen, Goodwin, & Harmer, 2004; Browning, Reid, Cowen, Goodwin, & Harmer, 2007). The SNRI duloxetine also acutely increases recognition of happy facial expressions (Harmer, Heinzen, O'Sullivan, Ayres, & Cowen, 2008), whereas mirtazapine had no impact on recognition of happiness (Arnone, Horder, Cowen, & Harmer, 2009). A 14-day administration of duloxetine also had no influence on recognition of happiness, but did decrease recognition of subtly sad facial expression (Bamford et al., 2015). Agomelatine for 7 days decreased recognition of sad facial expressions and also increased misclassification of facial expressions as neutral as well as marginally decreased misclassification of facial expressions as sadness (Harmer et al., 2011). Citalopram for 7 days had no effects on recognition of happy faces, but the citalopram group seemed to be more prone to misclassify negative emotions as happiness (Harmer, Shelley, Cowen, & Goodwin, 2004).

A single dose of citalopram has been also found to increase recognition of fear (Bhagwagar et al., 2004; Browning et al., 2007; Harmer, Bhagwagar, et al., 2003), although one study was not able to replicate the finding (Murphy, Norbury, et al., 2009).

Reboxetine had no effect on fear recognition (Harmer, Hill, et al., 2003), whereas mirtazapine decreased recognition of fearful faces (Arnone et al., 2009). Interestingly, a 7-day administration of either citalopram or reboxetine also decreased fear recognition (Harmer et al., 2004). An acute increasing and later decreasing effect of citalopram on fear recognition may be related to the increased anxiety seen in animal studies and in some patients at treatment initiation, followed by an anxiolytic effect (Handley, 1995; Harmer & Cowen, 2013). Accordingly, an acute decreasing effect of mirtazapine on fear recognition may be related to its early anxiolytic effect (Fawcett & Barkin, 1998).

Only one study so far has investigated the very early effects of antidepressants on facial expression recognition in depressed patients. Harmer et al. (2009) found that depressed patients recognized happiness less accurately than the healthy comparison group, but a single dose of reboxetine 4 mg given 3 h prior to testing abolished this negative bias. When considering only the depressed subjects, the drug group recognized significantly more accurately happiness than the placebo group. Tranter et al. (2009) found in an open-label study that a 2-week administration of citalopram or reboxetine improved the recognition accuracy of happiness, disgust, and surprise in depressed patients. Importantly, increased recognition accuracy of happy faces correlated with clinical improvement after 6 weeks of treatment. Another study with elderly depression patients further found that a one-week treatment with citalopram increased recognition of ambiguous happy facial expressions, but this change only marginally predicted clinical improvement after 8 weeks of treatment (Shiroma, Thuras, Johns, & Lim, 2014). Interestingly, when perceived social support at baseline was added to the regression model, the early change in happy facial expression recognition and social support became significant predictors of both response and remission.

Taken together, even though the results are partly mixed, there is some evidence that both serotonergic and noradrenergic antidepressants acutely increase recognition of happy facial expressions, i.e. potentiate the perception of positive social cues. After repeated administration, this effect may generalize to a broader positive bias, manifested as decreased recognition of sadness or increased misclassification of negative emotions as happiness. The three studies of depressed patients support the capacity of antidepressants to potentiate a positive bias and suggest that it may serve as a possible predictive marker. Antidepressants have been sometimes reported to

cause decreased experience of positive emotions, emotional “blunting” and emotional detachment (Price, Cole, & Goodwin, 2009). Recently antidepressant use was linked to difficulty in identifying feelings (Kajanoja, Scheinin, Karukivi, Karlsson & Karlsson, 2018). This finding seems contradictory to increased recognition of positive emotions. However, decreased awereness of emotions associated with antidepressant use may not be a side effect of medication but could instead be related to residual symptoms of depression or some characteristic differences between the users and non-users of antidepressants.

2.8.1.2 Attention

A single dose of citalopram increased attention to positive words in the dot probe task; the reaction time decreased when the probe replaced a positive rather than a neutral word (Browning et al., 2007). One-week administration of citalopram decreased attention to fearful faces (Murphy, Yiend, Lester, Cowen, & Harmer, 2009). Reboxetine (Harmer et al., 2004) or agomelatine (Harmer et al., 2011) for one week had no effect on the reaction times in the attentional dot probe task. These results suggest, consistently with the changes in facial expression recognition, an increased positive bias after a single dose of citalopram and decreased fear-related processing after repeated administration. Also in emotion-potentiated startle response studies, citalopram acutely increases fear-potentiated startle responses (Grillon, Levenson, & Pine, 2007), and decreases startle responses related to fearful or negative pictures after repeated dosing (Grillon, Chavis, Covington, & Pine, 2009; Harmer et al., 2004). A single dose of mirtazapine, on the other hand, decreased emotion-potentiated startle responses across emotion categories, similarly to the well-known anxiolytic drug diazepam (Arnone et al., 2009; Murphy, Downham, Cowen, & Harmer, 2008).

2.8.1.3 Emotional categorization and memory

In the emotional categorization task, a subject is asked to categorize extremely positive or negative personality characteristics as quickly as possible. The judgement is self-referring, as a subject is asked specifically to imagine overhearing someone describing her/him with the characteristic shown and to categorize the word accordingly. In the recall memory task, a subject is asked to recall as many words as possible from the previous task. In the recognition memory task, a subject is shown the same words as

well as an equal number of new positive and negative characteristics, and the task is to recognize the words shown previously from the distractors.

A single dose of citalopram had no effect on emotional categorization and memory (Browning et al., 2007), whereas a single dose of reboxetine increased the speed of categorization of positive words and increased the number of recalled positive words compared with negative ones (Harmer, Hill, et al., 2003). A single dose of duloxetine was found to increase the number of falsely recalled positive words, thus increasing positive bias (Harmer et al., 2008), and mirtazapine was found to increase the number of correctly recalled positive words (Arnone et al., 2009). A 7-day administration of reboxetine increased categorization speed of positive words, whereas the effect of citalopram did not reach statistical significance (Harmer et al., 2004). However, both reboxetine and citalopram, after one week, increased the number of recalled positive words. Harmer et al. (2009) found that depressed patients were significantly slower than healthy controls in categorizing positive words, but this negative bias was abolished after a single dose of reboxetine. One study showed emotional pictures to depressed patients and instructed them to categorize the pictures as either self-related or not (self condition), or as positive or negative (general condition) (Delaveau et al., 2016). They found a one-week administration of agomelatine to decrease response times to positive pictures only in the self condition and when the picture was categorized as self-related.

The capacity of antidepressants to increase speed of categorizing positive self-referential material in both healthy subjects and depressed patients suggests a shift towards positive self-referential processing, i.e. normalization of the negative bias associated with depression. Results of the memory task suggest that noradrenergic antidepressants (reboxetine, duloxetine, and mirtazapine) may have a rapid enhancing effect on emotional memory, whereas serotonergic citalopram does not.

2.8.2 Neural level

2.8.2.1 Healthy volunteers

A single dose of citalopram has consistently been shown to decrease amygdala responses to fearful faces (Anderson et al., 2007; Del-Ben et al., 2005; Grady et al., 2013; Murphy, Norbury, et al., 2009), although one study found increased amygdala responses (Bigos et al., 2008). The decreasing effect has been seen mostly in the right

amygdala. Other brain regions showing decreased responses to fearful faces include the orbitofrontal cortex (OFC) (Anderson et al., 2007; Del-Ben et al., 2005), striatum (Anderson et al., 2007; Grady et al., 2013), and fusiform cortex (Grady et al., 2013), although increased activity (in response to expressions of fear, anger, and disgust) in the fusiform cortex has been observed as well (Del-Ben et al., 2005). A single dose of citalopram has also been found to increase responses of the lateral and medial PFC to anticipation of negative stimuli (Brühl, Kaffenberger, & Herwig, 2009).

A single dose of escitalopram decreased activity of the left amygdala and increased activity of the right inferior frontal gyrus (IFG) during reappraisal of negative stimuli (Outhred et al., 2015). The same group also reported that a single dose of escitalopram increased amygdala responses and decreased IFG responses to positive images, decreased amygdala responses and increased IFG responses to negative images, and decreased IFG responses to neutral images in a sample of healthy female volunteers (Outhred et al., 2014). The authors speculated that decreased IFG responses to neutral stimuli may reflect decreased negative reappraisal, and thus, decreased negative bias.

A sub-chronic administration of citalopram (7 to 10 days) also decreases amygdala responses to fearful (Harmer, Mackay, Reid, Cowen, & Goodwin, 2006) or emotional (including fear, anger, disgust, and surprise) (Windischberger et al., 2010) faces. However, one study found increased amygdala responses to happy faces, but no effect on neural responses to fear (Norbury, Mackay, Cowen, Goodwin, & Harmer, 2007). Further, McCabe et al. (2010) found a 7-day administration of citalopram to decrease lateral OFC responses to aversive stimuli but also decrease medial OFC and ventral striatal responses to rewarding stimuli. A sub-chronic administration (7 to 14 days) of escitalopram has been shown to decrease responses of the amygdala, insula, and medial frontal gyrus to fearful faces (Arce, Simmons, Lovero, Stein, & Paulus, 2008; Maron et al., 2015; Windischberger et al., 2010). Two of these studies found no effect of escitalopram on responses to happy faces, and one did not specify the emotions. A 3-week administration of escitalopram decreased responses of the insula and ACC to anticipated negative stimuli (Simmons, Arce, Lovero, Stein, & Paulus, 2009).

A single dose of reboxetine was found to increase right amygdala responses to fearful faces (Onur et al., 2009), whereas 7 days of reboxetine decreased right amygdala

responses to fearful faces and increased responses of the fusiform cortex to happy faces (Norbury et al., 2007). Another study found a single dose of reboxetine to have no effect on amygdala responses to fearful or happy faces (Kukolja et al., 2008). Similar to citalopram, a single dose of reboxetine increased responses of the medial and lateral PFC to anticipation of a negative stimulus (Brühl et al., 2009). A one-week administration also increased medial orbitofrontal responses to rewarding stimuli and decreased lateral orbitofrontal responses to aversive stimuli in another study (McCabe et al., 2010).

Fewer studies have investigated the effect of other antidepressants on neural responses to emotional cues in healthy volunteers. A single dose of fluvoxamine decreased responses of the left amygdala and OFC, right putamen and insula, and bilateral hippocampus, but increased responses of the parietal and temporal cortices to unpleasant pictures (Takahashi et al., 2005). A single dose of mirtazapine decreased right amygdala and left fronto-striatal responses to fearful versus happy faces (Rawlings, Norbury, Cowen, & Harmer, 2010) and increased parietal cortical responses to rewarding stimuli in another study (Vollm et al., 2006). Two weeks of duloxetine decreased responses of the amygdala, insula, thalamus, and ventral ACC to fearful and angry faces (van Marle, Tendolkar, Urner, Verkes, Fernandez, et al., 2011); happy faces were not included. One study found duloxetine after 2 weeks' administration to increase reward-related processing in the ventral striatum (Ossewaarde et al., 2011), whereas another study reported increased amygdala responses during positive memory retrieval (Tendolkar, van Wingen, Urner, Jan Verkes, & Fernández, 2011).

Norbury et al. (2008) assessed the effect of a one-week administration of reboxetine on neural responses to a self-referential processing task. They found reboxetine to increase responses to positive relative to negative self-referential adjectives in the left precuneus and the right inferior frontal gyrus, and to decrease responses of the left precuneus, middle cingulate cortex (MCC), and medial frontal gyrus during the subsequent recognition of positive versus negative words. However, a single dose of reboxetine had no effect on categorization of self-referential adjectives, but decreased neural responses during retrieval of positive words in the subsequent memory test in the similar fronto-parietal regions, as did repeated dosing (Miskowiak et al., 2007). Also

a 3-week administration of escitalopram was found to decreases neural responses in the precuneus/PCC to self-referential words (Matthews et al., 2010).

2.8.2.2 Depressed patients

Most of the studies of depressed patients have used repeated administration of antidepressants, usually several weeks. Interpretation of the results from these studies is complex because of the confounding effect of improved mood.

As in the studies of healthy volunteers, long-term antidepressant treatment in depressed patients has been found to decrease amygdala responses to negative stimuli (e.g. decreased responses of the left amygdala after sertraline, citalopram, and fluoxetine treatment and decreased responses of the right amygdala after bupropion treatment (Anand, Li, Wang, Gardner, & Lowe, 2007; Arnone et al., 2012; Fu, Williams, Cleare, Brammer, Walsh, Kim, et al., 2004; Robertson et al., 2007; Sheline et al., 2001a)), although some studies have found no change in amygdala responses (e.g. after venlafaxine, mirtazapine, and duloxetine treatments (Davidson et al., 2003; Frodl et al., 2011; Fu et al., 2015)). Decreased responses, after treatment with several different antidepressants, to negative emotional stimuli have been also reported in other regions of the core emotion circuit of the brain, including the striatum (Frodl et al., 2011; Fu, Williams, Cleare, Brammer, Walsh, Kim, et al., 2004; Keedwell et al., 2008; Robertson et al., 2007), thalamus (Frodl et al., 2011; Fu, Williams, Cleare, Brammer, Walsh, Kim, et al., 2004), and insula (Frodl et al., 2011; Fu, Williams, Cleare, Brammer, Walsh, & Kim, 2004) (although increased responses of the insular cortex to negative stimuli have also been reported (Davidson et al., 2003)). Accordingly, increased activity in response to positive emotional stimuli after long-term antidepressant treatment has also been found in similar regions, including the amygdala, thalamus, and striatum (Schaefer, Putnam, Benca, & Davidson, 2006; Victor, Furey, Fromm, Ohman, & Drevets, 2013). However, some studies that have reported activity decreases in response to negative stimuli found no change in responses to positive stimuli after antidepressant treatment (Davidson et al., 2003; Sheline et al., 2001a). Decreased activity in response to aversive stimuli and increased activity in response to positive stimuli have been further reported in extrastriate visual regions (including lingual gyrus and fusiform cortex) (Fu et al., 2007; Robertson et al., 2007; Schaefer et al., 2006) and the primary visual cortex (Keedwell et al., 2008).

Whereas limbic and subcortical regions as well as visual regions show mostly decreased activity (in response to aversive stimuli) after antidepressant treatment, activity of the PFC seems to change in the opposite direction. Heller et al. (2013) found that increased activity in response to a negative emotion regulation task in the MPFC and right DLPFC correlated with decreased depression symptoms during a 6-month antidepressant treatment. Even though increased activity of the DLPFC is a well-replicated finding (Fales et al., 2009; Fu, Williams, Cleare, Brammer, Walsh, Kim, et al., 2004; Ma, 2015; Mayberg et al., 1999; Ruhe et al., 2012), reports of decreased activity also exist (Robertson et al., 2007; Rosenblau et al., 2012). Two meta-analyses, however, found long-term antidepressant treatment to increase responses of the DLPFC to positive stimuli (Delaveau et al., 2011) or to both positive and negative stimuli (Ma, 2015). Responses of the MPFC as well as the ACC (ventral/perigenual part) to negative stimuli, however, seem to decrease after antidepressant treatment in depressed patients (Fu, Williams, Cleare, Brammer, Walsh, & Kim, 2004; Robertson et al., 2007; Rosenblau et al., 2012), but increased responses of the ACC (Davidson et al., 2003) and the DMPFC (Ruhe et al., 2012) have been reported as well. One study with a small sample size of 8 depressed patients and 8 healthy controls assessed neural responses to self-referential adjectives over the course of approximately 9 weeks of antidepressant treatment (Lemogne et al., 2010). They observed that both dorsomedial prefrontal cortex (DMPFC) and DLPFC responses to self-referential processing were increased in depressed patients, but only DLPFC responses normalized, i.e. decreased, after antidepressant treatment. However, the first fMRI scan was not a baseline scan, but was performed during the first week after antidepressant initiation.

Only a few studies to date have assessed short-term effects of antidepressants on neural responses to emotional processing in depressed patients. One study evaluated neural responses to negative visual stimuli at baseline and after 2 weeks of venlafaxine treatment and found venlafaxine to increase activity of the left insular cortex (Davidson et al., 2003). However, depression symptom scores had already significantly declined compared with baseline, making it difficult to conclude whether the change was a direct effect of the antidepressant or an indirect effect of improved mood. Godlewska et al. (2012) compared neural response to fearful versus happy faces in depressed patients treated with escitalopram for one week with a placebo group and a control group of

healthy subjects. They found escitalopram to decrease amygdala responses to fearful faces compared with the placebo group or the control group, but no group differences in responses to happy faces. This change was apparent without any differences between the clinical depression ratings of the drug group and the placebo group, indicating a direct effect of the antidepressant. Delaveau et al. (2016) assessed neural responses to emotional self-referential processing task after one week and 6 weeks of agomelatine treatment in a study that was double-blind, randomized, and placebo-controlled for the first week. They found agomelatine to decrease responses of the right VLPFC to self-referential processing after one week and to increase responses of the ventral ACC after 6 weeks.

2.8.2.3 Conclusions

The most consistent finding from the studies of both healthy subjects and depressed patients is the decrease of amygdala responses to aversive stimuli after short-term or long-term antidepressant treatment. Results concerning other regions are more ambiguous, but activity decreases seem to extend to other core regions of the emotional network, including the striatum, thalamus, and insula. Increased activity of the lateral PFC has been observed mostly in studies of depressed patients and long-term antidepressant treatment, whereas healthy subjects seem to have decreased activity after short-term antidepressant treatment (Ma, 2015). Consistent with decreased limbic responses to negative stimuli, antidepressants seem to increase limbic responses to positive stimuli. Increased responses to positive stimuli have further been found in the visual regions, thalamus, and striatum.

Many inconsistencies remain about the specific location and direction of the activity changes. However, a recent meta-analysis found convergent changes in activity patterns in the emotion circuitry of the brain in both depressed patients and healthy subjects, including the bilateral amygdala, insula, VMPFC, ACC, and striatum (Ma, 2015). The activity was decreased in response to negative stimuli and increased in response to positive stimuli. Interestingly, in depressed patients consistent changes in amygdala responses were only found in studies using SSRI antidepressants, whereas the effects of SNRI antidepressants localized mainly in other regions. Also, the type of stimuli (faces vs. emotional pictures) used in the studies influenced the results,

implying that inconsistencies at least partly arise from differences in antidepressant and stimulus types used in the studies.

