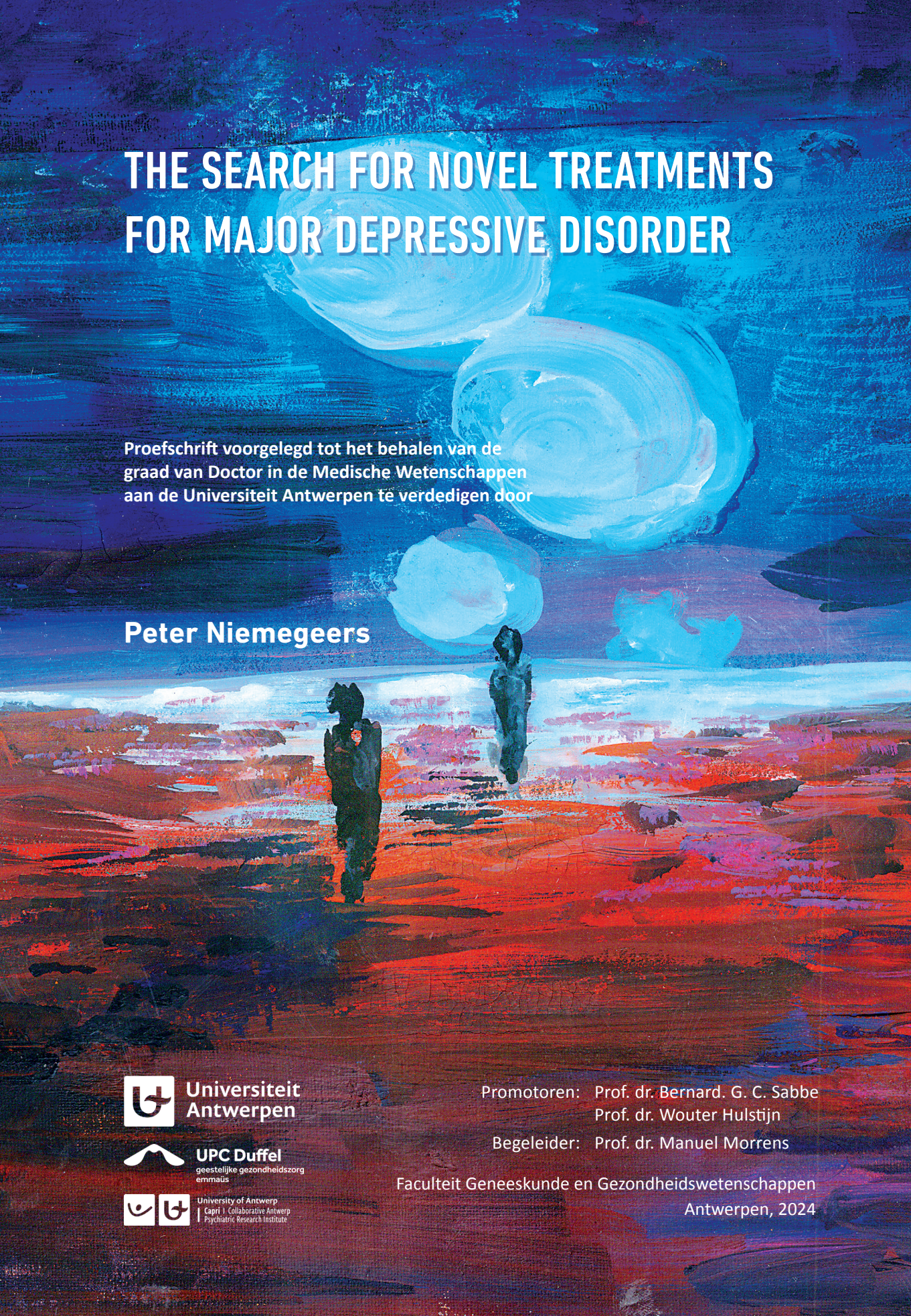
THE SEARCH FOR NOVEL TREATMENTS FOR MAJOR DEPRESSIVE DISORDER



Proefschrift voorgelegd tot het behalen van de graad van Doctor in de Medische Wetenschappen aan de Universiteit Antwerpen te verdedigen door

Peter Niemegeers

Universiteit Antwerpen

UPC Duffel
geestelijke gezondheidszorg
emmaüs

University of Antwerp
Capri | Collaborative Antwerp Psychiatric Research Institute

Promotoren: Prof. dr. Bernard. G. C. Sabbe
Prof. dr. Wouter Hulstijn
Begeleider: Prof. dr. Manuel Morrens

Faculteit Geneeskunde en Gezondheidswetenschappen
Antwerpen, 2024

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Peter Niemegeers

Cover:
Karo Vrints – www.karovrints.be

Layout en drukker:
Ridderprint | www.ridderprint.nl

ISBN/EAN:
978-94-6506-130-6

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Begeleider:	Prof. dr. Manuel Morrens
Leden van de interne doctoraatscommissie:	Prof. dr. Patrick Cras Prof. dr. Guido R. Y. De Meyer
Leden van de externe doctoraatscommissie:	Prof. dr. Chris Baeken Prof. dr. Philippe de Timary

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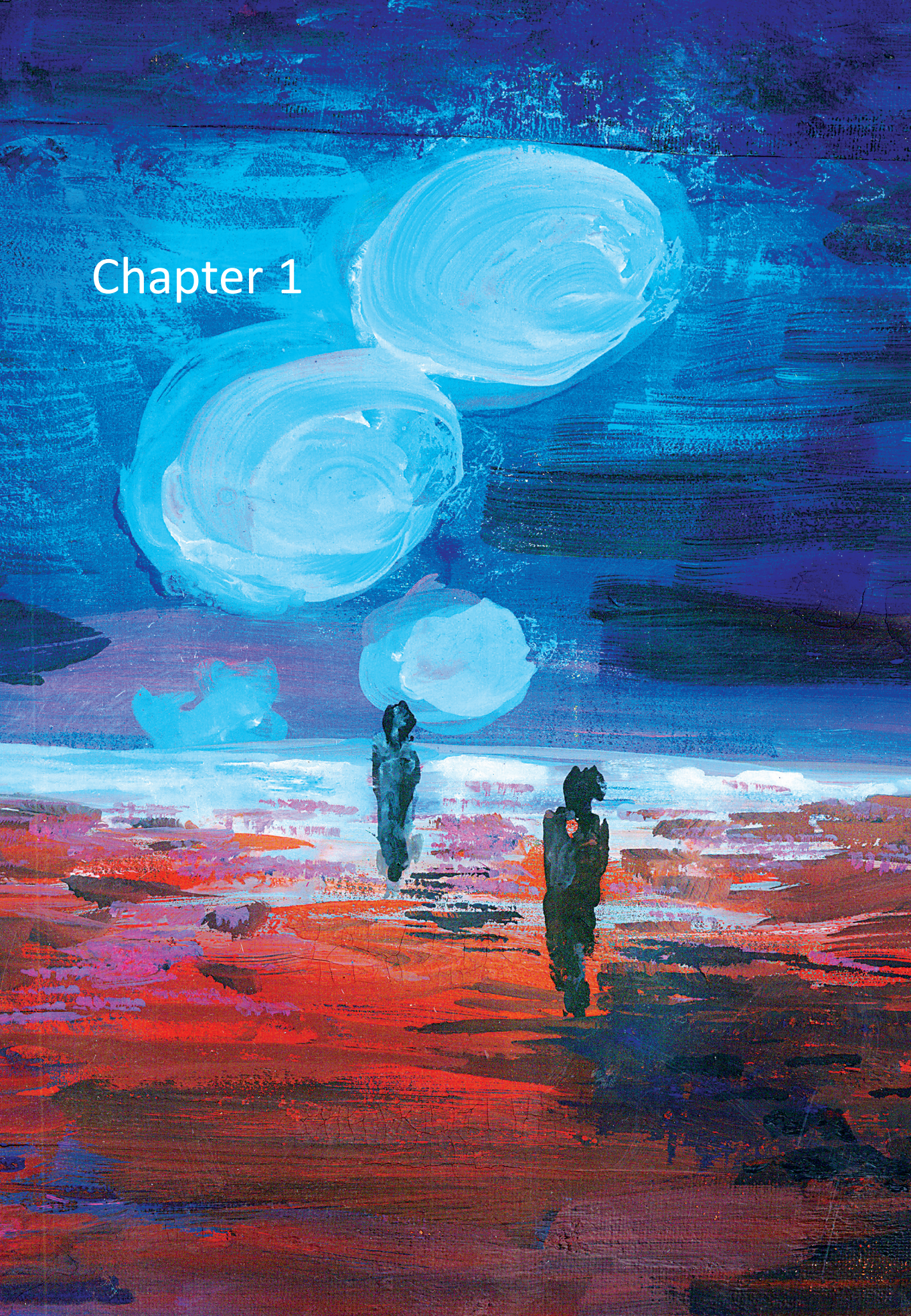
Table of Contents


Chapter 1

Introduction

Depression: a worldwide health crisis

Depression is a serious, recurrent, and highly prevalent psychiatric condition, which is now the leading cause of disability worldwide. It affects more than 300 million people worldwide, and around 800,000 people commit suicide yearly (World Health Organization, 2017). Up to one-half of suicide victims suffered from a mood disorder (Isometsa, 2014).

In the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-5), a major depressive episode (MDE) is specified as a minimum two weeks with persistent low mood or loss in interest and pleasure, accompanied by disturbances in appetite and weight, sleep disturbance, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness, or excessive or inappropriate guilt, diminished ability to concentrate or indecisiveness, and recurrent thoughts of death or suicidality (American Psychiatric Association, 2013). Besides the concentration problems, MDEs are associated with other cognitive dysfunctions such as decreased executive functioning and memory (Rock et al., 2014). Up to 67% of those with a depressive disorder also met the criteria for a current anxiety disorder (Lamers et al., 2011).