Taken together, these findings are compatible with the behavioural effects of antidepressants on emotional processing; antidepressants seem to decrease negative bias and increase positive bias in information processing. How these early changes relate to later therapeutic effect remains largely unknown. It has been suggested that time and interaction with the environment may be necessary for these early changes in automatic information processing to translate into conscious subjective experiences via re-learning (Harmer & Cowen, 2013). This suggestion is supported by a study that found that the predictive value of increased recognition of happy faces depended on perceived social support; only in patients with good social support did the early potentiation in processing of positive emotional cues translate into improved subjective mood (Shiroma et al., 2014).

2.8.2.4 Effect of antidepressants on functional connectivity

As depression is known to disrupt functioning of large-scale brain networks rather than single regions, it is relevant to investigate antidepressant effects not only on regional neural responses, but also functional connectivity between brain regions. Most studies have investigated functional connectivity during rest.

One study showed that an 8-week treatment with an SSRI or SNRI antidepressant decreased connectivity of the DMN (only the posterior sub-network; the anterior sub-network continued to have increased connectivity) in depressed patients (Li et al., 2013). A similar result was found in dysthymic patients treated with duloxetine for 10 days; hyperconnectivity of the DMN (particularly in the PCC) normalized (Posner et al., 2013). In healthy volunteers, a single dose of escitalopram (van de Ven, Wingen, Kuypers, Ramaekers, & Formisano, 2013) or sertraline (Klaassens et al., 2015) decreased, whereas a one-week administration of bupropion increased (Rzepa, Dean, & McCabe, 2017), functional connectivity within the DMN. Another study reported a 12-week treatment with duloxetine in depressed patients to decrease connectivity of the DMN and prefrontal regions, including the DLPFC, but to increase connectivity of the anterior DMN and the hippocampus and temporo-parietal cortex (Fu et al., 2015).

A 6-week treatment with sertraline was found to increase resting-state cortico-limbic connectivity in depressed patients (Anand et al., 2007). Another study found that a one-week administration of citalopram decreased connectivity between the amygdala and the VMPFC, whereas reboxetine decreased connectivity between the amygdala and the OFC (McCabe & Mishor, 2011). One study used a graph-theory approach to assess the effect of a single dose of citalopram on whole-brain resting-state functional connectivity, finding citalopram to decrease connectivity (measured as degree centrality) throughout most of the cortical and subcortical brain regions (Schaefer et al., 2014). Thus, it seems that antidepressants may trigger changes in functional connectivity of widespread brain networks during rest, spanning the DMN and the cortico-limbic emotion-regulating circuit, but also extending to other functional networks of the brain.

Only a few studies have assessed the effect of antidepressants on functional connectivity during processing of emotional information. A 2-week administration of duloxetine in healthy volunteers was found to increase functional coupling between the amygdala and anterior insula during an emotional face-matching task (van Marle, Tendolkar, Urner, Verkes, Fernández, et al., 2011). Functional coupling of the amygdala with the ACC, PFC, insula, thalamus, and striatum during visual processing of sad faces increased after an 8-week treatment with fluoxetine in depressed patients (Chen, Suckling, et al., 2007). Another study found increased connectivity between the ACC and limbic regions during processing of happy or neutral faces after 6 weeks of sertraline treatment in depressed patients (Anand, Li, Wang, Wu, Gao, & Bukhari, 2005). These findings suggest that antidepressant treatment, or recovery from depression, may improve limbic-cortical connectivity during emotional processing, possible reflecting improved cortical control over limbic responses to emotional stimuli.

2.8.3 Alterations in brain activity as predictive markers

Currently, no clinically useful biological markers exist to guide the treatment choice for individual patients. However, some promising neuroimaging findings about the activity or metabolism of certain brain regions as predictive markers have emerged.

One promising region to predict treatment response is the ACC, particularly the perigenual area (pgACC) (Phillips et al., 2015). A meta-analysis by Pizzagalli (2011) concluded that a higher pre-treatment resting-state activity of the pgACC predicts

better treatment response to antidepressants but also to other treatment modalities (including sleep deprivation and transcranial magnetic stimulation), while a lower pre-treatment activity predicted response to cognitive behavioural therapy (CBT) and electroconvulsive therapy. Increased pre-treatment responses of the pgACC to negative emotional stimuli also predict treatment response (Chen, Ridler, et al., 2007; Davidson et al., 2003), and the reduction of the ACC activity is associated with a reduction of depression symptoms after antidepressant treatment (Fu, Williams, Cleare, Brammer, Walsh, & Kim, 2004).

Amygdala activity may also have the capacity to predict treatment response. Increased pre-treatment activity in response to emotional stimuli has been shown to predict treatment response to antidepressants as well as to CBT (Phillips et al., 2015). One study found hyperactivity of amygdala responses to attenuate after paroxetine treatment only in the patients responding to the treatment (Ruhe et al., 2012). Another study, by contrast, found decreased pre-treatment and increased post-treatment amygdala responses to both threatening (fear and anger) and happy facial expression in treatment responders to SSRI (escitalopram or sertraline) and SNRI (venlafaxine) antidepressants, whereas pre-treatment hypoactivity of the amygdala in response to sad faces only predicted response to SNRI antidepressants (Williams et al., 2015).

Several other brain regions implicated in emotional processing and pathogenesis of depression have been identified to predict treatment response, but the results remain inconsistent about the specific location and the direction of the activity differences between responders and non-responders (Fonseka, MacQueen, & Kennedy, 2018). For example, one study found that pre-treatment insula hypometabolisim predicted response to CBT, whereas hypermetabolisim predicted response to escitalopram treatment (McGrath et al., 2013). Increased responses of the hippocampus and extrastriate visual cortex to happy facial expressions (Fu et al., 2007) as well as increased responses of the DMPFC, PCC and the superior frontal gyrus to negative facial expression (Samson et al., 2011) also predicted greater symptom improvement.

Functional connectivity alterations have been also observed to predict treatment response. For example, increased DMN connectivity (Fu et al., 2015; Guo et al., 2012) and decreased connectivity of the cognitive control network (Alexopoulos et al., 2012) at baseline are associated with poor treatment response. Recently, Dunlop et al.

(2017) showed that decreased resting state functional connectivity of the sgACC predicted response to antidepressant medication, whereas increased functional connectivity predicted response to CBT.

Predictive value of the early changes in neural responses to emotional stimuli after antidepressant treatment remains obscure. One recent study reported that decreased responses of the left amygdala and insula, ACC, supramarginal gyrus and thalamus to fearful versus happy facial expression after the first week of treatment with escitalopram predicted later clinical response (at 6 weeks) (Godlewska, Browning, Norbury, Cowen, & Harmer, 2016). Another study did not find any changes in neural responses to emotional images after the first week of combination treatment with fluoxetine and olanzapine to predict treatment response (Rizvi et al., 2013).

2.8.4 From simple, controlled stimuli to complex, naturalistic settings

It is important to note that antidepressant effects on emotional processing have been virtually always studied using strictly controlled, simple experiment paradigms, most typically briefly shown emotional facial expressions. These paradigms mostly reveal rapid, automatic responses to salient stimuli. However, as MDD is acknowledged as a disorder of brain circuits with abnormalities in high-order brain functions, it is relevant to investigate also higher brain functioning in response to complex stimuli. In real life, we encounter complex and dynamic emotional situations that provoke rapidly varying emotional reactions. Social interaction is a typical dynamic emotional situation where we perceive, interpret, and react to multiple and complex verbal and non-verbal signals with varying emotional content, intensity, and self-relatedness. Using more complex and dynamic emotional stimuli increases the ecological validity of the studies. Investigating antidepressant effects not only on simple and controlled, but also complex and freely processed dynamic stimuli offers a means of obtaining a better estimate on how antidepressants may modulate emotional processing in daily-life emotional situations.

2.9 FUNCTIONAL MAGNETIC RESONANCE IMAGING (fMRI)

In the following sections, I briefly discuss the basics of the main method of this thesis, fMRI. The three sections introducing the principles of the generation of fMRI signal as

well as preprocessing and analysis of data are mostly based on the textbooks of Huettel et al. (2009) and Friston et al. (2007).

2.9.1 Principles of fMRI

The key component of magnetic resonance imaging (MRI) is a static magnetic field, generated by a series of electromagnetic coils, and the targeted atomic nucleus is hydrogen (a single proton). The static magnetic field causes the spinning nuclei to precess, i.e. rotate around the central axes of the magnetic field. Precessing protons can be in a parallel (rotating parallel to the magnetic field), low-energy state or an antiparallel (rotating antiparallel to the magnetic field), high-energy state. Net magnetization is the difference between the number of spinning nuclei in the parallel state and the number of spinning nuclei in the antiparallel state. In the static magnetic field there are always more nuclei in the parallel state. When energy is delivered to the spin system by radiofrequency coil, some of the nuclei move to the high-energy state, converting the longitudinal magnetization into transverse magnetization. This is called excitation. When radiofrequency pulse is turned down, the nuclei return to low-energy state, emitting energy and restoring the longitudinal magnetization. This emitted energy (radiofrequency signal) can be measured by a receiver coil.

Pulse sequence can be specified to measure different types of signal when the nuclei return to low-energy state, and based on this, different tissues will correspond to different intensities in the image. Most commonly, the anatomical images of the brain are T1-weighted, where the intensity of voxels depends on the time it takes the nuclei to return to their low-energy state (T1 value of the tissue). T2*-weighted imaging (T2* time constant indicating the time of decay of the transverse magnetization and the increase of decay speed by field inhomogeneities) is the basis of fMRI because it is sensitive to the deoxygenated haemoglobin present, which is a key factor in fMRI blood oxygen level-dependent (BOLD) signal, as discussed below.

The energy requirement of the brain can be roughly simplified to oxygen consumption because 90% of the glucose is aerobically metabolized in the brain (Logothetis, 2002). Oxygen is brought to the neurons in the red blood cells by oxygenated haemoglobin, which then gives up its oxygen and converts to deoxygenated haemoglobin in the capillaries. Paramagnetic deoxygenated haemoglobin causes distortion in the magnetic field, resulting in different precession frequencies in nearby protons, i.e.

increasing magnetic inhomogeneities. Thus, the more deoxygenated haemoglobin present, the shorter the T2 decay and the lower the measured MR signal in T2*-weighted images (i.e. darker image). When neurons are activated, more haemoglobin is brought to the capillaries, and the BOLD signal increases (Fox & Raichle, 1986).

As BOLD contrast measures blood oxygenation, it is an indirect measurement of neuronal activation. The change in BOLD signal following neuronal activity is known as the haemodynamic response (HDR), which typically takes more than 10 seconds, although the actual neuronal activity is very short. Thus, even though the temporal resolution in fMRI is quite good, as one image can be typically acquired every few seconds, the slowness of the HDR sets limitations on obtaining precise measurements over time.

2.9.2 Preprocessing of fMRI data

During an fMRI experiment multiple volumes, comprising multiple slices, are acquired over a set of time. Usually also images from multiple subjects are acquired. Therefore, to achieve optimal results and comparability between subjects, the data must be preprocessed. Preprocessing steps usually include, particularly in event-related designs where a single stimulus is presented for a short period of time, a correction for slice-acquisition time. Difference in time of acquisition leads to the situation where the slice acquired later appears to reach the maximum of its haemodynamic response earlier. Slice-timing correction aims to interpolate the BOLD signal had the time of acquisition been the same for all slices.

Head movement correction is done by six-parameter (three translations and three rotations) rigid-body registration that involves matching the images acquired at different time-points by minimizing the mean squared difference between them. In spatial normalization, images from an individual subject are warped into a standard space by non-linear transformations to allow averaging the signal across subjects. The most commonly used template is the Montreal Neurological Institute (MNI) template. Before normalization, functional-structural co-registration can be applied so that the normalization of functional images can be done by using a high-resolution anatomical T1 image.

Finally, the images must be spatially smoothed. Blurring the fMRI data across adjacent voxels increases the signal-to-noise ratio if the filter matches the expected spatial correlation of the data. fMRI data always have spatial correlation and combining data from several subjects introduces even more of it. In spatial smoothing, a Gaussian spatial filter is applied and the width of the filter is expressed in millimetres at half of the maximum value (full-width-half-maximum). Typical filters are about 6 to 10 mm, i.e. about two or three voxels.

2.9.3 fMRI analysis

2.9.3.1 Regional BOLD responses

The statistical analysis of fMRI is typically based on the general linear model (GLM), which explains the response variable (or dependent variable, i.e. BOLD signal in each voxel) in terms of a linear combination of explanatory variables (or independent variables, or regressors) plus an error term. Given the data and the set of explanatory variables, a combination of parameters (parameter weights or betas defining how much each variable contributes to the overall data) that minimizes the error term can be estimated.

In fMRI experiments, the simple GLM is replaced by the set of matrices to account for not only several explanatory variables but also several time-points, and can be written in matrix notation as follows: $Y = X\beta + \varepsilon$. Y is a column vector for values of the response variable, ε is a column vector for error terms, and β is a column vector for parameter, rows expressing time points. X is the design matrix that has one row per time-point and one column per explanatory variable. The design matrix contains the timings and the durations of the explanatory variables, which are typically stimulus categories (e.g. happy vs. fearful faces) or tasks (e.g. attend vs. un-attend to stimuli). Values of the parameters and error term are calculated independently for each voxel, and thus, spatial structure of the data is not included in the GLM. The variables are convolved with the standard HDR using a basis function. Nuisance parameters, such as head movement parameters, can be added to the model without convolution process.

Contrasts are linear combinations of parameter estimates. As fMRI does not give information about the absolute amount of activity but rather about changes of activity over time, experimental conditions are usually compared with another condition, and this can be done using contrasts. When the contrasts are defined, statistical

significance can be evaluated, for example, by producing t-statistics. When the statistical test has been applied, the resulting statistics are gathered into an image, a statistical parametric map.

The fact that fMRI imaging volume typically contains over 100 000 voxels, resulting in over 100 000 t-statistics, creates a serious problem of multiple comparisons. Familywise error rate (FWER) controls for any false-positive results. A stringent method for controlling familywise error (FWE) is Bonferroni correction. It assumes that all tests, i.e. all voxel values, are independent, which in fMRI is not true due to the smoothness of the data. Random field theory can be used to find a height threshold (e.g. t-value) that gives the required FWER taken into account the smoothness of data. False discovery rate (FDR) is the probability of one or more false positives within those "declared active" (discoveries). Thus, when the number of reported positive results increases, the threshold for significance decreases. If only one voxel is reported activated, then FDR correction gives the same result as the Bonferroni correction. FDR correction is a more sensitive and less stringent method than FWE correction, particularly when there are many activated voxels found.

Yet another approach is region-of-interest (ROI) analysis, where a priori functional or anatomical ROIs are defined and statistical testing is applied to these regions only. ROI-analysis decreases the number of statistical comparisons and the need for multiple comparison correction. Another advantage is that this approach enables more flexible exploration of the signal, particularly in complex designs with multiple conditions, as one can extract the signal for each condition in specific ROIs. Downside of ROI analysis is, particularly in large ROIs, that it is not possible to know the exact location of the active voxels within the ROI. Also, anatomically defined ROIs, such as a gyrus or a sulcus, often include many functional sub-regions, thus decreasing the sensitivity of the analysis for the specific task investigated. Further, ROI analysis is only possible if one has an a priori expectation of the regions involved in the task/phenomenon investigated.

In addition to the height threshold of the activated region, also the size of the region, i.e. the number of continuously activated voxels, matters; it is less likely that a group of continuous voxels are activated by chance than a single voxel. Cluster-extent based thresholding takes into account the number of voxels in the activated cluster,

controlling for the false-positive probability of the region as a whole. First, a primary voxel-wise threshold, also called a cluster-defining threshold, is set to define clusters of contiguous suprathreshold voxels. The second threshold is the minimum allowable cluster size (number of voxels in the cluster). For calculation of statistical significance, the null distribution of cluster sizes under the null hypothesis of "no active voxels in the cluster" has to be approximated using theoretical methods. Cluster-based thresholding is popular as it is highly sensitive compared with the very stringent voxel-wise methods. However, it is not spatially specific, particularly if big clusters including several anatomical regions survive the thresholding (Woo, Krishnan, & Wager, 2014).

2.9.3.2 Functional connectivity

Functional connectivity is defined as temporal dependency of activity between anatomically separate brain regions (van den Heuvel & Hulshoff Pol, 2010). Biswall et al. (1995) reported that spontaneous activity fluctuation in the motor cortex during rest was correlated with fluctuations in other motor regions. Since then resting-state functional connectivity of the brain has been intensely studied and correlated fluctuations have been found in many other functional networks such as visual and higher order cognitive networks (van den Heuvel & Hulshoff Pol, 2010). Functional connectivity can be also assessed during cognitive tasks to reveal task-related connectivity. In its simplest form, functional connectivity is measured as a correlation of an average model time-series from a specific seed region with all other voxels of the brain, a so-called seed-based correlation method (Margulies et al., 2010). There are also several other methods to assess functional connectivity, such as independent component analysis aiming to find maximally independent spatial sources of signal without a priori selected seed regions, or dynamic causal modelling assessing effective connectivity, i.e. how activity changes of one region are caused by activity changes of another region (Goldenberg & Galván, 2015; Margulies et al., 2010).

Usually, functional connectivity is assessed over the whole scanning session/experiment. As mentioned earlier, investigating brain responses to complex, dynamic stimuli is relevant for better understanding of higher order cognitive functioning, particularly in the context of mental disorders. Thus, it is also important to investigate not only static but also dynamic, time-varying functional connectivity during complex emotional situations. Methods of assessing time-varying functional

connectivity (such as functional connectivity over a sliding time window) are typically forced to keep the temporal resolution fairly low to get reliable results (Glerean, Salmi, Lahnakoski, Jaaskelainen, & Sams, 2012). Seed-based phase synchronization is a method recently introduced to assess dynamic functional connectivity with maximal temporal resolution (Glerean et al., 2012). In phase synchronization methods, the BOLD signal is converted to phase time-series, i.e. instead of the amplitude of the signal, the phase information is used to assess temporal dependence of activity between regions. This enables assessment of instantaneous changes in functional connectivity during complex, dynamic stimuli (Glerean et al., 2012).

Recently, complex network analysis, known as graph theory, has been increasingly introduced in neuroscience to analyse the growing connection datasets. Graph theory enables characterizing the overall organization of a complex network. Network is a representation of a complex system, e.g. the brain, and it is defined by nodes and links. In the context of functional connectivity, nodes are brain regions that can be defined using different parcellation schemes. Links represent the connections between the nodes. The degree of a node describes the number of its connections, providing information of highly connected hub nodes of the network. Centrality reveals how many of the shortest travel roads in the network pass through the node, indicating a key role in overall communication efficiency (Rubinov & Sporns, 2010).

2.9.3.3 Inter-subject correlation

GLM, where an a priori defined model for signal change is required, is suitable for conditioned, fairly simple stimuli, but limits the analysis of complex, dynamic, freely processed stimuli. Inter-subject correlation (ISC) does not require a pre-defined model, but instead uses the signal of one subject to predict the signal of another subject (Hasson, Nir, Levy, Fuhrmann, & Malach, 2004). It was first demonstrated in 2004 that ISC analysis could track activity correlations between subjects in sensory and higher order association areas during free viewing of a movie clip (Hasson et al., 2004), and it has since been used successfully to study cognitive and emotional processes during complex stimuli in healthy subjects and patient groups (Nummenmaa, Lahnakoski, & Glerean, 2018). During a conditioned experiment ISC shows highly correlated results with GLM analysis (Pajula, Kauppi, & Tohka, 2012). Thus, ISC appears to be a feasible

method to track brain activity during natural, complex stimuli in a model-free manner (Pajula et al., 2012).

Investigating synchrony of brain activation between subjects is not trivial in the context of mental disorders. It is natural for humans to synchronize their actions and feelings with others during interaction. This is seen at the level of physiological responses such as synchronized pupil dilation, in automatic mimicry of facial expressions, eye gaze, and bodily postures, in synchronization of motor actions such as rocking when sitting on a rocking chair, and in more complex behaviour such as imitating another person's strategic decisions when competing (Hasson, Ghazanfar, Galantucci, Garrod, & Keysers, 2012; Prochazkova & Kret, 2017). This kind of synchrony is thought to be highly adaptive and essential for understanding another person's feelings and intentions. Behavioural mimicry, such as mimicry of gestures and postures, increases affiliation. Mimicry of emotional facial expressions evokes corresponding conscious emotional feelings, suggesting it to be an important mechanism in detecting someone else's emotions and reacting to them appropriately (Wild, Erb, & Bartels, 2001).

At the neural level, verbal and non-verbal communication, particularly successful communication, evokes brain-to-brain coupling (Hasson et al., 2012). Increased synchrony of brain activity has also been reported during simulation of a third person's feelings (Nummenmaa, Smirnov, et al., 2014), during shared attention (Koike et al., 2016), and when taking a mutual psychological perspective (Lahnakoski et al., 2014). Furthermore, consistency of brain activity across subjects during an emotional movie or narrative depends on the affective state reported by the subjects, and similarity of brain responses is associated with similarity of the reported affective state (Nummenmaa et al., 2012; Nummenmaa, Saarimäki, et al., 2014). Thus, it seems that synchrony of neural responses reflects similarity of mental states and mutual understanding of the environment. Mental disorders, on the other hand, often profoundly impair social functioning. Depressed patients typically isolate and alienate themselves from others, which might partly arise from excessive attention to one's own depressive feelings and thoughts and the decreased ability to detect, mentalize, and react to others' feelings. Indeed, recently it has been shown that depressed patients compared with healthy controls have less synchronized and dynamic responses to emotional content of complex, dynamic stimuli (Guo, Nguyen, Hyett, Parker, & Breakspear, 2015).

3 AIMS OF THE THESIS

The general aim of the studies of this thesis was to shed light on the system-level mechanisms of action of antidepressants by investigating their early effects on emotional processing. Two different study designs were planned with the aim of disentangling the direct effect of antidepressants on emotional processing from the secondary effects emerging via improved mood.

Study 1: Rapid effects of mirtazapine on emotional processing were assessed in healthy volunteers to avoid the confounding effect of depressed mood and mood improvement, as antidepressants are not expected to modulate the mood of healthy subjects. Mirtazapine was chosen as it is a commonly used antidepressant that does not increase anxiety at treatment initiation, unlike SSRIs sometimes do, complicating the assessment of the very early effects on emotional processing.

Study 2: The effects of escitalopram on emotional processing were assessed in treatment-seeking depressed patients at an early stage of the treatment, before any effect on depressive symptoms is expected to occur. Escitalopram was chosen since SSRIs are typically the first-line treatment for depression. Treatment-seeking patients were recruited to optimize the generalization of the results to general clinical populations of depressed patients.

4 GENERAL METHODS AND MATERIALS

4.1 PARTICIPANTS AND STUDY DESIGN

4.1.1 Study 1: healthy subjects

In Study 1 (experiments I and II), the participants were healthy, right-handed, 18- to 35-year-old, native Finnish-speaking volunteers. They were recruited via e-mail advertisement for university students and word of mouth. The participants were screened with the Structured Clinical Interview for DSM-IV Axis I Disorders (First, Spitzer, Gibbon, & Williams, 1997). Exclusion criteria were the following: current or lifetime psychiatric disorder, current use of illicit drugs or excessive consumption of alcohol (>24 U/week for men and >16 U/week for women), contraindication for MRI, use of antidepressant or antipsychotic agents, mood stabilizers, systemic corticosteroids, beta blockers, or benzodiazepines.

The study was originally designed as randomized, placebo-controlled, and double-blind. However, after scanning the first participants, it was clear that effective blinding was not possible due to the sedative effect of the study drug mirtazapine. As the blinding was broken for both researchers and subjects, the study was re-designed as an open-label study. The subjects were allocated to either receive one dose of mirtazapine 15 mg or be scanned as a control group without medication. During the open-label phase six participants from the mirtazapine group had to be excluded due to excessive sedation or sleeping during the fMRI (participants reported that she/he had fallen asleep during the task or was asleep after the task or response rate in the task was <90%). Data collection was continued until there were 15 subjects without excessive sedation in both groups (6 men, 24 women, mean age 24 years, SD 3.72). Thus, the final sample comprised 30 participants (15 in the mirtazapine group and 15 in the control group).

Two hours before the fMRI (assessment time 1), the participants were asked to complete questionnaires including the Beck Depression Inventory (BDI-II; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), the Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988), and a questionnaire of current affective states. The items of the questionnaire of affective states were derived from Russell's circumplex model of affect (Russell, 1980) and were answered on a five-point Likert scale. The words formed a circumplex with two dimensions, valence and arousal: tired (väsynyt) and bored (pitkästynyt) (negative valence, low arousal), sad (surullinen) and miserable (onneton) (negative valence, neutral arousal), nervous (hermostunut) and anxious (ahdistunut) (negative valence, high arousal), active (aktiivinen) and aroused (vireä) (high arousal, neutral valence), excited (innostunut) and peppy (pirteä) (positive valence, high arousal), cheerful (iloinen) and happy (onnellinen) (positive valence, neutral arousal), content (tyytyväinen) and calm (tyyni) (positive valence, low arousal), and tranquil (rauhallinen) and passive (passiivinen) (low arousal, neutral valence). The assessment of affective states was repeated right before the fMRI, two hours after the first assessment (assessment time 2).

4.1.2 Study 2: depressed patients

In Study 2 (experiments III and IV), 37 treatment-seeking patients with major depressive disorder were recruited from the Finnish Student Health Service (an

organization providing health care services for university students in Finland), units of Helsinki and Espoo. The participants were screened with the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1997). All participants had to meet the DSM-IV criteria for major depressive disorder. Subjects were native Finnish-speaking adults (18-65 years) with no current antidepressant medication (minimum four months prior to the study) or psychotherapy, and with current depression episode of mild or moderate severity (Montgomery-Åsberg Rating Scale (MADRS); Montgomery & Asberg, 1979, score 15-30).

The exclusion criteria were as follows: psychotic disorder, borderline, schizotypal, or schizoid personality disorder, primary anxiety disorder (evaluated as clinically primary to MDD by the interviewer), significant suicidal ideation or previous suicide attempt, severe unstable somatic illness, depression due to somatic illness or substance use, lifetime alcohol or drug dependence, alcohol or drug abuse during the last 12 months, current use of illicit drugs (cannabis during last three months, other drugs during last month), excessive consumption of alcohol (>24 U/week for men and >16 U/week for women), current use of an antipsychotic agent, mood stabilizer, systemic corticosteroid, beta blocker, or benzodiazepine, or a contraindication for MRI.

The study was investigator-initiated, double-blind, randomized, and placebo-controlled. The participants were randomized to receive either escitalopram 10 mg or placebo once a day for one week, after which fMRI was performed. Three subjects dropped out of the study during the first week, and one subject could not undergo fMRI due to excessive anxiety during the scanning. In experiment III, one subject's fMRI failed due to technical reasons. In experiment IV, two subjects had to be excluded due to excessive head motion during the scanning, and two other subjects' fMRI run ended before completion. Thus, 32 subjects were finally included in experiment III and 29 subjects in experiment IV. Comorbid anxiety disorder was diagnosed for 17 and 16 subjects in experiments III and IV, respectively. No significant differences emerged between the drug and placebo groups in comorbid anxiety disorders ($p>0.4$ in Fisher's exact test in both samples).

The subjects completed questionnaires, including BDI-II, BAI, and Perceived Social Support Scale Revised (PSSS-R; Blumenthal et al., 1987) twice during the study: before randomization (day 0) and on the measurement day (day 7). The Five Factor

personality traits were measured at baseline using a Finnish version of NEO Five Factor Inventory (Costa & McCrae, 1992). The subjects were also asked to complete the questionnaire of current affective states (see Section 4.1.1.) once per day during the study period (day 0 - day7) to track possible early changes in subjective affective states during antidepressant treatment.

4.2 Task and stimuli

4.2.1 Self-referential processing task

The task was modified from the emotional categorization task described by Norbury et al. (2008). During fMRI the participants were sequentially shown for one second 60 adjectives describing 30 unequivocally positive (e.g. honest, reliable, sympathetic) and 30 unequivocally negative (e.g. irresponsible, selfish, lazy) adjectives in Finnish as well as 20 neutral words (10 times “left” [vasen] and 10 times “right” [oikea]) in an event-related design in random order, with an inter-stimulus interval randomly varying between 5000 ms and 9500 ms. Presentation software (Neurobehavioral Systems Inc., Albany, CA, USA) was used for stimulus presentation. The duration of the task was 11 minutes. The participants were asked to imagine overhearing two people talking about them and describing them with the word presented on the screen. They were asked to imagine how they would feel and categorize the word accordingly to positive (i.e. they would feel pleasant when being described with the word) or negative (i.e. they would feel unpleasant) as quickly and accurately as possible, using a response key box. As a neutral control task, they were asked to press the left button when shown the word “left” and right button when shown the word “right”.

After fMRI, the participants were asked to complete a surprise memory test. First, the participants had to write down as many words as they could remember from the categorization task during fMRI (free recall task). After that, in a recognition memory task, 60 adjectives from the categorization task (targets) and 60 new adjectives (distracters) were shown on a computer screen for one second in random order. The participants were asked to indicate with key presses as quickly and accurately as possible whether or not they recognized the word from the categorization task. The distracters were matched with the target words by length, frequency (using a database of word frequencies in Finnish through WWW-Lemmie 2.0, which is a web-based tool in the Language Bank of Finland, administered by CSC – IT Centre for Science Ltd. in

Espoo, Finland), and imageability (rated by the research group similarly as in Cortese & Fugett, 2004).

4.2.2 Emotional narrative task

The experimental design of emotional narratives is illustrated in Figure 3. The participants listened to emotional or neutral narratives while being scanned with fMRI. The narratives were derived from the study of Nummenmaa et al. (2014) and included 10 pleasant, 10 unpleasant, and 10 neutral stories, each 40 s long. The narratives were spoken with a neutral female voice, without any prosodic cues about their emotional content. The subjects were asked to listen to the stories as if they were listening to the radio or podcast, trying to imagine the events of the stories vividly and to become immersed in the stories. Each story was preceded by a 5-s fixation cross and a 15-s short text describing the general setting of the forthcoming story. The 15-s epoch also served as a wash-out period for the emotions evoked by the previous story. The narratives were played to the subjects with a UNIDES ADU2a audio system (Unides Design, Helsinki, Finland) via plastic tubes through porous EAR-tip (Etymotic Research, ER3, IL, USA) earplugs. Sound was adjusted individually for each subject to be loud enough for them to hear the stories over the scanner noise.

In a previous study (Nummenmaa, Saarimäki, et al., 2014), 18 healthy subjects rated their time-varying emotional experiences while listening to the stories. The valence (pleasant-unpleasant) and arousal (arousal-calmness) dimensions were rated separately. These ratings averaged across subjects formed the time-series of valence and arousal dimensions that were used as predictors in the analyses. Results from the study of Nummenmaa et al. (2014) show that the stories evoked strong emotional reactions and activated the emotional circuits of the brain.

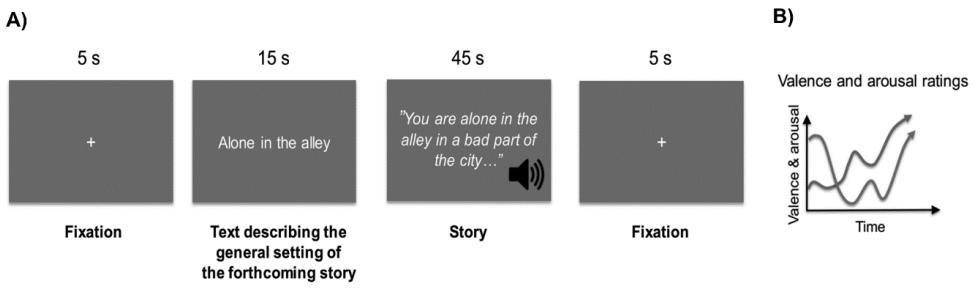

Figure 3. Experimental design of experiments II and IV. A. The subjects listened to emotional and neutral narratives. The narratives were preceded by a fixation cross for 5 s and a short title to describe the general setting of the next story for 15 s. B. Valence and arousal time-series from a previous study of Nummenmaa et al. (2014) were used to track brain responses to emotional content of the narratives.

4.3 fMRI acquisition and preprocessing

The MR imaging was performed on a 3 T MAGNETOM Skyra whole-body scanner (Siemens Healthcare, Erlangen, Germany) at the Advanced Magnetic Imaging Center, Aalto NeuroImaging, Aalto University School of Science, Espoo, Finland. The images were acquired with a T2*-weighted echo-planar imaging (EPI) sequence consisting of 33 slices (TR 1700 ms, TE 24 ms, FOV 202 mm, flip angle 70°, voxel size 3×3×4 mm, ascending interleaved acquisition with no gaps between slices). In the self-referential processing task, a total of 385 volumes were acquired, preceded by three dummy scans to avoid equilibration effects. In the emotional narratives task, a total of 1095 volumes were acquired, preceded by three dummy scans. T1-weighted structural images were acquired at a resolution of 1×1×1 mm (TR 2530 ms, TE 3.3 ms).

Preprocessing and analysis (except for functional connectivity and ISC) were performed with SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/). In all four experiments, the preprocessing steps for conventional BOLD-GLM analysis included realignment to the first EPI scan by rigid-body transformations to account for head movement, co-registration to the individual's structural image, normalization to a standard template (MNI) with linear and non-linear transformations, and smoothing with Gaussian kernel of full-width-half-maximum 8 mm. In experiments I, III, and IV, a correction for slice acquisition time preceded the other preprocessing steps. Also, in these experiments, normalization was performed using SPM's unified

segmentation/normalization algorithm (Ashburner & Friston, 2005), and the resulting deformation field was applied to the EPI images.

5 SPECIFIC EXPERIMENTS

5.1 EXPIRIMENT I: EARLY EFFECTS OF MIRTAZAPINE ON SELF-REFERENTIAL PROCESSING IN HEALTHY SUBJECTS

5.1.1 Aims of the experiment

Experiment I aimed to investigate how a single dose of mirtazapine influences neural responses to self-referential processing. Based on the facts that 1) mirtazapine has been shown to rapidly increase processing of positive versus negative stimuli (without the initial increase in threat processing seen typically in SSRIs) in healthy subjects, 2) self-referential processing activates the CMS of the brain, and 3) two other antidepressants, reboxetine and escitalopram, have been shown to modulate self-referential processing in the CMS, we expected mirtzapine to decrease neural responses to negative self-referential processing and increase neural responses to positive self-referential processing in the CMS, thus correcting the information bias seen in depression.

5.1.2 Analysis of baseline characteristics and questionnaires

SPSS Statistics software, version 21 (IBM Corporation, Armonk, NY, USA) was used for analyses of baseline characteristics and questionnaires. Baseline characteristics (age and comprehensive school grade point average) were analysed using independent samples t-test. A non-parametric Mann-Whitney U-test was used for BDI and BAI because of their skewed distributions in the study sample. For the affective state questionnaire, each sector of the circumplex was analysed separately (negative affect (NA), positive affect (PA), negative affect with high arousal (NA-HA), positive affect with high arousal (PA-HA), negative affect with low arousal (NA-LA), positive affect with low arousal (PA-LA), high arousal (HA), and low arousal (LA)). An individual change in each sector was calculated by subtracting assessment at time 1 from assessment at time 2, and these changes were then compared between the two groups using independent samples t-test. As an approximation of sedation, the single item “tiredness” assessed right before fMRI (assessment time 2) was compared between the groups.