The most prevalent psychiatric disorder in which MDEs occur is major depressive disorder (MDD). MDD is specified in the DSM-5 as the occurrence of one or more MDEs, without the occurrence of hypomania or mania (American Psychiatric Association, 2013). The 12-month prevalence of MDD in Europe is estimated at 6.9% (Wittchen et al., 2011) and the lifetime prevalence at 14.6% in high-income countries (Kessler and Bromet, 2013). MDD is more prevalent in the female gender, with males being 63% less likely to develop MDD than females (Abate, 2013). MDD accounts for 7.5% of the global *years lived with disability* (World Health Organization, 2017).

Several subtypes and specifiers of MDD are described in the DSM-5. These can refer to the symptomatology of the episode, such as melancholic features (i.e., a non-reactive mood and persistent anhedonia, a reduction of appetite and sleep), atypical features (i.e., reactive mood and rejection sensitivity, an increase in appetite and sleep), psychotic features, or with anxious distress (American Psychiatric Association, 2013).

These specifiers can also refer to the temporal course of the episode. One can either experience a single MDE in his lifetime or multiple episodes (recurrent MDD) (American Psychiatric Association, 2013). It should be noted that it has a recurrent course in a significant part of the patients, with a recurrence rate of 4.3% after five years, 13.4% after ten years, and 27.1% after 20 years (Ten Have et al., 2018).

Other specifiers can also refer to the specific moment of onset of MDEs, namely with peri-partal onset or with a seasonal pattern (American Psychiatric Association, 2013). This last distinct subtype of recurrent MDD is also called *Seasonal Affective Disorder* (SAD), in which MDEs predictably occur in a particular season (typically the winter) (American Psychiatric Association, 2013). The prevalence of this condition increases with increasing latitude, with a prevalence of 1% in Florida, 2% in the United Kingdom, and 9% in Alaska (Melrose, 2015).

Numerous pathophysiological mechanisms have been proposed to underpin MDD (Li et al., 2021). The upcoming section will review the major neurobiological mechanisms presumed to be associated with depression. Despite the advances in understanding the processes underlying MDD, current treatments often fall short of achieving complete remission, leaving residual symptoms (Xiao et al., 2018). Those unmet treatment needs are reviewed in the subsequent section.

In this thesis, several distinct research projects, all regarding different aspects of MDD, are presented. They were part of a larger research line aiming to study the pathophysiology of MDD and other psychiatric disorders, with a particular emphasis on cognition. Although the research projects are not always interconnected, they reflect the multifaceted nature of MDD. Throughout the introduction, reference will be made to the relevant chapters to provide context and outline.

Pathophysiology of major depressive disorder or unipolar depression

Throughout the past decades, different theories have emerged to explain the neurobiological origin of MDD. First, the monoamine hypothesis of MDD will be reviewed, after which the role of the stress system and the immune system will be explored. Finally, the involvement of the glutamate system and of the neuroplasticity theories will be examined.

Monoamine hypothesis of depression

In the 1950s, it was observed that the monoamine neurotransmitter depleting antihypertensive reserpine could cause depressive states (Muller et al., 1955). A few years later, the antidepressant effects of imipramine and iproniazid were serendipitously discovered (Kuhn, 1958, Crane, 1956). The observation that both agents increased monoamine neurotransmitter concentrations by reuptake inhibition (imipramine) or inhibition of the monoamine oxidase (iproniazid) led to the formulation of the

monoamine hypothesis of MDD, which proposed that MDD was caused by alterations in the levels of the neurotransmitters serotonin (5-HT), norepinephrine (NE), or dopamine (DA) (Hirschfeld, 2000, Coppen, 1967).

The different neurotransmitters are implicated in various functions: 5-HT is involved in mood, anxiety, circadian rhythms, and other functions (Best et al., 2010); NE is implicated in processes such as arousal, stress response, memory, and wakefulness (Maletic et al., 2017); DA is, among other things, regulates reward, motivation, and cognitive functions (Jesulola et al., 2018).

While the observation that most effective antidepressants work by increasing one or more of the neurotransmitters corroborates this hypothesis strongly, several considerations should be made. While monoamine concentrations increase within hours of the first administration of the antidepressant drug, the clinical effect is only visible after several weeks (Jesulola et al., 2018). This observation has been explained with several theories that associate the onset of antidepressant effect with desensitization of monoamine receptors or downstream effects on other systems (Harmer et al., 2017).

Recently, non-monoamine neurotransmitter systems came into the picture, such as the glutamate system, following the discovery of the rapid antidepressant effect of ketamine, a selective antagonist of the glutamatergic N-methyl-D-aspartate (NMDA) receptor (Sanacora et al., 2012). Below there is an overview of the neurotransmitters implicated in MDD.

Serotonin (5-HT)

Serotonin or 5-hydroxytryptamine (5-HT) is synthesized from tryptophan in two steps. Tryptophan is converted by tryptophan hydroxylase to 5-hydroxytryptophan (5-HTP), which is converted to 5-HT by aromatic amino acid decarboxylase (Best et al., 2010). 5-HT neurons project to a large variety to regions in the peripheral and central nervous system. The limbic brain areas (amygdala, hippocampus, and temporal lobes), as well as the thalamus, are heavily innervated by serotonergic neurons (**Figure 1**) (Delgado and Moreno, 2006). Serotonergic neurotransmission is very complicated, with a multitude of receptor types. The most implicated in MDD are the 5-HT_{1A}, 5-HT_{1B}, 5-HT_2, 5-HT_4, 5-HT_6, and 5-HT_7 receptors (Delgado and Moreno, 2006, Yohn et al., 2017). After the release in the synaptic cleft, it is metabolized by monoamine oxidase-A (MAO-A) to 5-hydroxyindoleacetic acid (5-HIAA) or taken back into the presynaptic neuron by the serotonin transporter (SERT) (Best et al., 2010).

An increase in MAO-A is observed in some patients with MDD, implicating an increased breakdown of 5-HT, NE, and DA (Chiuccariello et al., 2014). While it was initially observed that there was decreased 5-HIAA in the cerebrospinal fluid (CSF) of depressed patients,

the evidence turned out to be conflicting (Pech et al., 2018). Moreover, acute tryptophan depletion, which decreases 5-HT in the brain, is associated with an increase in depressive symptoms in recovered MDD patients, though only in those who responded to a serotonergic antidepressant (Bell et al., 2001).

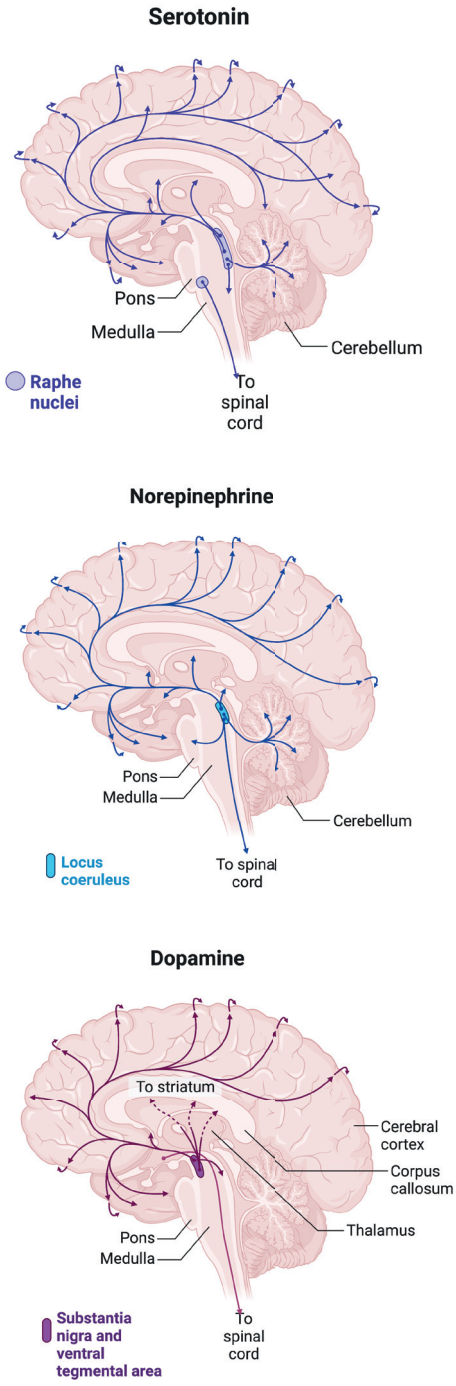
Another line of evidence suggests changes in receptor function. In several studies, an upregulation of the 5-HT_{2A}-receptor is observed in patients with MDD or a history of MDD, which can be an effect of low 5-HT levels (Shelton et al., 2009, Bhagwagar et al., 2006). Other studies found decreased binding of the 5-HT_{2A}-receptor (Newberg et al., 2012). Disturbances in 5-HT_{1A}-function, such as increased binding of the inhibitory 5-HT_{1A} receptors on PET-scans, are also observed (Kaufman et al., 2016). Downregulation of the 5-HT_{1A}-receptor is also associated with response to antidepressant drugs (Jacobsen et al., 2012). There is also evidence that MDD is associated with reduced function of SERT (Newberg et al., 2012). The observation that serotonergic antidepressants have a proven antidepressant effect also corroborates the hypothesis that 5-HT has a role in depression (Cipriani et al., 2018).

Norepinephrine (NE)

NE is synthesized from the amino acid phenylalanine and tyrosine. Phenylalanine can be converted to tyrosine. Tyrosine is first converted to dihydroxyphenylalanine (DOPA) and then to DA. DA is metabolized by dopamine beta-hydroxylase to NE. Noradrenergic neurons originate mainly from the locus coeruleus (LC) and project to several parts of the brain (**Figure 1**). Noradrenergic neurotransmission happens through the α-, and β-subgroups of receptors (Delgado and Moreno, 2006). In the synaptic cleft, it is metabolized by MAO-A and Catechol-O-methyltransferase (COMT), or taken back to the neuron by the NE transporter (NET) (Maletic et al., 2017).

Desensitized α_1-receptors are observed in MDD (Maletic et al., 2017). Post-mortem studies of depressed suicide victims show indeed increased binding of the adrenergic α_2-receptors, which suggests a decrease in NE function (Ordway et al., 2003, Valdizan et al., 2010). Elevated NET availability has also been observed in depressed subjects (Moriguchi et al., 2017). Moreover, NE reuptake inhibitors and mirtazapine, an antagonist of the presynaptic α_2-receptor, were shown to be effective antidepressants (Eyding et al., 2010, Holm and Markham, 1999, Nierenberg et al., 2003, Nelson et al., 1995). Parallel with the depletion studies with 5-HT, catecholamine depletion increased depressive symptoms, but only on those patients who responded to a noradrenergic antidepressant (Miller et al., 1996, Delgado et al., 1993).

Figure 1: Distribution of Monoamine Neurotransmitters in the Human Brain (Biorender.com, 2022a)



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Dopamine (DA)

The synthetization of DA is described above. In the synaptic cleft, dopamine is broken down by the MAO-A, MAO-B, and COMT enzyme (Dunlop and Nemeroff, 2007). There are different pathways of DA projecting neurons, of which the mesolimbic and mesocortical pathway are of most interest in MDD (**Figure 1**) (Delgado and Moreno, 2006).

A reduced dopaminergic function has been hypothesized to cause anhedonia, one of the core symptoms of depression (Dunlop and Nemeroff, 2007). Some studies found decreases in dopaminergic neurotransmission (Dunlop and Nemeroff, 2007, Belujon and Grace, 2017). It is suggested that MDD is associated with a dysregulation of the reward system (Belujon and Grace, 2017). The antidepressant bupropion, which is a NE and DA reuptake inhibitor, has proven efficacy, also suggesting the involvement of DA in MDD (Cipriani et al., 2018).

The Hypothalamic–Pituitary–Adrenal (HPA) axis in depression

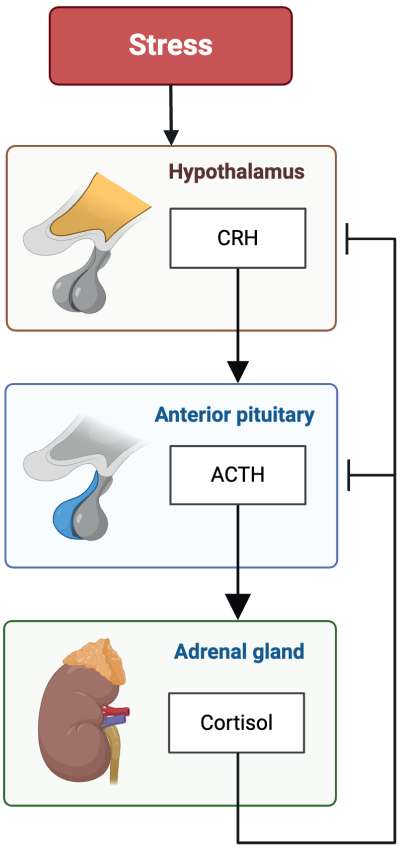
The hypothalamic-pituitary-adrenal (HPA) axis (**Figure 2**) is also implicated in the pathophysiology of MDD. The HPA-axis is activated upon stress in the broad sense (e.g., psychological stress, infection, etc.) (Smith and Vale, 2006). As the body encounters stress, the paraventricular nucleus of the hypothalamus will secrete Corticotropin-Releasing Hormone (CRH) and Arginine Vasopressin (AVP), which will stimulate the anterior pituitary to release Adrenocorticotropic Hormone (ACTH) that will activate the adrenal glands to produce cortisol (Smith and Vale, 2006). The secretion of CRH and AVP by the hypothalamus is controlled by the hippocampus, the amygdala, and the prefrontal cortex (Herman et al., 2016). Negative feedback happens through the binding of cortisol on the glucocorticoid (GR) and mineralocorticoid receptor (MR) (Harris et al., 2013).

It is theorized that MDD is associated with a hyperactive HPA-axis (Plotsky et al., 1998). Continued activation of the HPA-axis, related to chronic stress, leads to desensitization of the negative feedback loop, leading to prolonged and uncontrolled activation of the HPA-axis (Claes, 2004). Mainly the desensitization of the GR seems to play a pivotal role in the HPA-axis hyperactivity in MDD (Anacker et al., 2011).

About 40-60% of severely depressed patients have increased cortisol levels. Hypercortisolemia is mainly associated with melancholic and psychotic depression (Carroll et al., 2007, Gold et al., 1986, Parker et al., 2003). Increased levels of CRH are also observed in the CSF, as well as an increase in the size of the pituitary and adrenal glands (Varghese and Brown, 2001, Binder and Nemeroff, 2010).

This hypothesis is further corroborated by the observation of non-suppression in the Dexamethasone Suppression Test (DST). In healthy controls, the production of cortisol is inhibited for over at least 24h following the administration of dexamethasone, a corticoid that binds strongly on the GR (Findling et al., 2004). However, in a subgroup of patients with MDD, it is observed that there is no suppression of cortisol following dexamethasone, implicating malfunctioning negative feedback of the HPA-axis (Nelson and Davis, 1997). Similar results are observed in a similar test, the Dexamethasone/CRH (DEX/CRH) test. This test is like the DST, but CRH is also administered. While in healthy controls, there is a blunted cortisol response to CRH following dexamethasone, this is not observed in a subset of patients with MDD (Heuser et al., 1994, Van Den Eede et al., 2006).

Figure 2: The Hypothalamic-Pituitary-Adrenal axis (Biorender.com, 2022b)



ACTH: Adrenocorticotropic Hormone; CRH: Corticotropin Releasing Hormone.
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The immune system in depression

Converging evidence suggests the involvement of the inflammatory system in MDD. Pro-inflammatory states are associated with *sickness behavior*. This is a set of behavior changes during physical illness and is adaptive to fight infection. It includes malaise, weakness, fatigue, anhedonia, showing little interest in the surroundings, and reduction of appetite (Dantzer, 2001). This behavior is induced by pro-inflammatory cytokines, such as Interleukin (IL)-1, IL-6, and Tumor Necrosis Factor (TNF)-α, which are produced by cells of the innate immune system when they meet pathogens. These pro-inflammatory cytokines then serve as a signal of sickness to the brain and induce sickness behavior (Dantzer, 2009). While these peripherical produced pro-inflammatory cytokines do not pass the blood-brain barrier (BBB), it is proposed that they exert their central effects by passing through leaky regions of the BBB, activation of peripheral afferent nerves such as the Vagus nerve that in turn activate ascending catecholaminergic fibers, and by transportation by activated immune cells, mainly monocytes, to the brain (Miller and Raison, 2016).

There is an overlap between the symptoms of MDD and the sickness behavior mentioned above. Indeed, it has been repeatedly observed that pro-inflammatory cytokines are increased in MDD patients compared to controls, with evidence being particularly strong for IL-6 and TNF-α (Kohler et al., 2017, Dowlati et al., 2010). There are also increased acute phase reactants, such as C-reactive protein (CRP), measured in MDD patients (Dowlati et al., 2010, Miller et al., 2017).

MDD is also a frequent side effect of immune-stimulating treatments, with up to 40% developing MDD after treated with interferon (IFN)-α (Schafer et al., 2007). Depression is also often observed in patients with chronic inflammatory diseases (*e.g.,* rheumatoid arthritis, inflammatory bowel disease, and others), further corroborating the link between MDD and inflammation. (Ambriz Murillo et al., 2015, Pryce and Fontana, 2017, D'Mello and Swain, 2017). Moreover, it has also been repeatedly shown that administration of pro-inflammatory stressors, such administration of endotoxin or the *Salmonella typhi* vaccination, induce a pro-inflammatory state associated with a mild but significant transient decrease in mood (Strike et al., 2004, DellaGioia and Hannestad, 2010, Reichenberg et al., 2001, Eisenberger et al., 2009, Eisenberger et al., 2010, Benson et al., 2017, Kotulla et al., 2018, Wright et al., 2005, Brydon et al., 2009, Harrison et al., 2009).

Pro-inflammatory cytokines exert their effect on mood through several pathways. Firstly, there seems to be an effect on monoamine neurotransmitters, with the increase of expression of reuptake pumps through induction of p28 mitogen-activated protein kinase (MAPK) and a decrease of tetrahydrobiopterin (BH4), an essential co-factor for monoamine synthesis (Miller and Raison, 2016). Pro-inflammatory states also affect

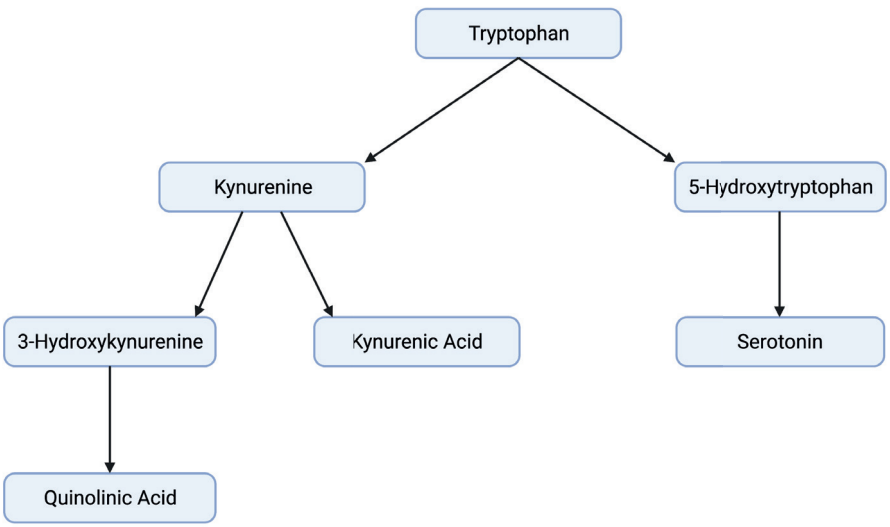
tryptophan metabolism by activating the *kynurenine-pathway* (**Figure 3**). Tryptophan, besides being metabolized to serotonin, can be metabolized by the enzyme indoleamine 2,3-dioxygenase (IDO) to kynurenine (KYN), which readily passes the BBB (Allison and Ditor, 2014). Pro-inflammatory cytokines stimulate the kynurenine-pathway by inducing IDO, shifting tryptophan metabolism away from serotonin production, thus depleting serotonin (Reus et al., 2015).