5.1.3 Analysis of behavioural data

A repeated measures analysis of variance (ANOVA) (group x valence) was used for the reaction times in the emotional categorization task and for the number of correct words in the free recall task. Due to skewed distributions, a Mann-Whitney U-test was used to analyse categorizing accuracy of positive and negative words and the number of incorrect answers in the free recall task. For the recognition memory task, to eliminate the effect of possible response biases, the non-parametric discrimination index A´ (Grier, 1971) was first calculated. The discrimination index A´ varies typically between 0.5 (chance level, hits = false alarms) and 1 (perfect recognition, hits = 100%, false alarms = 0%), and the following formula was used to calculate it: A' = 0.5 + [(H-FA)(1+H-FA)]/[(4H(1-FA)], where H=hits/targets ja FA=false alarms/distractors. Finally, a repeated measures ANOVA (group x valence) was used to compare the performance of the two groups.

5.1.4 Analysis of fMRI data

The first-level GLM included three explanatory variables – negative adjectives, positive adjectives, and neutral control words – as well as realignment parameters as nuisance variables. A high-pass filter of 60 s and AR(1) modelling of temporal autocorrelation were applied. Individual contrast images were created for the following contrasts: all adjectives>neutral words, positive adjectives>neutral words, negative adjectives>neutral words, positive adjectives>negative adjectives, and negative adjectives>positive adjectives. These images were then used in a second-level GLM to estimate population-level effects.

To detect brain regions that activate during self-referential processing, a one sample t-test with the contrasts above was first applied in the control group only. The statistical threshold was set at $p<0.05$, FDR-corrected at cluster level (primary voxel-wise threshold at $p<0.01$). To assess the effect of mirtazapine, the groups were next compared using an independent sample's t-test. The statistical threshold was set at $p<0.05$, FDR-corrected at cluster level (primary voxel-wise threshold at $p<0.05$).

To estimate the possible effect of sedation caused by mirtazapine, we added each participant's individual score of "tiredness" to the second-level model (one sample t-test), separately for each group. In case of significant dependence between the BOLD

responses and tiredness, adding tiredness as a covariate in the medication group's t-test should substantially diminish the responses.

5.1.5 Results of baseline characteristics and questionnaires

There were no significant differences between the groups in gender (3 males in both groups), age (mean (SD) 23.5 (1.51) for the drug group and 23.8 (4.95) for the control group, t= -0.22, p=0.825), or comprehensive school grade point average (mean (SD) 9.0 (0.40) for the drug group and 9.2 (0.54) for the control group, t= -1.52, p= 0.140). Neither were there differences in BDI (median 0 for the drug group and 1.0 for the control group, p=0.132) or BAI (median 2.0 for the drug group and 3.0 for the control group, p=0.239) scores between the groups.

In the affective state questionnaire, there was a significant difference between the groups in change (difference between assessment 2 and assessment 1) in NA-LA, PA-HA, HA, and LA (Table 2). The groups differed significantly also in subjective tiredness assessed right before fMRI (i.e. assessment at time 2, mean 3.20/1.93 mirtazapine/control, t=3.40, p=0.002).

Table 2. Mean change in affective state from assessment 1 to assessment 2 (for each sector of the circumplex of affective states separately) in both groups. PA=positive affect, NA=negative affect, LA=low arousal, HA=high arousal.

	Mean mirtazapine (SD)	Mean control (SD)	t value (p)
PA change	-0.40 (0.51)	-0.64 (1.08)	0.76 (0.454)
NA change	0 (0.38)	-0.07 (0.83)	0.30 (0.765)
PA-HA change	-1.20 (1.42)	0 (1.47)	-2.23 (0.034)
PA-LA change	-0.27 (0.88)	-0.14 (0.77)	-0.40 (0.692)
NA-LA change	2.00 (1.96)	-0.43 (1.16)	4.09 (0.001)
NA-HA change	-0.20 (0.68)	0.36 (0.84)	-1.97 (0.059)
LA change	0.93 (1.28)	-0.07 (1.33)	2.08 (0.048)
HA change	-1.67 (1.84)	-0.29 (1.64)	-2.10 (0.045)

5.1.6 Results of behavioural data

The groups did not differ in their accuracy to categorize positive and negative self-referential adjectives (median for positive words in the drug/control group 97%/100%, p=0.178, median for negative words in the drug/control group 100%/100%, p=0.356).

Both groups had significantly faster reaction times for positive than negative words (main effect of valence), but there was no significant main effect of group or group*valence interaction in the ANOVA of reaction times. There was a significant main effect of group in the free recall task (control group had more correctly recalled words), but no main effect of valence or group*valence interaction. No significant difference was present in the number of incorrect answers between the groups. In the recognition memory task, the mirtazapine group performed worse than the control group, but no effect of valence or group*valence interaction was observed (Table 3).

Table 3. Performance in emotional categorization and memory task.

		Mirtazapine		Control		Main effect of valence		Main effect of group		Interaction	
		Mean	SD	Mean	SD	F	P	F	P	F	P
Categorization response times, ms	positive	963.9	264.29	969.6	256.32	F(1,26)=7.256	0.012	F(1,26)=0.018	0.894	F(1,26)=0.588	0.450
	negative	1054.0	362.68	1019.8	259.76						
Free recall correct responses	positive	3.36	2.34	5.33	2.64	F(1,27)=1.114	0.301	F(1,27)=5.524	0.026	F(1,27)=0.203	0.656
	negative	3.14	2.03	4.80	2.08						
Recognition accuracy											
hits/targets %	positive	60.00	19.19	67.56	14.06						
	negative	52.67	17.82	60.67	20.05						
false alarms/distractors %	positive	35.40	15.38	21.38	12.92						
	negative	22.89	13.62	17.78	10.74						
A'	positive	0.68	0.13	0.82	0.07	F(1,28)=1.091	0.305	F(1,28)=9.669	0.004	F(1,28)=2.926	0.098
	negative	0.73	0.12	0.81	0.09						

5.1.7 fMRI results

5.1.7.1 Neural correlates of self-referential processing in healthy subjects without medication

Self-referential words (positive and negative) relative to neutral control words in the control group activated the expected regions: DMPFC, VMPFC extending to sgACC, PCC, left VLPFC and lateral OFC left hippocampus, left temporal cortex, occipital cortex, and cerebellum. Negative self-referential processing (negative adjectives > neutral words) activated similar regions, but positive self-referential processing (positive adjective > neutral words) additionally activated the left amygdala. In the contrast positive > negative adjectives, no significant clusters were found. Negative > positive self-referential processing activated the left putamen and globus pallidus as well as left fronto-insular cortex.

5.1.7.2 Effect of mirtazapine on self-referential processing

The mirtazapine group compared with the control group had significantly decreased responses of the bilateral DMPFC, right VMPFC, and right ventral ACC to self-referential processing (positive and negative adjectives > neutral words). The plot of mean signal change (parameter estimates) extracted from this cluster for all stimulus types (negative words > baseline, positive words > baseline and neutral words > baseline) showed that mirtazapine decreased neural responses to both positive and negative self-referential words (Figure 4, Table 4). There were no significant group differences in neural responses to negative self-referential processing (negative adjectives > neutral words), but a trend towards decreased responses of the DMPFC was observed (uncorrected p=0.008). The mirtazapine group further had decreased responses to positive self-referential processing (positive adjectives > neutral words) in the VMPFC and sgACC, DMPFC, left inferior parietal cortex (IPC), PCC, precuneus, and occipital cortex (Table 4). In the contrast of positive > negative self-referential adjectives, the mirtazapine group had decreased responses of the PCC and precuneus, hippocampus, parahippocampal gyrus and amygdala, left temporal cortex (middle temporal cortex and temporal pole), and left fusiform gyrus (Table 4). No significant group differences were present in the contrast of negative > positive adjectives. Adding subjective score of tiredness as a covariate in the mirtazapine

group one-sample t-test of each contrast did not essentially change the activation map. There also was no significant main effect of tiredness. Furthermore, adding tiredness as a covariate in the models comparing group differences did not weaken the results.

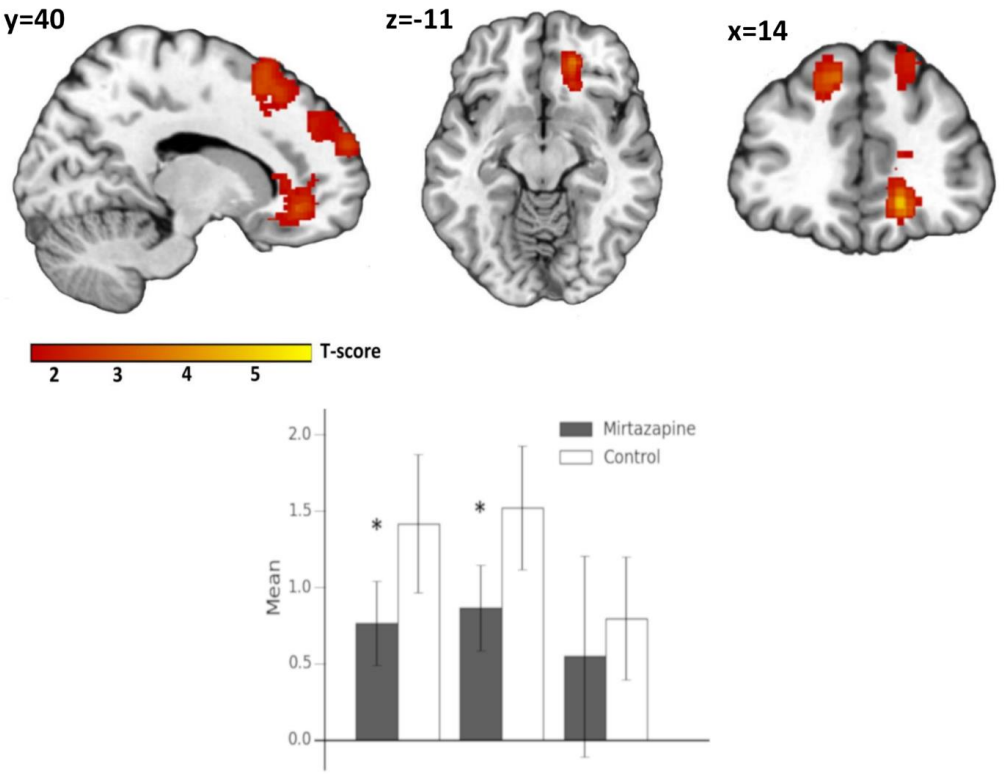

Figure 4. *A. Regions with decreased responses to self-referential adjectives (positive and negative) relative to neutral control words in the mirtazapine groups compared with the control groups (p<0.05, FDR-corrected at cluster level). B. Plot of mean signal change (parameter estimates) extracted from the cluster for each stimulus type relative to baseline. Error bars represent standard error of mean. *p<0.05.*

Table 4. *Peak activations of the clusters with significantly decreased activation in the mirtazapine groups compared with the control group (p<0.05, FDR-corrected at cluster level). PHG=parahippocampal gyrus, VMPFC=ventromedial prefrontal cortex.*

Contrast	Region	P-value	Z-value	Coordinates
Self-referential > neutral	VMPFC	0.043	4.20	18, 40, -8
Positive > neutral	VMPFC	0.001	4.07	18, 42, -8
	Occipital cortex	0.016	3.49	28, -52, 8
Positive > negative	PHG	0.001	3.62	-22, -40, -10

5.1.8 Discussion and conclusions

As expected, mirtazapine decreased responses of the CMS, specifically the MPFC and the ACC, to self-referential processing only 2 hours after a single dose. However, contrary to our hypothesis, a decreasing effect on negative self-referential processing was seen only at trend level, and mirtazapine was found to significantly decrease neural responses to positive self-referential processing. Signal change extracted from the MPFC/ACC cluster revealed decreased responses to both positive and negative words. The stronger effect on positive self-referential processing may be specific to healthy subjects, as healthy volunteers have a tendency to assess positive cues as more self-relevant than negative cues (Moran, Macrae, Heatherton, Wyland, & Kelley, 2006). It may also be related to the acute administration of the drug; reboxetine was previously found to decrease neural responses to negative self-referential processing after 7 days' administration, whereas a single dose had no effect (Miskowiak et al., 2007; Norbury et al., 2008). A meta-analysis also found invariably increased/decreased responses to positive/negative stimuli only after repeated dosing of antidepressants in healthy subjects, whereas the effect after acute administration was inconsistent (Klaassens et al., 2015). Further, it might be related to the general blunting effect of antidepressants on emotional experiences that is sometimes reported (Price, Cole, & Goodwin, 2009). In the emotional memory task, no valence-specific effect of mirtazapine was found, but the mirtazapine group generally performed worse than the control group in both recognition memory and free recall tasks. This may be due to the sedative effect of mirtazapine, although the fact that we did not find any group differences in reaction times does not support this reasoning.

5.2 EXPERIMENT II: EARLY EFFECTS OF MIRTAZAPINE ON NEURAL RESPONSES AND DYNAMIC FUNCTIONAL CONNECTIVITY DURING EMOTIONAL NARRATIVE PROCESSING

5.2.1 Aims of the experiment

Experiment II aimed to investigate whether/how a single dose of mirtazapine influences neural responses to complex, natural emotional stimuli, resembling daily-life emotional situations. The study examined the early effects of mirtazapine not only on regional neural responses, but also on functional connectivity between brain regions. Importantly, instantaneously varying functional connectivity during complex stimuli with varying emotional content was assessed.

5.2.2 Analysis of regional BOLD responses

The first-level GLM included valence and arousal time series as explanatory variables and realignment parameters as effects of no interest. A high-pass filter of 128 s and AR(1) modelling of temporal autocorrelation were applied. Individual contrast images were generated for positive and negative effects of valence and arousal. In the second-level models, the first-level contrast images were subjected to random effects analysis.

First, BOLD responses to valence and arousal dimensions in the control group were modelled by one-sample t-test to assess neural correlates of valence and arousal without drug effect. Next, the effect of mirtazapine was modelled comparing the mirtazapine group and the control group with two-sample t-test. The statistical threshold was set at $p<0.05$ (FDR-corrected at cluster level, primary voxel-wise threshold, $p<0.05$).

As in experiment I, to estimate the possible effect of sedation, neural responses in each group separately were further modelled, including each participant's individual score of tiredness as a covariate in one-sample t-test.

5.2.3 Analysis of functional connectivity

Average functional connectivity was calculated using Pearson's correlation and instantaneous dynamic functional connectivity using seed-based phase synchronization (SBPS; Glerean et al., 2012, code available at: https://github.com/eglerean/funpsy). To enable computationally reasonable analyses,

the data were first spatially down-sampled to 6-mm voxels due to the vast amount of voxel-wise connection ($3.5*10^8$ connections if considering all possible voxel-wise connections). Next, voxels outside the grey matter were excluded, resulting in 5183 voxels considered as functional nodes. This produced networks of ~13 million connections. Further preprocessing steps were performed following the recommendations of Power et al. (2014). BOLD time series were band-pass filtered at 0.01 – 0.08 Hz, signals at white matter, ventricles, and cerebral spinal fluid as well as head motion parameters (Friston expansion, 24 regressors) were regressed, but global signal was not regressed.

To assess average functional connectivity, a whole-brain network was computed for each participant as the pair-wise Pearson's correlation between all nodes time series. A two-sample t-test on the Fisher-Z-transformed correlation values was computed for each link to assess group differences. Mean frame-wise displacement was included as a regressor of no interest (Yan et al., 2013). Statistical significance and multiple comparison correction were computed with permutations using a Network-Based Statistic method (Zalesky, Fornito, & Bullmore, 2010). It computed a significance threshold for the positive and negative tail (as there were both positive and negative t-values), and the larger of the absolute values (i.e. the most conservative) was chosen. To assess the dynamic functional connectivity, first the BOLD signal was band-pass filtered at 0.04 – 0.07 Hz and analytic signal was built with Hilbert transform. Time series of phase differences between pairs of voxels for each individual was computed. Next, a two-sample t-test between the groups was computed for each link time series and each time point, resulting in a dynamic network of t-value link time series. To account for head motion-related variance, the instantaneous value of frame-wise displacement was used as a nuisance regressor. Finally, to separate the effects of valence and arousal, the data were divided into segments (high and low valence and high and low arousal). Valence and arousal time series were used to estimate link group differences co-varying with valence and arousal. Statistical significance was based on non-parametric permutation test. Full permutation distribution was approximated independently for each connection, with 10000 permutations per connection. Positive FDR of $q<0.01$ (Storey & Tibshirani, 2003) was used to control false discovery rate for the connectivity time series.

For visualization, nodes were grouped into predefined anatomical regions (using Automated Anatomical Labeling Atlas). To show the connections most notably modulated by mirtazapine, only 20% of hubs with the highest degree centrality, and betweenness centrality at connection density of 10% (Rubinov & Sporns, 2010) were included in the grouping. Finally, voxel-wise average node degrees were stored into node degree or 'hub' maps. In these maps, voxel intensities reflect the number of connections from each voxel that were statistically significantly modulated (either positively or negatively) by mirtazapine in the four different conditions. Since node degree maps are not statistical maps, the average 90th, 95th, and 99th percentiles were considered to represent the degree of importance of each node in the four conditions (corresponding to mean node degree values of 174, 224, and 331).

5.2.4 Results for regional BOLD responses

5.2.4.1 Effect of valence and arousal in the control group

Arousal was positively associated with increased activation in limbic areas (amygdala, hippocampus, and thalamus), striatum, the cortical midline structures (MPFC, cingulate, precuneus), primary and secondary motor areas, and the occipital cortex. Valence was negatively associated with activation of the dorsolateral prefrontal cortex (DLPFC), insula, limbic regions (amygdala and hippocampus), MCC, PCC, and the somatomotor cortex (left primary (SI) and secondary (SII) somatosensory cortex and primary motor cortex). Valence was positively and arousal negatively associated with activation of the auditory cortex (superior and transverse temporal gyri). The complete report of these results is presented in the original publication II.