Kynurenine is further metabolized into quinolinic acid (QUIN) and kynurenic acid (KYNA). QUIN is mainly produced by microglia and monocytes; KYNA is produced primarily by astrocytes (Reus et al., 2015). Besides the effect of the kynurenine-pathway on serotonin, these metabolites have effects of their own, which is a second mechanism by which inflammation can cause mood changes.

While KYNA seems to be neuroprotective through NMDA receptor antagonism, QUIN has neurotoxic effects through agonism of the NMDA receptor and decreasing glutamate reuptake and increasing glutamate release of the astrocytes, leading to excitotoxicity (Miller and Raison, 2016).

Chapter 2 and **3** will examine the link between inflammation and psychosocial stress and MDD. These chapters will discuss a study on the effects of inflammatory and psychosocial stressors in patients with recurrent MDD in remission.

Figure 3: The Kynurenine Pathway



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The glutamatergic system in depression

Some evidence has also linked glutamate and γ-aminobutyric acid (GABA) to MDD. Glutamate is an amino acid, and the primary excitatory neurotransmitter throughout the central nervous system (CNS) (Zhou and Danbolt, 2014). GABA, on the other hand, is the primary inhibitory neurotransmitter of the CNS (Mohler, 2012). Glutamate, and to a lesser extent GABA, are ubiquitous and the CNS, to the extent that the brain can be conceptualized as a "glutamate excitatory machine", in which glutamate has a stimulating role and GABA acts as a break (Sanacora et al., 2012).

Several lines of evidence show that there are disturbances in both glutamate, GABA, and the balance between both in MDD. In some studies, MDD seems to be associated with elevations of glutamate, as is observed in plasma, CSF, and post-mortem brain tissue of patients with mood disorder (Sanacora et al., 2012). Functional neuroimaging shows that MDD is associated with increased glutamate in the occipital cortex and decreased glutamate in de dorsolateral prefrontal cortex and anterior cingulate cortex (Li et al., 2018). Ketamine, an antagonist of the glutamatergic NMDA-receptor, has a rapid and profound antidepressant effect, which further suggests the involvement of glutamate in MDD (Grady et al., 2017). In line with this observation, in **Chapter 5** a case report is presented of the MDD with resistance to electroconvulsive therapy (ECT), treated with ketamine augmentation.

On the other hand, decreased levels of GABA are observed in plasma, CSF, and on PET scans in MDD patients (Luscher et al., 2011). GABA also inhibits the Hypothalamic–Pituitary–Adrenal (HPA)-axis, which has a role in depression (see below), and MDD patients are observed to have altered $GABA_A$-receptor function (Luscher et al., 2011, Herman et al., 2004). Moreover, benzodiazepines were observed to have antidepressant effects in some MDD patients (Benasi et al., 2018).

Neuroplasticity theories of depression

An often replicated finding in MDD is that there is a reduction in the size of the hippocampus, as well as the prefrontal cortex, which is hypothesized to be due to decreased neurogenesis and increased apoptosis (Liu et al., 2017). It is also observed that there is a decrease in neurotrophic factors such as Brain-Derived Neurotrophic Factor (BDNF) (Krishnan and Nestler, 2008). BDNF is an important neurotrophic factor and acts by activating the tropomyosin receptor kinase B (TrkB) receptor (Lee and Kim, 2010).

BDNF might be the link between the aforementioned hypotheses of depression. First, it has been shown that reuptake inhibition of monoamines by antidepressants increases the transcription of BDNF through an increase of cAMP response element-binding protein (CREB) (Krishnan and Nestler, 2008). Indeed, it is observed that antidepressant treatment reverses hippocampal atrophy (Gradin and Pomi, 2008).

Second, there is also a link between HPA-axis and neurogenesis. The hypercortisolemia due to HPA-axis hyperactivation leads to decreased neurogenesis and increased apoptosis in the hippocampus. This observation is also seen in non-psychiatric disorders such as Cushing's disease (Conrad, 2008, Ferrari and Villa, 2017). Indeed, there appears to be a link between the hyperactivation of the HPA-axis and decreased levels of BDNF (Kunugi et al., 2010).

Finally, several lines of evidence suggest that pro-inflammatory states decrease neurogenesis. (Hayley, 2014). Pro-inflammatory states are suggested to decrease BDNF. In preclinical studies, the administration of LPS or pro-inflammatory cytokines reduces BDNF concentrations (Zhang et al., 2016). Decreases of BDNF are also possible through increased activation of the NMDA receptors (Hardingham et al., 2002, Miller and Raison, 2016).

Unmet treatment needs

The treatment of MDD consists mainly of pharmacotherapy and psychotherapy. A multitude of antidepressants is available for the treatment of MDD. First-line pharmacological treatment usually consists of treatment with an antidepressant such as a selective serotonin reuptake inhibitor. In the case of non-response, several switching and augmentation strategies are available. For a thorough review, we refer to Dupuy et al. (2011). When there is no treatment response to multiple courses of pharmacotherapy and psychotherapy, ECT is a highly effective treatment option (UK ECT Review Group, 2003).

Incomplete recovery on standard treatment

In the treatment MDEs, a reduction of ≥50% of the symptoms on a depression rating scale is considered a response to treatment. The absence or near absence of depressive symptoms is considered remission, usually defined as a score below a certain cut-off point on a depression rating scale (Novick et al., 2017). The concept recovery is less clearly defined, with some authors defining it as a certain period in remission (Furukawa et al., 2008) and others defining it as full functional remission (Novick et al., 2017).

Low remission rates

While remission and recovery are the goals of depression treatment, this is often not achieved with the current therapies. Generally, in antidepressant trials, remission rates are around 30-40%, and response rates around 60-70% (Entsuah et al., 2001, Khan and Brown, 2015, Steffens et al., 1997).

In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Trial, a group of 2876 patients with MDD were treated with four different treatment steps. After these treatment steps, the cumulative response rate was only 67% (Sinyor et al., 2010). In the STAR*D-trial, remission and response rates after the first treatment step (i.e., citalopram) was only 28% and 47%, respectively (Trivedi et al., 2006).

Indeed, up to 15% of patients fail to respond to any pharmacological treatment (Berlim and Turecki, 2007). The definition of treatment-resistant depression (TRD) is unclear in the literature, with using the relatively loose criterion of failure to respond to two adequate medication trials and others using more stringent criteria up to the failure to respond to electroconvulsive therapy (ECT) (Berlim and Turecki, 2007, Fekadu et al., 2018).

Generally, ECT is considered an adequate treatment step if patients fail to respond to pharmacological treatment (Leiknes et al., 2012). While ECT has impressive remission rates (95% for psychotic depression and 83% for non-psychotic depression), there is still a minority that does not respond to it (Petrides et al., 2001). To our knowledge, there are no guidelines on how to proceed after ECT failure. As such, in **Chapter 5**, a case report of ketamine augmentation for a case of TRD resistant to ECT is discussed.

Residual symptoms

As discussed in the previous paragraph, a significant number of patients do not remit after treatment. Moreover, many patients even experience residual symptoms in remission. In a study by Sheehan et al. (2011), 38% of treated MDD patients achieved remission, 32% achieved functional remission, and only 23% achieved combined functional and symptomatic remission. As such, more complete functional recovery is proposed as the treatment goal (Fiorillo et al., 2018, van der Voort et al., 2015). While residual symptoms reduce psychosocial functioning and quality of life, they are also a significant risk factor for recurrence (Bockting et al., 2006).

In the STAR*D-trial, over 90% of remitted patients had at least one residual symptom (Nierenberg et al., 2010). Several common residual symptoms seen in remitted patients are cognitive problems (in 44%), fatigue (35%), and sleep disturbances (39%) (Conradi et al., 2011, Fava et al., 2014, Fiorillo et al., 2018).

Fatigue is present in over 90% of the patients with MDD and persists in up to 49% after remission (Fava et al., 2014, Ghanean et al., 2018). It is also associated with decreased work performance (Demyttenaere et al., 2005).

Another common residual symptom is cognitive dysfunction. MDEs are associated with deficits in executive functioning, memory, and attention (Rock et al., 2014). It is present in up to two-thirds of the patients (Rock et al., 2014, Afridi et al., 2011). It can also persist in almost half of the patients who are in remission (Conradi et al., 2011).

These cognitive symptoms can reduce psychosocial functioning. In a large European cross-sectional study (n = 21 425), attention and concentration problems, together with feelings of embarrassment, mediated most strongly activity and role functioning limitations in MDD (Buist-Bouwman et al., 2008). In this sense, some authors propose cognitive remission as one of the goals in MDD treatment (Bortolato et al., 2016, Culpepper et al., 2017). The cognitive symptoms may even predate the onset of depressive symptoms, as in several studies, poor episodic memory performance predicted the onset of depressive symptoms (Airaksinen et al., 2007, Simons et al., 2009).