5.2.4.2 Effect of mirtazapine on regional BOLD responses

The mirtazapine group compared with the placebo group had significantly decreased responses to arousing events of the stories (positive arousal) in regions including the bilateral amygdala-hippocampal complex, thalamus, the CMS, IPC (angular gyrus), visual, somatosensory (SI, SII), and motor cortices. The mirtazapine group compared with the placebo group had significantly decreased responses to unpleasant events (negative valence) in the right anterior insula and the lateral PFC. Overlapping effect of mirtazapine on the responses to high arousal and negative valence was seen in the ventromedial prefrontal cortex (VMPFC) and the ventral ACC, visual, right somatosensory and motor cortices, IPC, and cerebellum (Figure 5).

Adding subjective score of tiredness as a covariate in the mirtazapine group one-sample t-test of each contrast did not essentially change the results. There also was no significant main effect of tiredness. When the narratives were modelled as boxcar functions without considering the parametric modulation of valence and arousal, the mirtazapine group had no significantly decreased responses to the narratives. However, the mirtazapine group had increased responses to the narratives in the bilateral posterior hippocampus, PCC, and visual cortex.

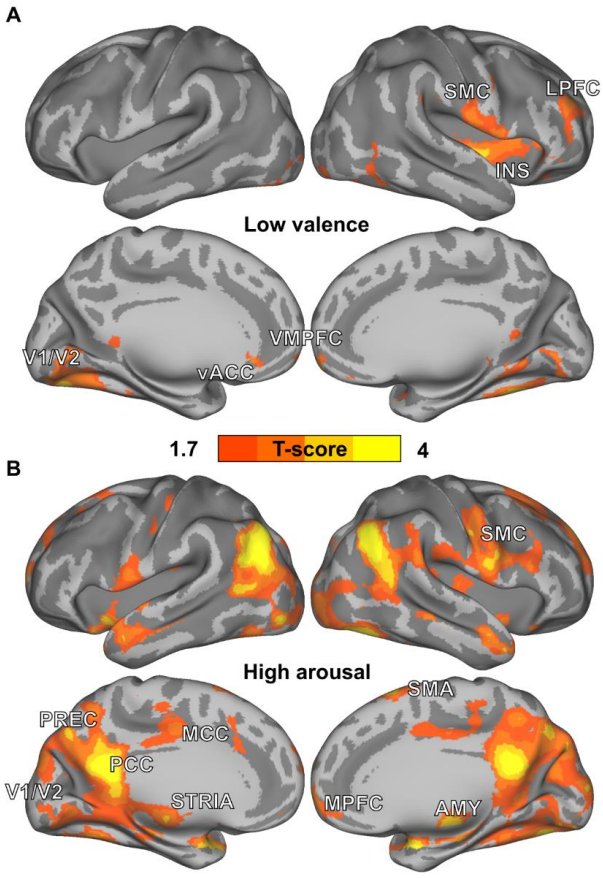

Figure 5. Regions with decreased activity in response to A. negative and B. arousing events of the narratives in the mirtazapine groups compared with the placebo group ($p<0.05$, FDR-corrected at cluster level). AMY=amygdala, INS=insula, LPFC=lateral prefrontal cortex, MCC=middle cingulate cortex, MPFC=medal prefrontal cortex, PCC=posterior cingulate cortex, PREC=precuneus, SMA=supplementary motor area, SMC=sensorimotor cortex, STRIA=striatum, THA=thalamus, vACC=ventral anterior cingulate cortex, VMPFC=ventromedial prefrontal cortex, V1=primary visual cortex, V2=secondary visual cortex.

5.2.5 Effect of mirtazapine on functional connectivity

5.2.5.1 Average functional connectivity

The control group showed on average higher connectivity values across the whole experiment, with the most important differences involving functional connections in subcortical areas (thalamus, putamen, brainstem). The mirtazapine group had increased average connectivity between middle cingulate (MCC) and premotor areas (precentral gyrus). Detailed results are presented in the original publication II.

5.2.5.2 Dynamic functional connectivity

High-valence and low-arousal networks had the highest number of links of all the networks of connections significantly co-varying with valence and arousal for both control and mirtazapine groups.

The mirtazapine group compared with the placebo group had significantly increased functional connectivity associated with high valence in the CMS (MPFC, ACC, MCC, PCC, and IPC) and limbic regions (thalamus and hippocampus) (Figure 6, top right panel). This was driven by increased connectivity between MPFC and middle temporal cortex (MTC), MPFC and MCC, IPC and MTC, and IPC and MCC (Figure 7.A, bottom). The mirtazapine group compared with the placebo group had attenuated functional connectivity associated with high valence in the somatosensory and motor cortices, MCC, and occipital regions (primary visual cortex, lingual gyrus, and fusiform gyrus) (Figure 6, top right panel). This resulted from decreased connectivity between occipital areas and frontal areas, temporal areas, MCC, and somatosensory cortex (Figure 7.A, top). The mirtazapine group compared with the placebo group had decreased functional connectivity associated with low valence mainly in the thalamus, striatum, fronto-insular cortex, and anterior CMS (MPFC, ACC, and MCC) and increased functional connectivity associated with low valence in the posterior CMS (PCC and precuneus) (Figure 6, top left panel).

The mirtazapine group compared with the placebo group had increased functional connectivity associated with low arousal in DMPFC and lateral PFC (lateralized left), insula, IPC, and occipital cortex, including lingual gyrus, fusiform gyrus, and parahippocampal gyrus (Figure 6, bottom left panel). This resulted mostly from increased connectivity between IPC and frontal areas, occipital and frontal areas, and

within frontal areas (Figure 7.B, bottom). The mirtazapine group compared with the placebo group had decreased functional connectivity associated with low arousal in temporal cortex, limbic regions (thalamus, hippocampus, and amygdala), VMPFC, and ventral ACG, somatomotor cortex and occipital regions, including the primary visual cortex (Figure 6, bottom left panel). This was driven by decreased connectivity between temporal and occipital areas, temporal areas and somatosensory cortex, and within occipital areas (Figure 7.B, top). Mirtazapine had virtually no effect on functional connectivity associated with high arousal.

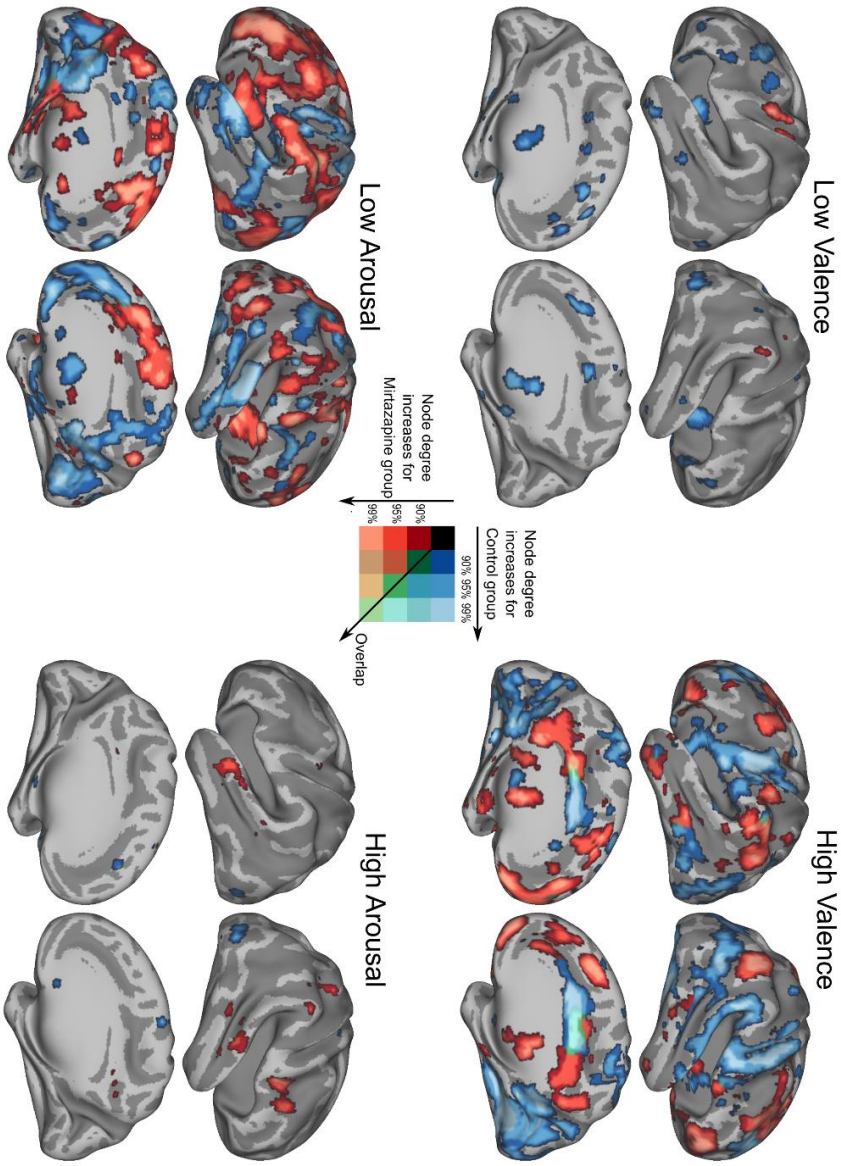

Figure 6. Node degree maps showing the amount of significantly increased (indicated in red) or decreased (indicated in blue) connections in the mirtazapine group compared with the control group, from each voxel during high and low valence and arousal.

A)

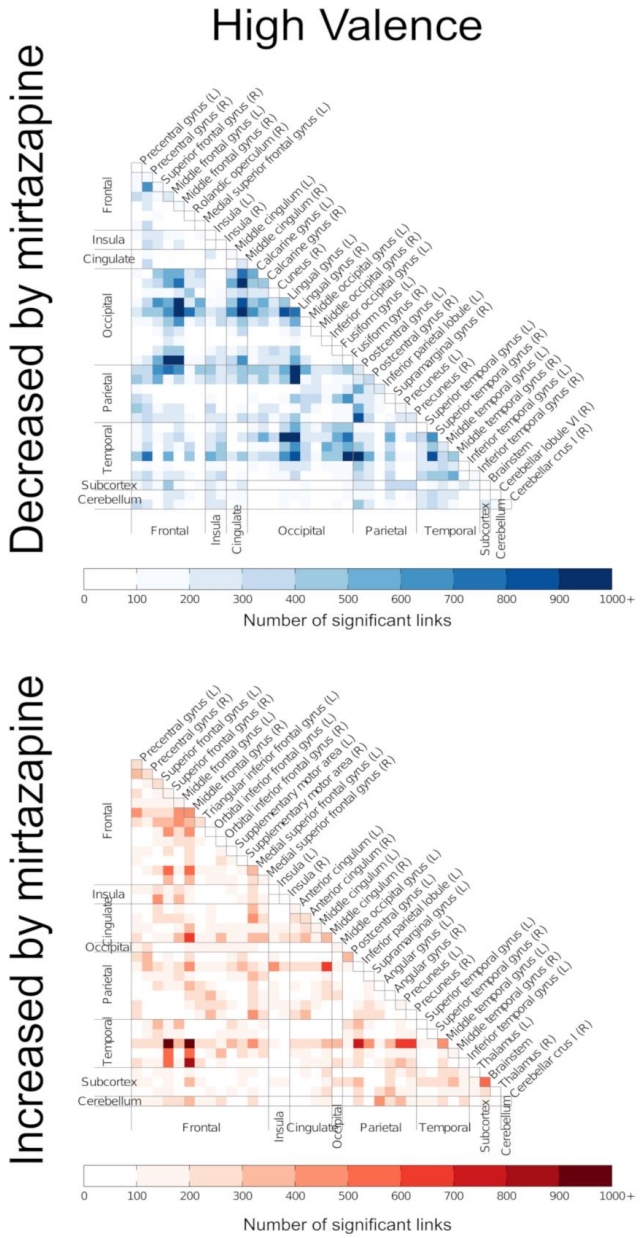

Figure 7.A). Summary connectivity maps presenting the main network hubs in which interconnectivity was decreased (top row) or increased (bottom row) in the mirtazapine group compared with the placebo group during high valence parts of the narratives. The reported value is the number of significant links between two regions of interest (based on Automated Anatomical Labeling Atlas).

B) Low Arousal

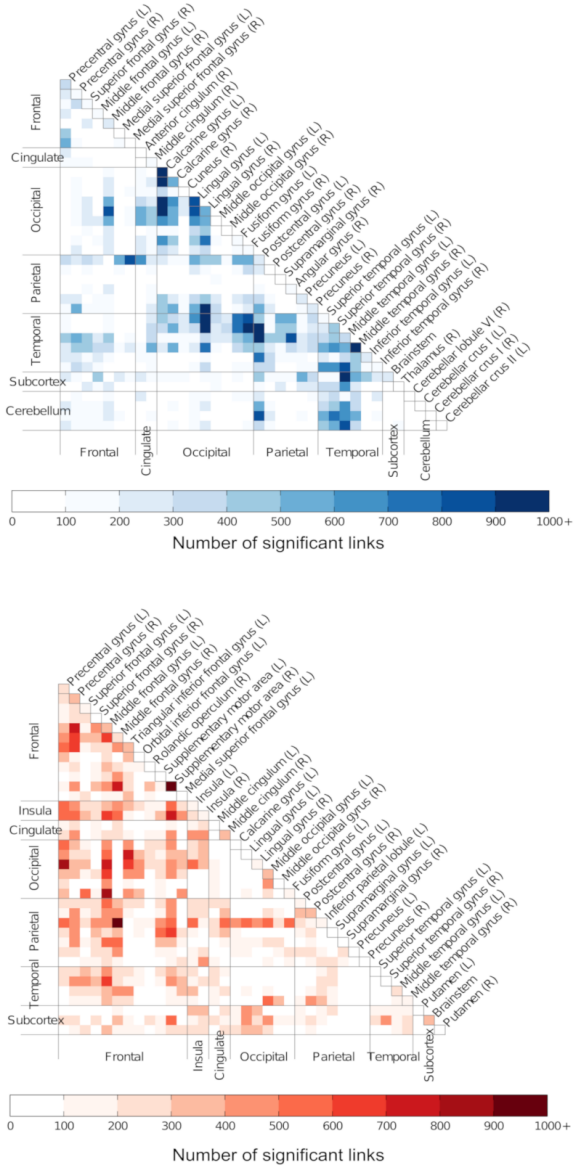

Figure 7.B). Summary connectivity maps presenting the main network hubs in which interconnectivity was decreased (top row) or increased (bottom row) in the mirtazapine group compared with the placebo group during low arousal parts of the narratives. The reported value is the number of significant links between two regions of interest (based on Automated Anatomical Labeling Atlas).

5.2.6 Discussion and conclusions

A single dose of mirtazapine modulated neural responses and dynamic functional connectivity associated with emotional content extracted from auditory narratives. The results go beyond the previous findings about the early effects of mirtazapine on simple emotional stimuli, showing that the effect extends to complex stimuli resembling daily life emotional situations.

Mirtazapine specifically decreased regional neural responses to low valence in the fronto-insular cortex, implicated in generation of affective state and subjective emotional feeling as well as emotional regulation. Moreover, decreased responses were seen in the somatosensory cortex and anterior CMS (in these regions also in response to arousing episodes of the narratives), also important in emotion generation (Saarimäki et al., 2016). This modulation of activity in core regions of emotion generation and regulation in response to negative valence may be related to the antidepressant effect of mirtazapine. Mirtazapine decreased neural responses to high arousal in the CMS and core emotional regions, such as the amygdala, thalamus, and striatum, linked to the tracking arousal dimension of emotion and implicated in modulating vigilance and behavioural responses to salient cues (Davis & Whalen, 2001; Nummenmaa, Saarimäki, et al., 2014; Vogt, 2005). This might be related to the rapid anxiolytic effect of mirtazapine. Mirtazapine increased functional connectivity associated with high valence in the CMS and limbic regions, suggesting potentiated processing of positive events. Decreased functional connectivity associated with high valence in the somatomotor and visual regions might be related to the general negative or “blunting” effect of antidepressants on emotional experiences that is sometimes reported (Moran et al., 2006).

5.3 EXPERIMENT III: EARLY EFFECT OF ESCITALOPRAM ON SELF-REFERENTIAL PROCESSING IN MAJOR DEPRESSIVE DISORDER

5.3.1 Aims of the experiment

Experiment III aimed to reveal the early effects of the antidepressant escitalopram on self-referential processing in depressed patients. Increased and negatively biased self-referential processing is a key factor in the psychopathology of depression (Northoff, 2007; Phillips et al., 2010). Antidepressants are known to have rapids effects on self-

referential processing in healthy subjects (Miskowiak et al., 2007; Norbury et al., 2008), but the effect of SSRIs on self-processing of depressed patients remains unclear. Escitalopram was hypothesized to modulate responses of the CMS, particularly in the MPFC and ACC, to self-referential processing. Specifically, escitalopram was expected to decrease neural responses to negative self-referential processing and increase neural responses to positive self-referential processing.

5.3.2 Analysis of baseline characteristics and questionnaires

SPSS Statistics software, version 21 (IBM Corporation, Armonk, NY, USA) was used for analyses of baseline characteristics and questionnaires as well as behavioural data. Independent samples t-test was used to compare comprehensive school grade point average of the two groups. Due to skewed distributions, a non-parametric Mann-Whitney U-test was used to analyse age, duration of current depression episode, and number of previous episodes. A mixed model ANOVA was used to analyse mood and anxiety ratings. The significant main effects and interactions were further analysed with post hoc comparisons using Bonferroni correction. Each sector of the circumplex model in the affective state questionnaire was analysed separately.

5.3.3 Analysis of behavioural data

Repeated measures ANOVAs (group×valence) were used for the reaction times in the emotional categorization task and for the number of correct words in the free recall test. Greenhouse-Geisser correction was used where assumption of sphericity was not met. The significant effects were further explored with post hoc comparisons using Bonferoni correction. For the word recognition task, the non-parametric discrimination index A' was calculated (see Section 5.1.3). A repeated measures ANOVA (group×valence) was used to compare the performance of the groups.

5.3.4 Analysis of fMRI data

Individual contrast images were created as in experiment I (positive and negative > neutral words, positive > neutral words, negative > neutral words, positive > negative words, and negative > positive words, see Section 5.1.4). At the second level, first the effect of escitalopram was assessed by comparing the escitalopram group and the placebo group with independent samples t-test. Next, the effect of depression without any medication was assessed by comparing the placebo group (depressed patients)

and the control group (healthy subjects) from Study 1. The placebo group and the healthy control group did not significantly differ in age (p=0.258 in independent samples t-test), gender (p=0.427 in Fisher's exact test), or education level (both groups consisted of university students or subjects with a university degree). The statistical threshold in the whole-brain analysis was set at p<0.05, FDR-corrected at cluster level (primary uncorrected voxel-wise threshold at p<0.01). A region of interest (ROI) analysis with an a priori ROI of the MPFC and the ACC was performed. The ROI was selected based on its essential role in self-referential processing, in neural circuits of depression, and in neural effects of antidepressants. It was created with WFU PickAtlas software (Maldjian, Laurienti, Kraft, & Burdette, 2003) using anatomical masks of the MPFC (medial superior frontal gyrus) combined with the ACC from the Automated Anatomical Labeling Atlas (Tzourio-Mazoyer et al., 2002). ROI analyses and percentage signal changes were computed with MarsBaR software (http://marsbar.sourceforge.net/*)*.

5.3.5 Results of baseline characteristics and questionnaires

The groups did not significantly differ in gender (8/17 male in drug group, 6/15 male in placebo group), comprehensive school grade point average, duration of current depressive episode, or number of previous episodes, but the drug group was older than the placebo group (Table 5). The placebo group had somewhat higher average scores of neuroticism and lower scores of agreeableness than the drug group (Table 5).

Table 5. *Baseline characteristics. Grade point average=grade point average of comprehensive school, MDE=major depression episode.*

	Drug group	Placebo group		
	Mean (SD)	Mean (SD)	t	p
Neuroticism	28.8 (7.75)	34.6 (4.62)	-2.43	0.022
Agreeableness	34.1 (4.63)	29.3 (7.22)	2.22	0.035
Conscientiousness	23.1 (6.02)	20.5 (6.30)	1.17	0.251
Openness	28.9 (6.66)	30.7 (5.77)	-0.77	0.447
Extraversion	18.6 (6.83)	21.1 (9.44)	-0.83	0.414
Grade-point average (4-10)	8.7 (0.65)	8.9 (0.56)	-0.79	0.439

	Drug group	Placebo group	
	Median	Median	p[a]
Number of previous MDEs	1	1	0.888
Duration of this MDE (weeks)	31	43	0.331
Age (years)	27	23	0.046

[a]Mann-Whitney U-test

The placebo group also had higher BDI scores than the drug group (significant main effect of group), and the scores decreased with time in both groups (significant main effect of time) but there was no significant group*time interaction (Table 6). A significant effect of time was found also in MADRS scores, but no significant effect of group or group*time –interaction.

Table 6. *Mixed model analysis of variance (ANOVA) of the questionnaires.*

		Drug group	Placebo group	Main effect of week		Main effect of group		Interaction	
		Mean (SD)	Mean (SD)	F	P	F	P	F	P
MADRS	week 0	22.1 (3.91)	24.5 (4.05)	F(1,30)=15.08	0.001	F(1,30)=2.39	0.133	F(1,30)=0.09	0.765
	week1	20.2 (4.56)	22.3 (4.95)						
BDI	week 0	22.7 (5.79)	31.3 (6.73)	F(1,27.414)=15.7	0.001	F(1,29.288)=13.18	0.001	F(1,27.414)=0.87)	0.360
	week1	20.5 (5.22)	27.4 (7.92)						
BAI	week 0	13.5 (9.31)	19.5 (9.72)	F(1,27.798)=0.15	0.697	F(1,29.256)=2.06	0.162	F(1,27.798)=3.49	0.072
	week1	14.5 (9.46)	17.9 (8.76)						
PSSS-R	week 0	47.3 (12.49)	41.1 (7.54)	F(1,27.739)=0.04	0.845	F(1,29.043)=2.46	0.128	F(1,27.739)=0.83	0.370
	week1	45.9 (10.71)	41.9 (8.08)						

In the ANOVA of the daily affective states a significant main effect of time ($F(7,28.064)=4.34$, $p=0.002$) and group*time interaction ($F(7,28.064)=3.42$, $p=0.009$) for NA was found. In the post hoc comparisons, the only significant differences were in the drug group between day 0 and day 3 (mean NA 5.64 at day 0 and 4.07 at day 3, $p=0.043$) and between day 3 and day 5 (mean NA 5.94 at day 5, $p=0.010$). There was also a significant group*time interaction in the ANOVA of PA ($F(7,26.204)=4.28$, $p=0.003$), PA-HA ($F(7,26.500)=4.40$, $p=0.002$), and HA ($F(7,26.713)=2.53$, $p=0.039$), but no post hoc comparison after Bonferroni correction was significant.

5.3.6 Behavioural results

One subject from the drug group was excluded from the analysis of reaction times as an extreme outlier (median reaction time > 3 SD from the group mean), and one subject from the drug group was excluded from the free recall memory test because of missing data. In the ANOVA of reaction time in the emotional categorization task (Table 7), there was a significant main effect of valence and a group*valence interaction. The three following one-way ANOVAs found a significant group difference for positive but not negative or neutral words. In post hoc tests using Bonferroni-adjusted alpha levels of 0.017, the drug group categorized positive words significantly faster than the placebo groups, with no difference in reaction times for positive words between the drug group and the controls or between the placebo group and the controls. No group differences were present in the free recall task or recognition accuracy.

Table 7. *Performance in emotional categorization and memory task.*

		Escitalopram		Placebo		Controls		Main effect of valence			Main effect of group		Interaction		
		Mean	SD	Mean	SD	Mean	SD	F	ε	p	F	p	F	ε	p
Categorization															
Median response times, ms	positive	874.2	134.9	1115.6	322.2	969.6	256.4	F(1.373,57.656)=11.558	0.686	0.001	F(2,42)=1.998	0.148	F(2.746,57.656)=3.367	0.686	0.028
	negative	958.1	137.5	1179.6	483.7	1019.8	259.8								
	neutral	85.4	180.6	890.4	182.7	957.1	208.7								
Free recall															
Correct responses	positive	4.31		5.27		5.33		F(1,43)=2.119		0.153	F(2,43)=0.449	0.641	F(2,43)=0.233		0.793
	negative	4.13		4.53		4.8									
Recognition accuracy															
Hitrate	positive	64.84	13.42	65.53	13.58	67.56	14.06								
	negative	65.99	16.26	62.77	16.97	60.67	20.05								
FA rate	positive	21.16	10.51	19.34	14.04	21.38	12.92								
	negative	17.59	9.63	16.22	14.30	17.78	10.74								
A'	positive	0.81	0.05	0.81	0.10	0.82	0.07	F(1,44)=0.068		0.282	F(2,44)=0.034	0.934	F(2,44)=1.748		0.186
	negative	0.84	0.05	0.82	0.09	0.81	0.09								

5.3.7 fMRI results

5.3.7.1 Effect of escitalopram: ROI analysis

In the predefined ROI of the MPFC/ACC the escitalopram group compared with the placebo group had significantly increased responses to positive relative to negative self-referential processing (positive > negative words) (p=0.033). The percentage signal change extracted from the ROI revealed that the escitalopram group had increased responses to positive words (Figure 8). No significant group differences were found in any other contrast in this region.

5.3.7.2 Difference between depressed patients and healthy controls: ROI analysis

Depressed patients (the placebo group) had significantly decreased responses of the MPFC/ACC to positive relative to negative words compared with healthy controls. Percentage signal changes revealed that depressed patients receiving placebo had lower responses to positive than negative self-referential words, whereas healthy controls had equal responses to both positive and negative words, compatible with the escitalopram group (Figure 8). No significant group differences were found in any other contrast.

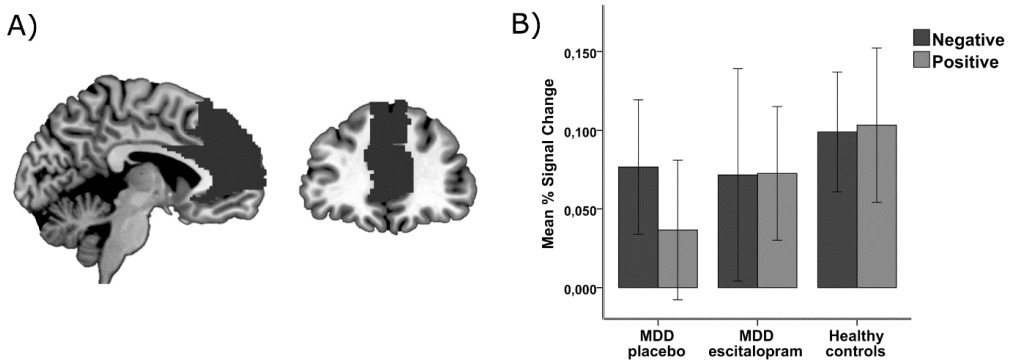

Figure 8. *A. A priori ROI of the MPFC and ACC (from Automated Anatomical Labeling Atlas). B. Plot of percentage signal change extracted from the ROI for positive and negative words in the escitalopram group, placebo group, and healthy controls. Error bars represent standard error of mean.*

5.3.7.3 Effect of escitalopram: whole-brain analysis

In the whole-brain analyses, the escitalopram group compared with the placebo group had significantly decreased responses to self-referential processing (positive and negative > neutral words) in two clusters located in the posterior medial parietal and frontal cortex (Figure 9A). The parietal cluster comprised regions of the anterior precuneus, somatosensory cortex, superior parietal cortex (SPC), and right angular gyrus. The frontal cluster comprised regions of the MCC, primary motor cortices, supplementary motor area (SMA), and precentral sulcus (corresponding to the frontal eye field (FEF) region; Fox et al., 2005) (Table 8). Extracting percentage signal changes from these clusters showed that the escitalopram group had particularly higher responses to neutral control words (Figure 9B and 9C).

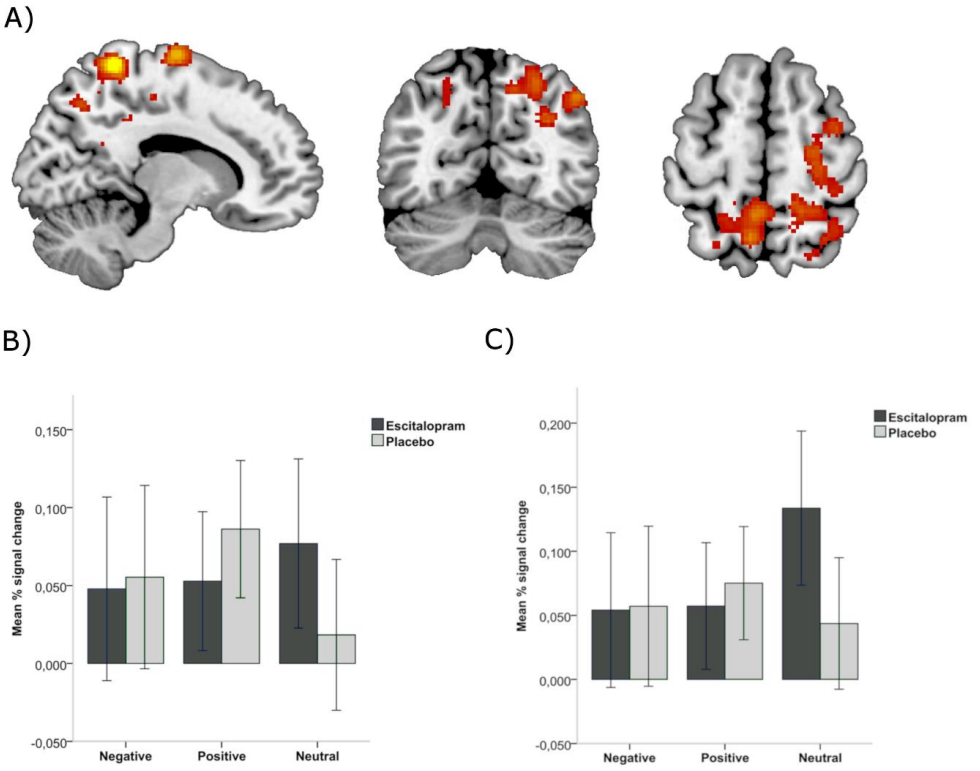

Figure 9. A) *Regions with decreased responses to self-referential (positive and negative) adjectives relative to neutral control words in the escitalopram group compared with the placebo groups (p<0.05, FDR-corrected at cluster level). Plot of percentage signal change for positive, negative, and neutral words from B) the anterior cluster (including MCC, primary motor cortices, SMA, and medial end of the precentral sulcus) and C) the posterior cluster (including precuneus, somatosensory cortex, SPC, and right angular gyrus). Error bars represent standard error of the mean.*

Table 8. *Peaks of the clusters where the escitalopram group compared with the placebo group had significantly decreased activity. SFG= superior frontal gyrus, PostCG=postcentral gyrus.*

Contrast	Region	P-value	Z-value	Coordinates
Self-referential > neutral	Precuneus	0.001	4.63	12, -46, 70
	Right SFG	0.010	3.60	14, -10, 76
Positive > neutral	Right PostCG	0.001	4.59	14, -44, 70

Since these two clusters seemed to include the fronto-parietal regions implicated in both the default mode network (DMN) and the attention system, additional analyses were designed to further explore the clusters. ROI analysis based on automated meta-analyses of 1) the default mode network and 2) the attention network generated by Neurosynth (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011) (www.neurosynth.org) was performed to determine on which brain network the effect of escitalopram was most prominent. ROIs were created from the clusters of the "reverse inference maps", which are results of automated meta-analyses displaying regions reported more often in studies that load highly on the chosen feature ("default mode" or "attention network") than those that do not load highly on this feature (Figure 10, see details in the original publication). Only in the MPFC/ACC-ROI and the PCC-ROI from the DMN and the MCC-ROI from the attention network was no significant group difference found. Other ROI analyses with clusters from both networks revealed significantly decreased responses in the escitalopram group ($p<0.05$; but in hippocampus-ROI of the DMN $p=0.051$), suggesting a decreasing effect of escitalopram on both functional networks.

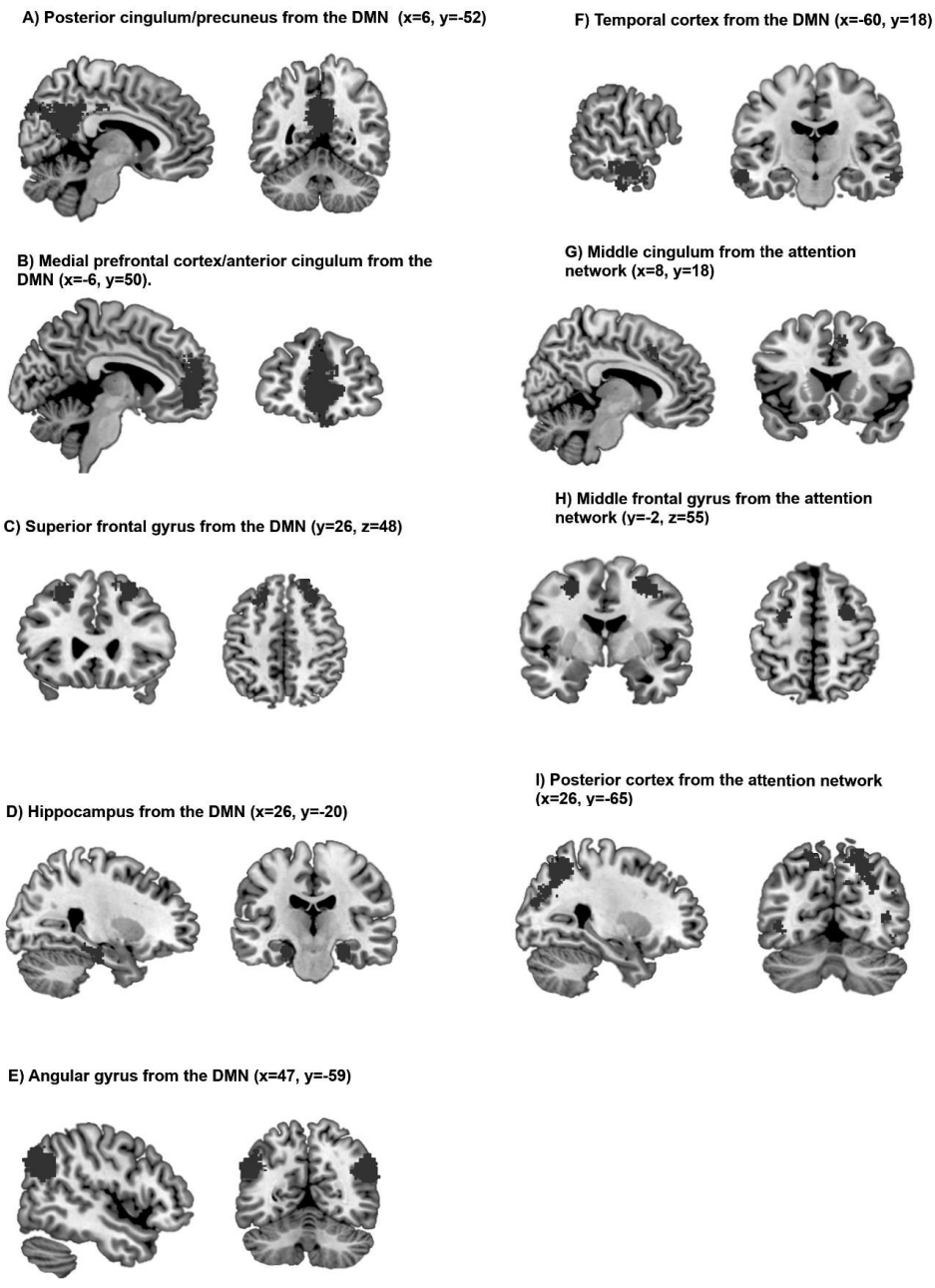

Figure 10. *ROIs based on the clusters from the reverse inference maps generated by Neurosynth using the terms "default mode" and "attention".*

In the contrast of positive self-referential processing (positive > neutral words), the escitalopram group also had decreased responses compared with the placebo group in similar regions as above, additionally spanning the posterior thalamus. No significant group differences were found in the contrasts of negative > neutral words, positive > negative words, or negative > positive words in the whole-brain analysis. However, a trend towards decreased responses to negative self-referential processing (negative > neutral words) in the escitalopram group was observed in a cluster centred in the precuneus (uncorrected p=0.017).