There is no clear pathophysiological origin of this cognitive dysfunction. In the monoamine hypothesis, cognitive dysfunction is proposed to be associated with a decreased catecholaminergic function (Clark and Noudoost, 2014). It can also be related to HPA-axis hyperactivity, and one polymorphism of the glucocorticoid receptor is associated with reduced cognitive function (Keller et al., 2017). Pro-inflammatory states, changes in glutamate neurotransmission, and reduced neuroplasticity have also been associated with changes in cognitive function (Sanacora et al., 2012, Sartori et al., 2012, Albert, 2019). The nicotinic acetylcholine receptor (nAchR) is also a well-researched target in the field of cognition, with several studies showing a cognition improving effect of nAchR stimulation (Quisenaerts et al., 2013a, Quisenaerts et al., 2013b). The nAchR has also been proposed as a potential target for depression, with the potential of mood-improving and pro-cognitive effects (Philip et al., 2010, Philip et al., 2012). In **Chapter 4**, we will review a study on the pro-cognitive effects of nicotine in healthy volunteers.

The effect of antidepressants on cognition has conflicting findings. While some studies find cognitive improvement paralleling reductions in depressive symptoms, others find no effect of antidepressants on cognition (Rosenblat et al., 2015, Sayyah et al., 2016, Shilyansky et al., 2016). However, while the pro-cognitive effect of bupropion was observed (Gualtieri and Johnson, 2007), other studies found no effects of venlafaxine (Shilyansky et al., 2016), duloxetine, and escitalopram (Herrera-Guzman et al., 2010). Recently, vortioxetine, a novel antidepressant with combining direct serotonin receptor modulating activity and serotonin reuptake inhibition, was shown to increase cognition in depressed patients (Baune et al.,

2018, McIntyre et al., 2016, Vieta et al., 2018, Frampton, 2016). Some studies explored the efficacy of stimulants for cognitive improvement (DeBattista et al., 2004, Madhoo et al., 2014). However, they are not (yet) mainstay treatment and may carry the risk of side effects (Culpepper et al., 2017).

Several lines of evidence also suggest an increased negative bias in patients with a MDE (Lu et al., 2017, Duque and Vazquez, 2015, Li et al., 2017). These cognitions can be identified as "hot" (emotion-laden) cognition, compared to the aforementioned non-emotion-laden "cold" cognitions. These "hot" cognitions are hypothesized to partially mediate the "cold" cognitions (Roiser and Sahakian, 2013, Miskowiak and Carvalho, 2014). The negative emotional bias in depression has been shown to be reversed with a single dose of reboxetine, before any clinical effect on depressive symptoms was seen (Wells et al., 2014, Harmer et al., 2009). In **Chapter 3,** we will further explore the effects of several stressors (inflammation or psychosocial stress) on these "cold" and "hot" cognitions.

High recurrence rate after successful treatment

MDD is a recurrent illness, and at least 60% will relapse after the first episode (American Psychiatric Association, 2013), with some studies reporting a higher percentage. For example, a 15-year follow-up study found a recurrence rate of 85% (Mueller et al., 1999). While continued antidepressant treatment is highly effective and halves the risk for recurrence, some people still relapse (Sim et al., 2015). Residual symptoms are a significant risk factor for relapse in depression (Hiranyatheb et al., 2016).

The onset of MDD is usually associated with psychosocial stress (Charney and Manji, 2004). However, with recurrent episodes, stress seems to be less and less related to episode onset (i.e., the *kindling hypothesis*). Indeed, Kendler et al. (2000) observed that during the first nine episodes, the role of psychosocial stress in episode onset declined progressively. With further episodes, there appeared to be no connection anymore between psychosocial stress and episode onset.

Two theories are proposed for this phenomenon. The *stress autonomy* model states that after several episodes, mood episodes occur independent of stressors, leading to the spontaneous reoccurrence of depressive episodes. The *stress sensitization* model says that the number of episodes is positively associated with sensitization to stress. As such, minor stressors, which are not identified in studies, can lead to a recurrence of a mood episode (Monroe and Harkness, 2005, You and Conner, 2009).

It should be noted that in the literature different authors use different terminology. Authors such as Monroe and Harkness (2005) equal kindling to stress autonomy and treat stress sensitisation as a different theory. On the other hand, other authors such as You and Conner (2009) treat stress autonomy and stress sensitisation as two different hypotheses explaining the kindling phenomenon.

Chapter 2 will examine more in depth this phenomenon of stress sensitivity, investigating whether patients with recurrent MDD in remission exhibit greater sensitivity to specific stressors (in this study, an inflammatory or a psychosocial stressor is used). Chapter 6 will explore the preventive treatment of SAD or winter depression, where MDEs emerge at predictable moments (namely the winter season).

Thesis overview

MDD is a common psychiatric disorder with multiple underlying pathophysiological mechanisms, as reviewed above. With current therapeutical approaches, many patients still experience residual symptoms, such as cognitive dysfunction, or do not respond to treatment at all. Moreover, in most patients, MDD is a recurrent disorder.

This thesis aims to examine new strategies to address these unmet needs in treating MDD. The focus of this thesis will be primarily on the pharmacological and biological aspects of depression treatment. As mentioned before, this thesis will present different research projects focusing on various aspects of the pathophysiology and treatment of MDD.

MDD is in most patients a recurrent condition, with some studies reporting up to 85% recurrence after a first episode (Mueller et al., 1999). While continued antidepressant treatment effectively prevents recurrence (Sim et al., 2015), further understanding the mechanisms of recurrence would be beneficial for future prevention strategies. As such, in **Chapter 2**, a study will be discussed in which the sensitivity to stress is examined in a sample of MDD patients in (partial) remission. The stressors used were either an inflammatory stressor, as inflammation is increasingly implicated in MDD, a psychosocial stressor, or a combination of both. The effects of mood and biomarkers were explored.

As previously stated, cognitive dysfunction is a frequent residual symptom after resolution of MDD (Conradi et al., 2011). **Chapter 3** further explores in detail the data from the study of **Chapter 2** to determine whether the earlier stated stressors also lead to changes in cognitive function in patients with (partially) remitted MDD.

Despite it being a frequent residual symptom, few treatment options are available for cognitive dysfunction, with the evidence of the positive effects of current antidepressants being conflicting (Rosenblat et al., 2015, Sayyah et al., 2016, Shilyansky et al., 2016). The nicotinergic system is often implicated in cognition. **Chapter 4** presents a study to examine the cognitive-enhancing effects of nicotine in healthy volunteers as a proof-of-concept for possible research in clinical populations.

Despite the existence of residual symptoms, the majority of patients respond to treatment (Khan and Brown, 2015). However, a significant minority of patients do not respond to treatment (Berlim and Turecki, 2007), with some even not responding to ECT (Petrides et al., 2001). In **Chapter 5**, a case will be presented with MDD resistant to ECT, which achieved remission with ketamine add-on treatment.

Seasonal affective disorder (SAD) is a little-researched subtype of MDD where depressive episodes are associated mainly with certain seasons (usually winter) (Melrose, 2015). **Chapter 6** reviews the use of preventive treatment of MDEs during winter months with bupropion, an atypical antidepressant.

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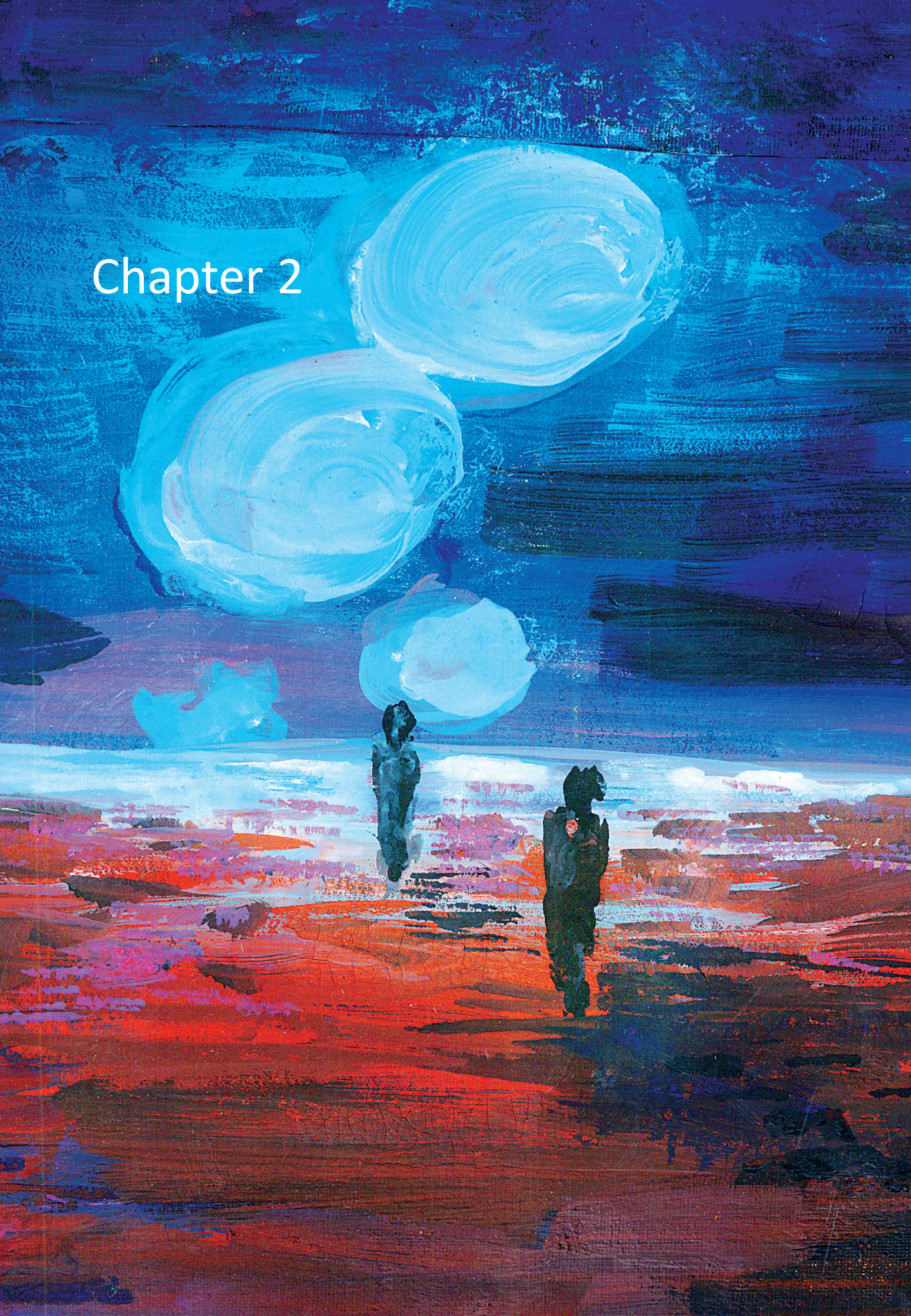