5.3.7.4 Difference between depressed patients and healthy controls: Whole-brain analysis

In the whole-brain analysis, in the contrast of positive > negative words depressed patients (placebo group) had lower responses of the DMPFC and the perigenual ACC (peak voxel at the right DMPFC; MNI coordinates 6, 38, 46) compared with healthy controls (FDR-corrected, p=0.073, FWE-corrected, p=0.046, Figure 11). However, the responses of the escitalopram group did not significantly differ from those of healthy controls. No significant differences between depressed patients and healthy controls were found in any other contrast.

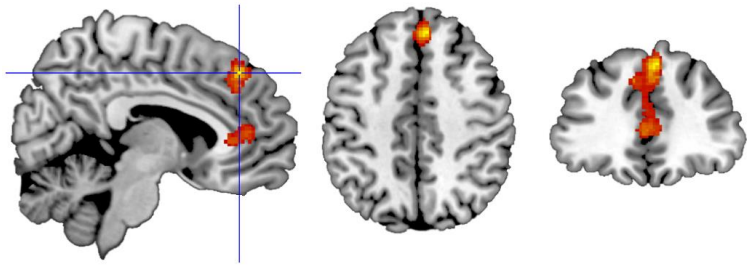

Figure 11. *Regions with decreased responses to positive relative to negative self-referential adjectives in depressed patients (the placebo groups) compared with healthy controls (cluster-level FDR-corrected p=0.073, FEW-corrected p=0.046). The crosshair is at the peak voxel of the cluster (MNI coordinates 6, 38, 46).*

5.3.7.5 Controlling for BDI and neuroticism

Given the observed differences in the BDI and neuroticism scores at baseline, it was further tested whether adding individual BDI or neuroticism scores in the second-level models changes the results. In the contrasts of positive and negative > neutral words

and positive > neutral words, controlling for BDI or neuroticism did not weaken the results of group comparisons. In the contrast of positive > negative words, the group difference in the MPFC/ACC was no longer significant when controlled for neuroticism ($p=0.066$) or BDI ($p=0.408$). However, the mean percentage signal change for positive or negative words extracted from the MPFC/ACC did not significantly correlate with either individual BDI or neuroticism score in either of the groups ($p>0.19$ in all correlation analyses).

5.3.8 Discussion and conclusions

Consistent with our hypothesis, we found a one-week treatment with escitalopram to increase responses to positive relative to negative self-referential processing in the MPFC and the ACC. Depressed patients receiving placebo had decreased responses of the MPFC/ACC to positive relative to negative self-referential processing compared with healthy controls, whereas neural responses of the escitalopram group in this region did not differ from those of unmedicated healthy controls. These results suggest that escitalopram normalizes the negatively biased self-referential processing of depressed patients in the anterior CMS. The escitalopram group also categorized faster positive self-referential words compared with the placebo group, suggesting increased attention to positive words (Harmer et al., 2004) and further implicating potentiated positive self-referential processing. Importantly, the change in self-referential processing was found before escitalopram had any effect on depressive symptoms or self-reported affective state, implying a direct effect of the antidepressant. This early increase in positive versus negative self-referential processing in the MPFC/ACC, a core region of self-related processing, particularly linked to self-referential processing in the emotional domain (Northoff, 2007; Yoshimura et al., 2009) and to conscious self-awareness (Davey, Pujol, & Harrison, 2016), may in time lead to a more positive conscious experience of self.

We also found escitalopram to decrease neural responses to self-referential processing (both positive and negative) relative to the neutral control task, mostly driven by increased responses to the control task, in the posterior medial cortex, centred in the precuneus. The precuneus is part of the DMN, but the anterior/dorsal part of the precuneus has been suggested to have different functions based on its connections to visual, somatomotor, and cognition-related regions, rather than DMN

regions (Buckner, Andrews-Hanna, & Schacter, 2008; Margulies et al., 2009). The DMN is typically thought to have a role in internally focused tasks, but has been also implicated in attending to the external environment, particularly in passive tasks requiring low cognitive load (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010). The cluster where attenuated self-referential processing was found in this experiment spanned the regions implicated in passive external monitoring ("passive watchfulness"), such as the precuneus, somatosensory cortex, and the SPC (Andrews-Hanna et al., 2010; Davey et al., 2016), as well as regions of the dorsal attention network such as the SPC, SMA, and the FEF (Corbetta & Shulman, 2002; Vincent et al., 2008). Furthermore, the complementary ROI analysis using the known regions of the DMN and the attention network as ROIs suggested escitalopram to actually modulate neural responses in this contrast (positive and negative words > neutral words) in the regions belonging to both networks, but not in the "core self" regions of the DMN such as the MPFC and the PCC (Davey et al., 2016). Thus, the localization of the effect and the fact that it was mostly driven by increased responses to the neutral control task suggest that escitalopram may improve the ability to shift attention from internal to external milieu.

No group differences were found in the memory tasks, and neither was there any difference between depressed patients and healthy controls in categorization speed. Possibly, the effect of antidepressants may not be strong enough to be seen at the behavioural level despite clear differences in brain responses. Also, even though some previous studies have found antidepressants to influence emotional memory, there are no earlier studies of depressed patients receiving SSRI antidepressant. In our study, the memory task was performed on average 90 minutes after the categorization task, whereas in previous reports it has been performed after a significantly shorter time.

5.4 EXPERIMENT IV: EARLY EFFECTS OF ESCITRALOPRAM ON NEURAL RESPONSES AND INTER-SUBJECT CORRELATION DURING EMOTIONAL NARRATIVES IN MAJOR DEPRESSIVE DISORDER

5.4.1 Aims of the experiment

Experiment IV aimed to investigate whether/how a one-week treatment with escitalopram modulates neural responses to natural, dynamic emotional stimuli in

depressed patients to shed light on the effects of the antidepressant on processing of everyday-like emotional situations. Inter-subject correlation (ISC) analysis was used to track brain responses to complex, dynamic stimuli in a model-free manner.

5.4.2 Analysis of baseline characteristics and questionnaires

Baseline characteristics and mood and anxiety ratings as well as daily affective states were analyzed as in experiment III.

5.4.3 BOLD-GLM analysis

At the first level, individual subjects' brain responses to valence and arousal dimensions of the narratives were assessed as in Experiment II. However, in this experiment the valence time series was divided into positive and negative valence to enable a more specific assessment of the effect of escitalopram on positive and negative valence. Thus, the model included three explanatory variables – positive valence, negative valence, and arousal – as well as realignment parameters as effects of no interest to account for head motion. A high-pass filter of 256 s and AR(1) modelling of temporal autocorrelation were applied. At the second level, an independent samples t-test was used to compare the groups. Statistical threshold was set at $p<0.05$, FDR-corrected at cluster level (primary uncorrected voxel-wise threshold at $p<0.01$).

5.4.4 Analysis of inter-subject connectivity

FSL tools called by the bramila pipeline (https://version.aalto.fi/gitlab/BML/bramila, a Matlab pipeline for running preprocessing over Aalto computational cluster and to perform further preprocessing steps not included in FSL) were used to preprocess the data for ISC. Preprocessing steps included slice timing correction, head motion correction based on rigid rotation, co-registration to the MNI 152 2mm template with a two-step registration method as implemented by FSL, spatial smoothing (6mm isotropic), temporal detrending using savitzky golay filter of length 240 s, and regressing out of 24 head motion parameters (Friston expansion (Power et al., 2014)).

ISC was performed using the Intersubject Correlation Toolbox (Kauppi, Pajula, & Tohka, 2014). An intersubject correlation matrix was computed for each voxel between each subject pair. The top off-diagonal triangle elements of the two groups were compared by computing a t-value to assess group differences. Statistical inference

was performed using permutation of the subject labels (5000 iterations) and multiple comparison correction using Benjamini Hochberg FDR with $q < 0.05$. Next, ISC was repeated separately for the positive and negative valence time points. Statistical inference and multiple comparison correction were performed as in the previous ISC, but q threshold was set to 0.05/2 to account for the two tests (positive and negative valence) performed.

5.4.5 Results of baseline characteristics and questionnaires

Results of baseline characteristics and symptom questionnaires were essentially the same as in experiment III (see Section 5.3.5), as the study samples were almost identical. The detailed results can be seen in the original publication IV.

5.4.6 BOLD-GLM results

No significant group differences emerged in neural responses to positive, negative or arousing events of the stories in GLM analysis. However, there was a trend towards increased responses to positive valence in the ventral MPFC, the ACC, and the left VLPFC in the escitalopram group compared with the placebo group ($p=0.004$, uncorrected at cluster level, $p=0.113$, FDR-corrected at cluster level, peak of the cluster at 14, 48, 0 in MNI space). No significant group differences were found in neural responses to the narratives per se (without modelling for the emotional content).

5.4.7 ISC results

The escitalopram group compared with the placebo group had more synchronized brain responses (i.e. more similar activation) across all the stories (without modelling for the effect of emotional content) in temporal auditory and language processing regions (superior temporal cortex (STC), primary auditory cortex), frontal premotor regions (precentral gyrus, supplementary motor area (SMA), medial frontal gyrus (MFG)), CMS (including MCC, PCC, precuneus, DMPFC), medial OFC, lateral PFC (LPFC, MFG), right lateral OFC (LOFC, orbital inferior frontal gyrus), and IPC. Less synchronized activation in the escitalopram group was found in brain regions, including the MTC, temporal pole and insular cortex, hippocampus and parahippocampal gyrus (PHG), occipital cortex and fronto-parietal attention regions (SPC, FEF region, and dorsal PFC) (Figure 12).

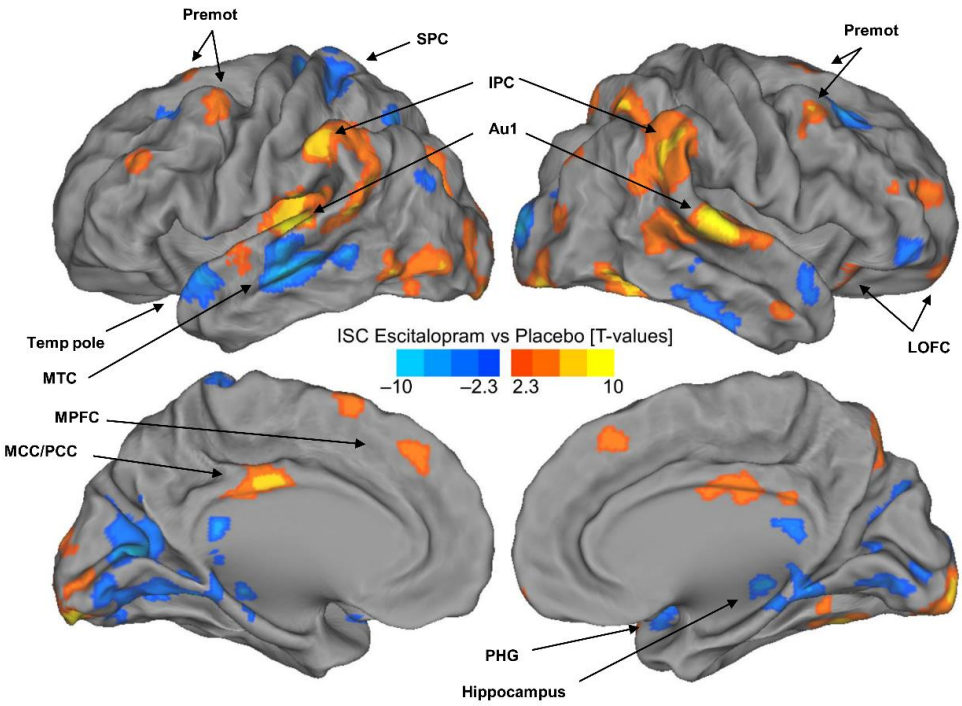

Figure 12. *Regions with higher (warm colours) and lower (cold colours) inter-subject correlation (ISC) in the escitalopram group compared with the placebo group. Au1=primary auditory cortex, IPC=inferior parietal cortex, LOFC=lateral orbitofrontal cortex, MCC/PCC=middle/posterior cingulate, MPFC=medial prefrontal cortex, MTC=medial temporal cortex, PHG=parahippocampal gyrus, Premot=premotor cortex, SPC=superior parietal cortex, Temp pole=temporal pole.*

During positive parts of the stories the escitalopram group compared with the placebo group had more synchronized responses in the MPFC, ACC, precuneus, and IPC as well as in the temporal auditory and language processing regions, premotor regions, and the lateral OFC extending to the anterior insula. Regions with lower synchrony in the escitalopram group relative to the placebo group during positive episodes of the stories were mainly absent: lower ISC was found in the left MTC, occipital cortex, and the paracentral lobule (Figure 13B, Table 9).

Table 9. *Peaks of the clusters with significantly higher and lower inter-subject correlation (ISC) in the drug group than the placebo group during positive episodes of the narratives. Clusters are presented in order of cluster size. Coordinates in MNI space. L=left, R=right, LPFC=lateral prefrontal cortex, Premot=premotor region.*

Positive valence; escitalopram > placebo

Region	Cluster size	x	y	z	max T-value
Superior temporal gyrus R	2392	64	-24	12	9.25
Superior temporal gyrus L	2233	-56	-28	12	10.98
Cerebellar crus II L	1655	-20	-78	-42	7.14
Supplementary motor area R (Premot)	1273	2	24	56	6.47
Orbital inferior frontal gyrus R	505	44	22	-12	8.69
Orbital inferior frontal gyrus L	307	-44	22	-12	6.56
Middle frontal gyrus R (Premot)	285	40	8	52	5.75
Superior parietal lobule R	224	28	-66	50	4.95
Precuneus L	217	-10	-54	58	5.97
Inferior occipital gyrus L	191	-52	-76	-8	5.69
Middle cingulum L	168	-2	-20	32	5.16
Fusiform gyrus L	132	-38	-60	-20	6.10
Middle frontal gyrus R (LPFC)	90	34	54	18	5.78
Middle occipital gyrus R	72	34	-84	36	5.16
Precuneus R	66	10	-60	66	4.20

Positive valence; escitalopram < placebo

Region	Cluster size	x	y	z	max T-value
Middle temporal gyrus L	268	-64	-28	-2	-8.30
Calcarine gyrus L	227	-20	-64	20	-6.86
Paracentral lobule L	104	-14	-26	72	-6.27

During negative parts of the stories the escitalopram group had higher synchrony of brain responses in the temporal auditory and language processing regions, premotor regions, right MOFC, IPC, right caudate, and precuneus. Lower synchrony during negative parts of the stories in the escitalopram group was found in the left MTC and the temporal pole extending to the insula, right VLPFC, and occipital cortex (Figure 13B, Table 10).

Table 10. *Peaks of the clusters with significantly higher and lower inter-subject correlation (ISC) in the drug group than the placebo group during positive episodes of the narratives. Clusters are presented in order of cluster size. Coordinates in MNI space. L=left, R=right, Premot=premotor region.*

Negative valence; escitalopram > placebo

Region	Cluster size	x	y	z	max T-value
Superior temporal gyrus L	2154	-56	-28	14	14.33
Angular gyrus R	1219	56	-50	28	7.46
Superior temporal gyrus R	1093	42	-26	12	10.88
Supramarginal gyrus L	492	-62	-36	40	7.61
Lingual gyrus L	278	-16	-94	-16	8.10
Precuneus R	167	6	-76	52	6.15
Cerebellar crus II R	144	18	-78	-48	6.09
Middle frontal gyrus L (Premot)	103	-26	4	60	4.81
Orbital middle frontal gyrus R	100	26	60	-10	6.60
Cerebellar crus II L	86	-20	-78	-38	6.04
Precuneus L	73	-8	-54	14	5.38
Inferior occipital gyrus L	68	-48	-82	-4	4.67
Caudate R	68	16	6	10	4.67

Negative valence; escitalopram < placebo

Cluster ID	Cluster size	x	y	z	max T-value
Calcarine gyrus L	2208	-14	-74	14	-9.48
Middle temporal gyrus L	578	-64	-30	-2	-8.74
Cerebellar crus I R	311	44	-50	-28	-8.11
Middle temporal gyrus L	235	-52	2	-16	-6.24
Lingual gyrus R	184	14	-46	-6	-5.84
Parahippocampal gyrus L	111	-24	2	-30	-6.36
Cerebellar lobule VI L	86	-32	-62	-22	-6.60
Orbital inferior frontal gyrus R	67	48	30	-2	-5.22

Aiming to further disentangle the effect of emotional content of the stories on ISC, the ISC during positive relative to negative valence was assessed separately in both groups. Stronger ISC during positive versus negative episodes of the stories in the escitalopram group was found in the left precuneus, left LOFC and insula, DMPFC, and cerebellum, whereas weaker ISC was found in the left VLPFC, right DLPFC, STC, middle and posterior cingulate and occipital cortex (Figure 13A, the table with peaks of the cluster can be found in the original publication). In the placebo group, weaker ISC during positive versus negative events of the stories was seen in similar regions as in the drug group (but not the DLPFC or the PCC), additionally including

the amygdala, hippocampus, SMA, and precentral gyrus, but no regions with stronger ISC were found (Figure 13A).