Chapter 2

Differential Effects of Inflammatory and Psychosocial Stress on Mood, Hypothalamic-Pituitary-Adrenal Axis, and Inflammation in Remitted Depression

This chapter has been published as:
Niemegeers, P., de Boer, P., Dumont, G. J. H., Van Den Eede, F., Fransen, E., Claes, S. J., Morrens, M. & Sabbe, B. G. C. 2016. Differential Effects of Inflammatory and Psychosocial Stress on Mood, Hypothalamic-Pituitary-Adrenal Axis, and Inflammation in Remitted Depression. Neuropsychobiology, 74, 150-158.

Abstract

Background/Aims: Major depressive disorder (MDD) is highly recurrent. This may be due to increased stress sensitivity after remission. Both inflammatory and psychosocial stressors are implicated in the pathogenesis of MDD, but the additive or differential effect is unclear.

Methods: We conducted a single-blind placebo-controlled study to investigate the effects of inflammatory stress (i.e., typhoid vaccination), psychosocial stress (i.e., Trier Social Stress Test [TSST]), or a combination of both in women (25–45 years old) with (partially) remitted recurrent MDD (n = 21) and healthy female controls (n = 18). We evaluated the effect on mood measured by the Profile of Mood States, markers of the hypothalamic-pituitary-adrenal (HPA) axis activity, and inflammatory system activation. The study was performed during two testing days, separated by a washout of 7–14 days. In a crossover design, subjects received one of the interventions on one day and placebo on the other.

Results: A lowering of mood was seen in patients (β [95% CI] = -4.79 [-6.82 – -2.75], $p < 0.001$) only after vaccination, but not after the TSST or the combination; this effect was not observed in controls. Controls experienced a significantly different response on Adrenocorticotropic Hormone (ACTH) after vaccination, with a general rise in ACTH not observed in patients. In both groups, the TSST activated the HPA-axis and suppressed the inflammatory parameters.

Conclusions: There is a differential effect of inflammatory and psychosocial stress on mood and HPA-axis activation in patients with remitted recurrent MDD. This may be an interesting treatment target in MDD.

Introduction

Major depressive disorder (MDD) is a highly recurrent illness and a major cause of disease burden (Ferrari et al., 2013). While the exact pathophysiology remains unclear, MDD onset is associated with psychosocial stress (Hammen et al., 2009), as patients experience more negative life events in the year before the first episode (Horesh and Iancu, 2010). Psychosocial stress activates the *hypothalamic-pituitary-adrenal* (HPA) axis, resulting in glucocorticoid production. Chronic stress and the resulting hyperactivity of the HPA-axis may eventually result in depressive symptoms (Chrousos, 2009). Accumulating evidence shows that the inflammatory system is also involved in the pathogenesis of depression. Compared to healthy controls, patients with MDD have increased levels of proinflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) (Dowlati et al., 2010, Liu et al., 2012). Furthermore, treatment of somatic disorders with interferon-α, a proinflammatory cytokine, induces depression in up to 50% of treated patients (Capuron et al., 2002).

At least 60% of patients with MDD will relapse after remission of a single episode (American Psychiatric Association, 1994). While the first episodes of MDD are clearly associated with psychosocial stress, with recurrent episodes, psychosocial stress seems to be progressively less related with episode onset (Kendler et al., 2000). Currently, there are two main theories explaining this phenomenon. The *kindling model* states that after numerous episodes, depressive episodes become independent of stressors, thereby leading to the spontaneous recurrence of depressive episodes (Kendler et al., 2000). The *sensitization model* states that the number of depressive episodes is positively associated with sensitization to the effects of stress. Thus, even minor (not identifiable) stressors lead to a relapse, clouding the association between stress and episode onset (Monroe and Harkness, 2005, Horesh and Iancu, 2010).

Cross-sensitization between different kinds of stressors is possible (Post, 2010). For example, previous studies in rats showed that an inflammatory challenge potentiates a later response to psychosocial stress (Schmidt et al., 1995, Hayley et al., 1999). Conversely, prior psychosocial stress increased HPA-axis activation and inflammatory response to an inflammatory challenge in rats (Johnson et al., 2002a, Johnson et al., 2002b, Frank et al., 2012). In one study, psychosocial stress increased the negative effects of inflammatory stress in healthy males (Brydon et al., 2009a). Compared with healthy controls, women with a history of MDD showed an amplified inflammatory response post-partum, suggesting a sensitized inflammatory response (Maes et al., 2001).

Although the negative effects of inflammation on mood have been demonstrated in healthy controls (Wright et al., 2005, Strike et al., 2004), to our knowledge, no study has examined the effects of an inflammatory stressor on current or remitted MDD. In the

present study, we evaluated the effects of inflammatory and psychosocial stress, and the combination thereof, on mood, inflammation biomarkers, and the HPA-axis, in remitted MDD patients and healthy controls. We hypothesized that MDD patients, even when remitted, show an increased sensitivity to these stressors, indicating a vulnerability factor. We also hypothesized that there would be a cross-sensitization between inflammation and psychosocial stress, with both having additive or synergistic effects. The *Salmonella typhi* vaccination was used as the inflammatory stressor, as it has been shown to induce a transient decrease in mood (Wright et al., 2005, Strike et al., 2004); the "Trier Social Stress Test" (TSST) was used as the psychosocial stressor (Kirschbaum et al., 1993). The first objective was to evaluate the effects of the interventions on mood, measured using the Profile of Mood States (POMS) questionnaire. Secondly, we explored the differential effects of these stressors on several biomarkers of inflammation and HPA-axis functioning.

Methods and Materials

Participants

Twenty-one women with (partially) remitted and recurrent MDD and 18 female controls aged 25–45 years provided informed consent and participated in the study. Three patients dropped out during the study and were replaced. Only women were selected because of possible sex differences in stress and inflammatory response (Rohleder et al., 2001). The patient group had moderate to severe recurrent MDD (without psychotic features), currently in (partial) remission, using the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revised (DSM-IV-TR) (American Psychiatric Association, 1994), with the most recent depressive episode being within the last 24 months and a minimum 3-month stable period. Patients had to have a score below 15 on the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), a body mass index (BMI) of 18–30 kg/m^2, and be medically stable with respect to vital signs, clinical examination, and clinical laboratory tests (blood and urine sample). Exclusion criteria were another axis 1 diagnosis; substance abuse or dependence within the past 6 months (excluding nicotine and caffeine); acute suicidal behavior; a history of serious disease; prior exposure to the TSST; exposure to severe psychosocial stress within the previous 6 months; or typhoid vaccination within the previous 5 years. Participants treated with more than one antidepressant or drugs compromising the immune system were excluded. Controls were recruited using advertisements. Patients were recruited from the participating institutions and the surrounding private practices of psychiatrists, psychologists, and general practitioners.

The study was conducted at the University Department of Psychiatry, campus Psychiatric Hospital Duffel, Belgium, and the University Psychiatric Center KU Leuven, campus Leuven, Belgium. Approval for the study was obtained from the central and local Ethics Committees, and the Belgian Health Authorities. This study complied with the regulations of the participating institutions, the International Conference on Harmonization Good Clinical Practice guidelines, and the European Directive 2001/20/EC. It was registered under the identifiers *NCT01533285* (ClinicalTrials.gov-database) and *2011-004898-80* (EudraCT-database)

Study Design

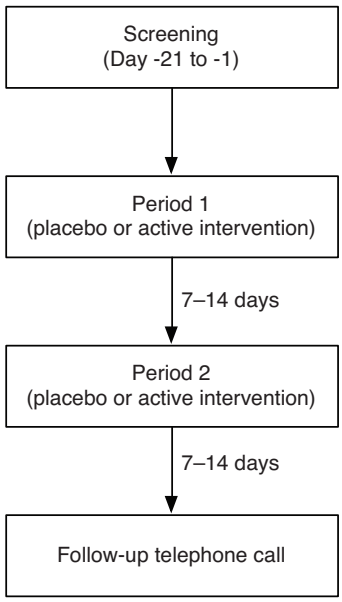
We conducted a two-way, randomized, single blind, placebo-controlled crossover study to assess the effects of an inflammatory stressor, a psychosocial stressor, and the combination thereof on mood, cytokine levels, and HPA-axis markers. The first visit consisted of an eligibility screening and also administration of the Childhood Trauma Questionnaire (CTQ), a retrospective self-report questionnaire of childhood abuse and neglect (Bernstein and Fink, 1997). Eligible participants were randomized by the sponsor to one of the treatment sequences using a computer-generated sequence. Only participants were blinded. The study consisted of two treatment periods separated with a washout of 7–14 days, and a follow-up telephone call 7–14 days after the last treatment period, to inform about possible late side effects of the intervention (**Figure 1**). There were six possible treatment sequences: for each treatment group a sequence with placebo on the first period and active treatment on the second period and vice versa).

At the start of each treatment day, an alcohol breath test and urine drug and pregnancy screening were administered. If applicable, the TSST was administered at 12:00 PM. The TSST is a social stress paradigm in which the participant is asked to do a five-minute fictitious job interview after a three-minute preparation and a five-minute arithmetic exercise for a cold and distant audience, while speaking into a microphone and being video recorded (Kirschbaum et al., 1993).

At 12:20 PM, the subject received either a placebo injection (0.5 mL NaCl 0.9%) or the typhoid vaccine (0.5 mL containing 25 µg *Salmonella* Typhi capsular polysaccharide; Typhim® Vi, Sanofi Pasteur MSD, Diegem, Belgium). Both the placebo and typhoid vaccine were transferred to similar looking syringes.

Throughout the testing periods, vital signs were monitored regularly. The participant left the study center after the last post-dose measurements.

Figure 1: Study design



Assessments

Mood

Mood was measured with the POMS (brief form), which was administered at baseline and 60, 90, 150, 180, 240, and 360 minutes post-dose. The POMS is a self-report questionnaire that measures current mood, yielding scores for total mood and six subscales: activity/vigor, anger/hostility, confusion/bewilderment, depression/dejection, fatigue/inertia, and tension/anxiety (McNair et al., 1989).

Biological Measures

Serum samples were taken to measure levels of inflammatory cytokines (i.e., interferon-γ [IFN-γ], tumor necrosis factor-α [TNF-α], and interleukin-6 [IL-6]), as well as markers of HPA-axis activation (i.e., adrenocorticotropic hormone [ACTH] and cortisol). Blood samples were taken through an indwelling catheter immediately before the start of the treatment (11:55 am), immediately post-treatment (12:21 pm), and 30, 60, 90, 150, 180, 240 and 360 minutes post-treatment. At 15 minutes post-treatment, an extra cortisol and ACTH sample was taken.

HPA-axis markers were analyzed at PRA International, Zuidlaren, the Netherlands. ACTH and Cortisol were analyzed using a Siemens® IMMULITE 2000 Immunoassay System.

Inflammatory markers were analyzed at Janssen Biobank, Beerse, Belgium. The cytokine assays were quantitative electrochemiluminescence immunoassays, performed with Meso Scale Discovery® V-PLEX Proinflammatory Panel 1 (human) kits. The detection ranges were as follows: ACTH, 1.1 to 278 pmol/L; cortisol, 28 to 1380 nmol/L; IFN-γ, 0.2–0.9 to 1060–1320 ng/L; TNF-α, 0.06–0.3 to 320–352 ng/L; and IL-6, 0.07–0.3 to 743–833 ng/L.

Statistics

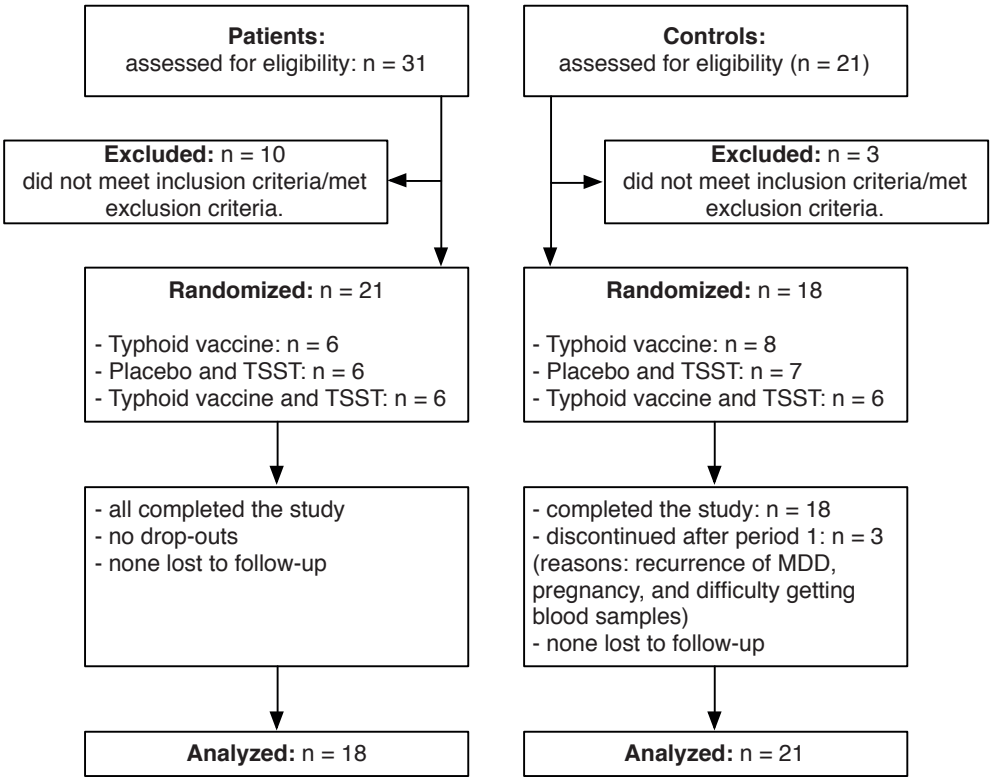
Baseline differences between the groups were examined using an unpaired *Student's t*-test or *Wilcoxon-Mann-Whitney*-test for non-normal data. For the mood and biological data, the mean pre-dose score was used to measure baseline differences. For the biological markers, values below quantifiable levels were replaced with the lowest quantifiable concentration. Non-continuous variables were tested with the chi-square test.

The effect of the intervention on the different outcomes was estimated using a linear mixed model. All available data from non-completers was included. As the biological data and the data of several POMS subscales (namely, anger/hostility, depression/dejection, and tension/anxiety) was not normal, a log-transformation was applied. The mixed model included as fixed effects the group (control group or patient), intervention (placebo, typhoid vaccine without TSST, placebo with TSST, or the typhoid vaccine with TSST), time point, and the appropriate interactions. Pre-dose score/concentration, treatment period, study center, body mass index, age, CTQ, pre-dose MADRS score, and antidepressant use were also included as fixed effects; subject was included as a random effect. When a significant interaction was found, between-group comparisons were performed (e.g., between placebo and the three different treatments), using Bonferroni-correction for multiple testing. The estimated differences (β) between placebo and the intervention are reported with the 95% confidence interval (CI).

Results

An overview of baseline characteristics is summarized in **Table 1**. While there were no significant differences in demographics and biomarkers between patients and controls, patients had higher scores on the MADRS and the CTQ, as well as a lower POMS score. Fourteen patients (66.7%) were concomitantly treated with an antidepressant. The use of concomitant medication can be found in **Table S1** of the supplement at the end of the chapter. An overview of the participant flow can be found in **Figure 2**. A graphical representation of the effects of the interventions on each time point and group is provided in **Figure S1-S12** of the supplement at the end of the chapter.

Figure 2: Participant flow



TSST: Trier Social Stress Test

Mood

Total score on the POMS (Figure 3 and Figure S1)

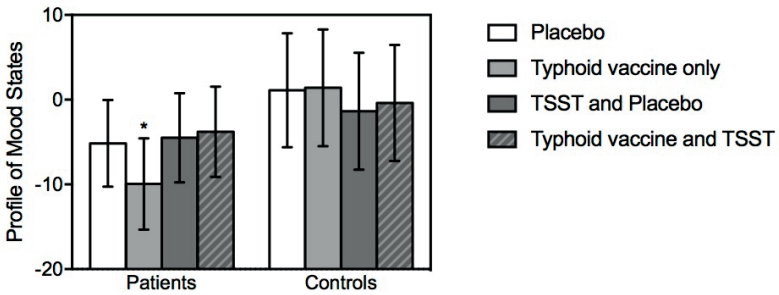
Patients reacted significantly differently on the interventions than controls, as the group × intervention interaction was significant ($p < 0.001$). A significant general lowering of mood was found in patients after the vaccine without TSST (β [95% CI] = -4.79 [-6.82 – -2.75]; $p < 0.001$). There were no significant effects on mood of the other two interventions in patients, neither were there of any of the interventions in controls.

Table 1: Baseline demographic and clinical characteristics

	Mean (SD), unless specified otherwise		
Measure	**Patients (n = 21)**	**Controls (n = 18)**	**p-value**
Demographics			
Age	33.9 (7.02)	32.7 (6.65)	*n.s.*
BMI	24.0 (2.80)	22.4 (3.18)	*n.s.*
Education years	15.2 (2.40)	15.7 (2.97)	*n.s.*
Right-handedness (%)	85.0%	82.4%	*n.s.*
Antidepressant use (%)	66.7%	0.0%	< .001
Ethnicity (%):			*n.s.*
European descent	95.2%	88.9%	
Maghrebi descent	0.0%	11.1%	
African descent	4.8%	0.0%	
Clinical characteristics			
MADRS	6.38 (5.29)	0.64 (1.07)	< .001
CTQ	42.7 (16.66)	31.4 (6.58)	.008
POMS	-14.60 (17.34)	0.92 (7.60)	< .001
Biomarkers			
HPA-axis measures			
Cortisol (nmol/L)	295 (132)	313 (146)	*n.s.*
ACTH (pmol/L)	2.58 (1.924)	2.35 (1.586)	*n.s.*
Inflammation measures			
IFN-γ (ng/L)	6.63 (6.40)	7.34 (13.60)	*n.s.*
TNF-α (ng/L)	1.81 (1.46)	1.48 (0.37)	*n.s.*
IL-6 (ng/L)	0.76 (0.49)	0.68 (0.38)	*n.s.*

ACTH: Adrenocorticotropic hormone; BMI: body mass index; CTQ: Childhood Trauma Questionnaire; IFN-γ: Interferon-γ; IL-6: Interleukin-6; MADRS: Montgomery-Åsberg Depression Rating Scale; *n.s.*: not significant; POMS: Profile of Mood States; TNF-α: tumor necrosis factor-α

Figure 3: Least square means of the general Profile of Mood States score after each intervention



*: p < 0.05; TSST: Trier Social Stress Test

Subscales of the POMS

Activity/Vigor (Figure S2)

A significant group × intervention interaction was observed (p = 0.010), meaning that patients reacted significantly different than controls. There was a lowering in vigor/activity in patients after the vaccine without TSST (β [95% CI] = -1.55 [-2.50 – -0.60]; p =0.008). There was no effect of the other interventions in patients, neither was there an effect of any of the interventions in controls.