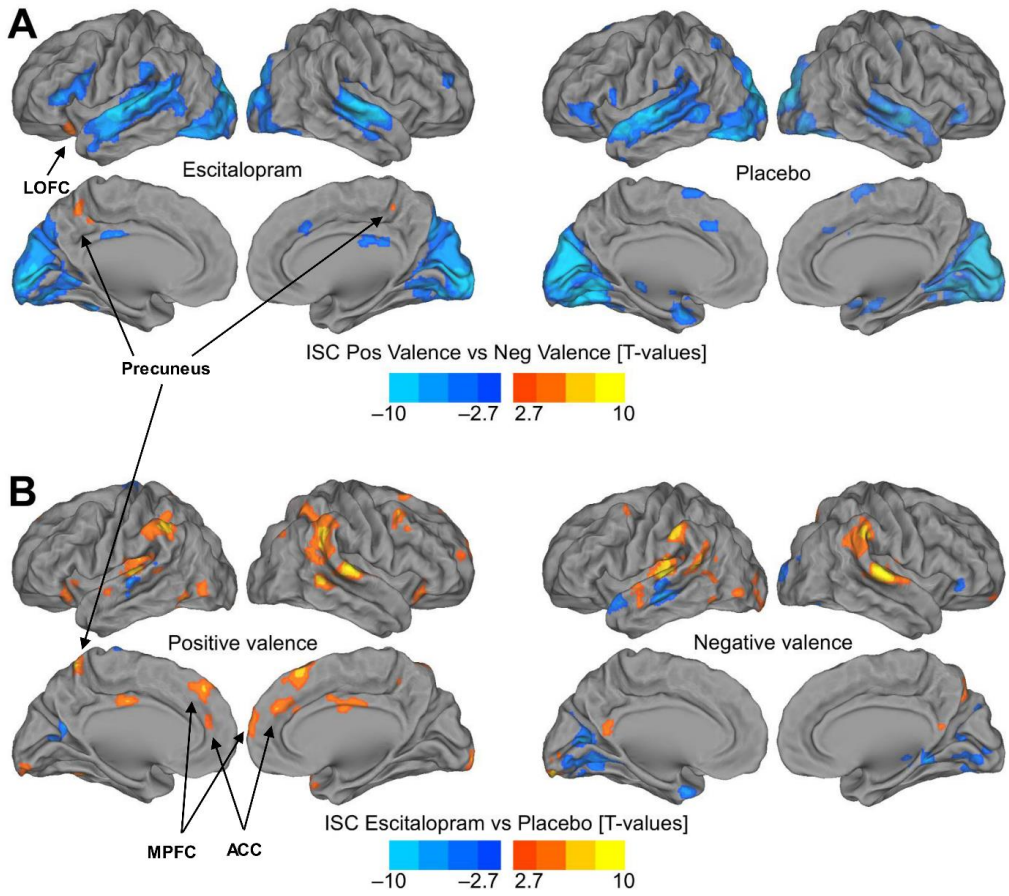

Figure 13. *A. Regions with higher inter-subject correlation (ISC) during positive (warm colours) relative to negative (cold colours) episodes of the narratives in the escitalopram (left panel) and the placebo groups (right panel) separately. B. Regions with higher (warm colours) and lower (cold colours) ISC during positive (left panel) and negative (right panel) episodes of the narratives. ACC=anterior cingulate, LOFC=lateral orbitofrontal cortex, MPFC=medial prefrontal cortex.*

5.4.8 Discussion and conclusions

At the early stage of the treatment before any effect at the symptom level was achieved, escitalopram was found to modulate brain responses to complex and dynamic emotional stimuli. This demonstrates that the effect of escitalopram on automatic limbic responses to simple visual stimuli previously reported (Godlewska et al., 2012) extends to responses of larger-scale brain regions to complex, daily-life-like emotional situations. With the conventional GLM analysis, no significant differences between the escitalopram and the placebo group were found, whereas a model-free ISC analysis detected robust group differences, suggesting that ISC is a powerful means to investigate early antidepressant effects on emotional processing in naturalistic, free processing conditions. ISC has been shown to be sensitive in detecting differences in brain responses between patient groups and healthy controls processing complex stimuli, e.g. in schizophrenia, when no differences can be detected with GLM (Mäntylä et al., 2018), but it has not been used before to investigate antidepressant effects.

The escitalopram group had more consistent neural responses specifically during positive parts of the stories in the precuneus, the MPFC, and the ACC. Moreover, when comparing ISC during positive versus negative events of the stories, ISC was higher during positive events in the precuneus and the LOFC extending to the insula in the escitalopram group, but was completely absent in the placebo group. On the other hand, ISC was stronger during negative events in both groups; consistently with a previous finding in healthy volunteers (Nummenmaa et al., 2012), negative valence evoked more similar brain responses. These results suggest that in both groups of depressed patients negative valence synchronized brain activity, whereas positive valence synchronized brain responses only in the escitalopram group. Furthermore, the trend-level finding of increased responses to positive valence in this MPFC/ACC in the escitalopram group compared with the placebo group suggests that ISC in this region reflects activity increases, implying potentiated processing of positive events. Stronger ISC during positive events in the brain regions related to emotion generation, regulation, and self-processing suggest improved ability to mentalize others' positive feelings and update one's own emotional state accordingly. However, as the participants were not asked to report their emotional reactions to the stories, this remains speculative.

Higher consistency of activity in the escitalopram group compared with the placebo group across all stories was seen in the temporal cortex, including the primary auditory cortex and the STC implicated in speech comprehension, the premotor cortex and the IFG (as well as the IPC) implicated in complex narratives comprehension, and regions of the DMN (precuneus, MCC/PCC, MPFC, IPC). ISC in the DMN during narrative processing has been previously reported and suggested to reflect mutual deactivation in the DMN during processing of complex stimuli (Wilson, Molnar-Szakacs, & Iacoboni, 2008). In the present study, it is not possible to conclude whether ISC reflects mutual activation or deactivation, as GLM did not reveal group differences. Importantly, ISC may also arise from mutual dynamic fluctuations of the DMN activity due to varying intensity and engagement of the narratives that GLM cannot detect. Stronger ISC in the escitalopram group may thus reflect improved ability of the DMN to appropriately down- and upregulate during processing of complex emotional stimuli, thus normalizing the aberrant DMN function associated with depression (Hamilton et al., 2011; Sheline et al., 2009). On the other hand, ISC in the auditory and narrative processing regions, partly overlapping with regions implicated in emotional empathy (IFG, premotor regions, IPC) (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003; Nummenmaa, Hirvonen, Parkkola, & Hietanen, 2008), may reflect improved ability to attend to and immerse into the stories, to imagine and empathize with others' mental states, and to become "emotionally synchronized" with others, instead of being caught up in one's own consistently negative feelings.

6 GENERAL DISCUSSION

The four experiments of this thesis investigated the early effects of two different antidepressants on neural responses to self-referential processing and spoken emotional narratives in healthy volunteers and treatment-seeking depressed patients. In all experiments, significant changes in emotional processing were found at a very early stage of treatment, without any parallel changes in mood. This implies that the change in emotional processing does not derive from improved mood, but rather precedes it, suggesting it to be a potentially important factor in the mechanism of action of antidepressants. A change in emotional processing was seen in both healthy subjects and depressed patients receiving mirtazapine or escitalopram, two

antidepressants with different neurotransmitter receptor binding profiles. This, combined with the previous findings of antidepressant effects on emotional processing mainly studied in healthy controls, supports the early modulation of emotional processing as a common phenomenon across different antidepressant drugs and different populations, likely contributing significantly to the later therapeutic effect of these antidepressants.

6.1 SELF-REFERENTIAL PROCESSING

A single dose of mirtazapine in healthy volunteers and a one-week treatment with escitalopram in depressed patients both, as expected, modulated neural responses to self-referential processing relative to the neutral control task in the CMS. Self-related processing bias appears to have particular importance in the development and maintenance of depression. Self-blame and feelings of worthlessness are well-known symptoms of depression, and self-blame is associated with a higher risk for suicide attempts (Grunebaum et al., 2005). Increased self-focus, particularly ruminative processing, is associated with increased levels of negative affect and predicts future depressed mood (Wisco, 2009). The reverse is also true; increased negative affect can trigger increased self-referential processing (Mor & Winquist, 2002). Furthermore, evidence suggests that self-related processing exacerbates negative mood particularly in depressed patients and in individuals with higher baseline rumination, indicating cognitive vulnerability to depression, but not in healthy subjects with a lower baseline rumination (Clasen, Fisher, & Beevers, 2015; Wisco, 2009). In light of this evidence, attenuation of self-referential processing may be essential for the mood-improving effect of antidepressants.

However, the role of valence appeared distinct in the two studies. In healthy volunteers receiving a single dose of mirtazapine, the responses to both positive and negative self-referential processing decreased in the MPFC/ACC, with a more pronounced decrease in responses to positive valence. However, in depressed patients increased responses to positive relative to negative self-referential processing were found in the MPFC/ACC after short-term escitalopram treatment compared with placebo. This change was accompanied by an increase in categorization speed of positive self-referential words in the escitalopram group, whereas mirtazapine had no valence-specific effect on categorization speed in healthy volunteers. This normalization of

negatively biased self-processing in depressed patients only is plausibly due to the lack of negative bias in self-referential processing of healthy subjects; an antidepressant in depressed patients corrects the negative bias in self-referential processing, whereas in healthy subjects the healthy positive bias already exists. In accord with this, a recent meta-analysis found that a decrease in neural responses to positive emotional stimuli, seen in the striatum, MPFC, and ACC, was unique to healthy subjects; no activity decreases were seen in depressed patients. This difference was found even when including only studies of repeated dosing (Ma, 2015). However, the valence-related difference in depressed and healthy subjects in the studies of this thesis may also be related to the different antidepressants used, or at least partly also to acute versus repeated dosing.

6.2 SPOKEN EMOTIONAL NARRATIVES

Both a single dose of mirtazapine in healthy volunteers and a one-week treatment with escitalopram in depressed patients were found to modulate brain responses to complex, dynamic emotional stimuli. The analysis methods of the two studies were partly different, and thus, direct comparison of the results is not meaningful, but the two studies nevertheless bring some important new insight into the mechanism of action of antidepressants. First, the auditory emotional narratives significantly increase the ecological validity of the experiment compared with the simple conditioned stimuli commonly used. Second, the fact that the narratives lacked any prosodic cues about the emotional content means that high-order linguistic and cognitive-emotional processing was required to extract and process their emotional content. Thus, the results suggest that antidepressants may not only modulate automatic processing of simple and highly salient cues, such as fearful faces, but also higher order cognitive-emotional processing of complex and natural stimuli. This brings the antidepressant effect on emotional processing one step closer to daily-life emotional situations, giving support to the theory, although not directly testing it, that modulated emotional processing at the neural level may translate into modulated, less negatively biased, daily-life emotional experiences that may in time lead to recovery from depression.

A single dose of mirtazapine modulated instantaneously varying functional connectivity in the CMS and limbic regions while listening to positive parts of the stories. A one-week treatment with escitalopram in depressed patients was found to increase

synchrony of brain responses in the MPFC, ACC, and precuneus specifically during positive parts of the stories. Taken together, using an ecologically valid emotional task and different methods of analysing the brain functioning, i.e. regional brain responses with GLM, dynamic functional connectivity, and inter-subject correlation, two different antidepressants were found to potentiate processing of positive emotional information in the anterior CMS, among other regions. The main results of the two other experiments, assessing antidepressant effect on self-referential processing, also localize in the anterior CMS. Thus, this brain region appears to have a pivotal role in the key results of the studies of this thesis overall.

6.3 MPFC AND ACC AS TREATMENT TARGETS

Abundant evidence supports the important role of the MPFC and ACC in the pathogenesis of depression. They have been identified as core regions of self-referential processing, particularly implicated in conscious self-awareness (Davey et al., 2016) and integrating emotional content into self-referential information (Northoff et al., 2006). Accordingly, this region is suggested to be a key neural substrate of excessive and negatively biased self-focus in depression (Lemogne, Delaveau, Freton, Guionnet, & Fossati, 2012). The MPFC and ACC are essential parts of the DMN. Abnormal activity of the DMN, particularly its aberrant connectivity with the MPFC/ACC, has been linked to internally focused, ruminative information processing style of depressed patients (Hamilton et al., 2015). The DMPFC (located near the region found to track biased self-referential processing of depressed patients earlier (Lemogne et al., 2009) as well as in experiment III of this thesis) has been also suggested to act as a central hub between the networks showing impaired functioning in depression. “Hot-wiring” these synergistically malfunctioning networks together may underlie the variety of depressive symptoms, seemingly arising from distinct brain regions, such as increased and negative self-perception, difficulty in focusing on cognitive tasks, and emotional and autonomic dysregulation (Sheline et al., 2010). Furthermore, the MPFC and ACC, with their connections to the ventral striatum, also have a central role in reward processing, known to be impaired in depression (Phillips et al., 2015). The role of the MPFC/ACC as a central hub interconnecting several malfunctioning brain regions and networks in depression raises it a plausible important target of treatment interventions.

This is supported by the fact that the ACC activity has been shown to predict treatment response not only to antidepressant medication, but across different treatment modalities (Pizzagalli, 2011). Interestingly, in a recent meta-analysis (Marwood, Wise, Perkins, & Cleare, 2018) activity changes after psychotherapy were also seen particularly in the ACC, suggesting that the classical dual-process model proposing psychotherapy to act mainly via improved top-down regulation from the PFC and antidepressants to act via reduced bottom-up automatic processes from the limbic system may be too simplistic. Psychotherapy acting via the ACC (and the interconnected MPFC) is intuitively reasonable, as increased self-focus and biased self-perception are important targets of psychotherapy (Teasdale et al., 2000). It is possible that the improved regulation of emotional and self-referential processing and the balance between internally and externally focused processing via normalized functioning of the ACC/MPFC are important mechanisms of action across treatment modalities.

7 LIMITATIONS OF THE STUDIES

There are several limitations in the studies presented in this thesis that should be noted. First of all, Study 1, including experiments I and II, was an open-label study. This was due to the sedative effect of mirtazapine that made effective blinding practically impossible. Thus, a second important limitation is the sedative effect of mirtazapine, which might have influenced the results. However, in both experiments I and II, adding the individual score of tiredness (as an estimate of sedation) in the drug group model had virtually no effect on responses in any of the contrasts, and neither was there any significant main effect of tiredness. In experiment I, we also did not find any effect of mirtazapine on categorization speed of neutral or emotional words. This suggests that, after excluding the subjects with a response rate of less than 90% and the ones sleeping during the task, there was no such sedation in the remaining subjects that would have influenced motor function known to be sensitive to sedation (Kim et al., 2004). This applies also to experiment III, as the same overly sedated subjects as in experiment I were also excluded here, even though the narrative task did not require responding. In experiment III, the fact that there were no group differences in mere sensory processing of the narratives, without modelling for the emotional content,

further suggests that the sedative effect did not significantly influence the sensory processing of the narratives.

All of the depressed patients and the majority of the healthy volunteers were university students, mostly young adults. Thus, the two samples were well-matched, enabling their comparison, but this may hinder the generalization of the results to older and less educated populations. However, the fact that the depressed patients were all treatment-seeking, with current depression episode lasting on average more than 6 months and half of the patients having comorbid anxiety disorders strengthen the clinical significance of the results, as the sample resembles the average patient population encountered by clinicians in daily practice.

There are a few limitations specific to Study 2. First, the placebo group had significantly higher BDI and neuroticism scores and lower agreeableness scores compared with the drug group. In experiment III, after controlling for BDI or neuroticism in second-level models, the difference between the groups in neural responses of the MPFC/ACC to positive relative to negative self-referential adjectives was no longer statistically significant. However, there was no significant correlation between the BDI or neuroticism score and the signal extracted from this region, suggesting that the effect was not driven by these baseline group differences. Furthermore, there was no significant baseline group difference in the interview-based MADRS scores, which supports the view that the differences in neural responses did not derive from differences in depression severity.

Also, the cross-sectional study design in both Studies 1 and 2 should be mentioned as a limitation, as it does not allow assessment of increased/decreased activation by the drug directly, merely enabling indirect assessment as higher/lower activation relative to the placebo or control group.

8 IMPLICATIONS FOR THE FUTURE RESEARCH

The studies of this thesis bring new insights into the mechanism of action of antidepressants, but leave many questions unresolved, thus calling for more research. The early effect of antidepressants on self-referential processing, particularly in the anterior CMS, is clinically highly relevant, as discussed earlier. Experiment III of this thesis showed for the first time that short-term treatment with escitalopram corrected

the biased self-referential processing in depressed patients. This result should be replicated, preferably in a larger cohort of patients. Direct comparison of different treatment interventions, such as different antidepressants and psychotherapy, in the same study would also be beneficial. The role of valence in antidepressant effects on emotional and self-referential processing also remains elusive and should be further studied with acute versus repeated dosing and in healthy subjects versus depressed patients.

Advancement of imaging and analysis techniques have enabled the introduction of naturalistic and complex experiment paradigms to neuroimaging studies. Experiments II and IV showed that antidepressants rapidly modulate brain activity and connectivity during processing of complex and dynamic emotional stimuli. These findings encourage the future research of the antidepressant effect on emotional processing to extend it to complex, daily-life-like emotional stimuli and analysis methods suitable for complex, free processing settings such as ISC and dynamic functional connectivity measurements. The use of ecologically valid experiment paradigms in fMRI could be combined with ecologically valid methods assessing emotional experiences in real-life, such as momentary assessment method, to investigate how changes in emotional processing translate into real-life emotional experiences.

Predictive markers for treatment response have typically been investigated by measuring baseline characteristics, e.g. pre-treatment brain activity. Better understanding of the early system-level action of antidepressants may help to find markers to predict treatment response at the early stage of treatment, which may be a more sensitive method than predicting response before treatment initiation. Considering the poor treatment outcomes in depression and the fact that treatment response can be assessed only after several weeks of treatment, it would be extremely beneficial to find biological markers directing treatment at an early stage. Importantly, these markers would also help to develop new treatment options. Longitudinal studies are required to investigate whether the early changes in emotional processing predict treatment response. The predictive value of a priori defined brain regions and tasks in individual patients should be tested in large patient cohorts to identify predictive markers useful in clinical practice. Early change in activity of the ACC/MPFC during processing of particularly positive and/or self-referential information may be a possible predictive marker warranting further investigations.

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