Anger/Hostility (Figure S3)

Patients reacted significantly different on the interventions (group × intervention interaction: p = 0.009). A lowering of anger/hostility was seen in patients after placebo and TSST (β [95% CI] = -0.05 [-0.52 – -0.09]; p =0.008). The other interventions had no effect.

Confusion/Bewilderment (Figure S4)

The groups did not react differently on the interventions. A significant effect of intervention was found (p < 0.001). An increase in confusion/bewilderment was observed after placebo and TSST (β [95% CI] = 0.47 [0.16 – 0.77]; p = 0.008), while there was a decrease after vaccine and TSST (β [95% CI] = -0.39 [-0.70 – -0.09]; p = 0.036). No effect was observed after vaccine without TSST).

Depression/Dejection (Figure S5)

A significant effect of intervention was found (p = 0.023). The both groups did not differ significantly in their reactions on the interventions. While examination of the single intervention did not show any significant effects of the interventions, there was a trend for an decrease in depression/dejection after the vaccine and TSST (β [95% CI] = -0.15 [-0.27 – -0.03]; p = 0.055).

Fatigue/Inertia (Figure S6)

Patients reacted significantly different on the intervention compared to controls ($p < 0.001$). While an increase in fatigue/inertia was seen in patients after vaccine without TSST (β [95% CI] = 0.91 [0.10 – 1.71]), this was not significant after multiple testing correction. On the other hand, in controls, a significant increase in fatigue/inertia was seen after placebo and TSST (β [95% CI] = 1.41 [0.62 – 2.21]; $p = 0.003$).

Tension/Anxiety (Figure S7)

The groups reacted significantly different, with a significant group × intervention interaction ($p = 0.008$). In patients, an increase in tension/anxiety was seen after the vaccine without TSST (β [95% CI] = 0.40 [0.10 – 0.73]; $p = 0.039$). The other interventions had no effect in patients. In controls, an increase was seen after the vaccine with TSST (β [95% CI] = 0.33 [0.11 – 0.58]; $p = 0.011$), but no effects were seen after the other treatments.

Biological Measures

Measures of the HPA-axis

ACTH (Figure S8)

A significant group × intervention interaction was found ($p < 0.001$), suggesting that patients reacted differently on the interventions than controls. There was a trend for a general rise of ACTH after vaccine without TSST in controls (β [95% CI] = 0.27 [0.06 – 0.49]; $p = 0.056$), but not in the patients.

There was a significant time point × intervention interaction ($p < 0.001$), though no significant group × time point × intervention interaction, meaning that the groups did not differ significantly in response. A significant rise of ACTH occurred immediately after the TSST in both populations, both in the placebo and TSST group (β [95% CI] = 1.00 [0.53 – 1.54]; $p < 0.001$) and the vaccine with TSST group (β [95% CI] = 0.79 [0.33 – 1.31]; $p = 0.012$).

In conclusion, a trend for a general rise of ACTH was found in controls after the typhoid vaccine without TSST, but not in patients, in which the two groups differed significantly. In contrast, both groups reacted similarly after the TSST (with placebo and with the typhoid vaccine), with a rise of ACTH immediately after the TSST.

Cortisol (Figure S9)

Both groups reacted similarly on the interventions, as there were no group interactions. A significant time point × intervention interaction was found ($p < 0.001$), with a rise immediately after (β [95% CI] = 136.4 [69.1 – 216.3]; $p < 0.001$) and 15 min (β [95% CI] =

120.4 [56.1 – 196.7]; p = 0.001) after placebo and TSST. This effect was however not found after the TSST in combination with the typhoid vaccine.

Cytokines

IFN-γ (Figure S10)

Patients and controls reacted significantly differently on the intervention (group × intervention: p = 0.028). The placebo and TSST intervention lead to a decrease in IFN-γ in both groups (patients: β [95% CI] = -0.79 [-1.04 – -0.52]; p < 0.001; controls: β [95% CI] = -0.66 [-0.91 – -0.39]; p < 0.001). However, in patients there was also a significant increase after the typhoid vaccine and TSST combination (β [95% CI] = 0.84 [0.53 – 1.18]; p < 0.001).

The time point × intervention interaction was also significant (p < 0.001). As there was no group × time point × intervention the analysis applies to both groups. After placebo and TSST, there was a decrease in IFN-γ at 180 minutes (β [95% CI] = -0.76 [-1.16 – -0.35]; p = 0.011), 240 minutes (β [95% CI] = -1.06 [-1.42 – -0.67]; p < 0.001), and 360 minutes (β [95% CI] = -1.48 [-1.83 – -1.10]; p < 0.001). On the other hand, after the combination treatment, an increase was seen at 240 minutes (β [95% CI] = 0.96 [0.46 – 1.51]; p = 0.002) and 360 minutes (β [95% CI] = 0.98 [0.45 – 1.55]; p = 0.004).

In conclusion, in both groups there was a lowering of IFN-γ after placebo and TSST. This lowering was more pronounced from 180 minutes post-intervention onward. The effect of the typhoid vaccine with the TSST on IFN-γ is conflicting: while there seems to be a general rise in patients compared to controls after the intervention, there also is a rise in both groups from 240 minutes post-intervention onward.

TNF-α (Figure S11)

No significant differences between the both groups were found. A significant effect of intervention was found (p = 0.011), showing a decrease in TNF-α after placebo and TSST (β [95% CI] = -0.06 [-0.02 – -0.09]; p = 0.007). The other interventions had no effect on TNF-α levels.

IL-6 (Figure S12)

No significant effects of the intervention were found. Interestingly, while on baseline no significant difference was found between both groups, there was a significant effect of group, suggesting an increased concentration of IL-6 in patients (β [95% CI] = 0.78 [0.14 – 1.62]; p = 0.015).

Discussion

This is the first study to examine the effect of inflammatory stress in patients in remitted MDD, as well as the first study to examine the differential effects of both an inflammatory and a psychosocial stressor in this population. We hypothesized that patients would be more sensitive to the negative effects of inflammatory and psychosocial stress mood and that the combination of both would have an additive or synergistic effect.

In patients, inflammation, but not psychosocial stress, had negative effects on mood. This suggests that there is indeed an increased sensitivity for the effects of inflammatory stress on mood in remitted MDD patients. Examination of the subscales reveals that this mood decrease was partly due to a decrease in vigor/activity and a non-significant increase in fatigue/inertia. There was also an increase in tension/anxiety, but no change in the depression/dejection subscale. The changes in vigor/activity and fatigue/inertia suggest that patients were more sensitive to the development of *sickness behavior* following inflammatory stress. Previous research indeed showed that increased inflammation is particularly associated with the somatic symptoms of depression and anxiety (Duivis et al., 2013, Norcini Pala et al., 2016). This can explain why the inflammatory stressor affected only activity, fatigue, and anxiety, but not depressive mood. However, research on mice showed that sickness behavior following inflammatory stress was an early effect, while depressive symptoms followed later (Dantzer et al., 2008). A similar pattern is seen in patients treated with interferon, where an increase in neurovegetative symptoms (such as fatigue and psychomotor impairment) is an early side effect of the treatment, while depressive symptoms usually occur later in treatment (Capuron et al., 2002). This early increase in neurovegetative symptoms was also shown to predict cognitive depressive symptoms later in therapy (Wichers et al., 2005).

No negative effects were observed of the TSST, as would be expected (van Winkel et al., 2015). However, it should be noted that in previous studies, mood was measured directly after TSST, while in this study mood was only first measured 60 minutes post-intervention. Examination of the subscales of the mood scale did reveal some changes after the TSST (increased confusion/bewilderment in both groups, decreased anger/hostility in patients, and increased fatigue/inertia in controls), which don't seem to follow a clear pattern.

The TSST activated the HPA-axis in both groups, further validating it as a paradigm for induction of HPA-axis activation. The TSST decreased inflammatory cytokines, probably due to cortisol's anti-inflammatory effect. While this anti-inflammatory effect may seem positive, it should be noted that the onset of MDD is associated more with chronic stress, while the TSST is a short and relatively mild stressor. Prolonged psychosocial stress and the associated HPA-axis hyperactivation lead to glucocorticoid receptor desensitization and

glucocorticoid resistance, culminating in reduced anti-inflammatory effects (Pariante and Lightman, 2008, Raison and Miller, 2003, Pariante, 2004). However, recent evidence shows that glucocorticoids are not exclusively anti-inflammatory, and can, in certain contexts, enhance pro-inflammatory responses, possibly through microglia activation, which is associated with psychiatric disorders including major depressive disorder (Sorrells et al., 2009, Kato et al., 2013).

Pro-inflammatory states are also known to activate the HPA-axis, which acts as a negative feedback loop controlling the immune response (Silverman et al., 2005, Bellavance and Rivest, 2014). This expected response was observed in controls following vaccination, but was absent in patients. This may be due to HPA-axis dysfunction (reduced activation of the HPA-axis in the current study) in the patient group, which has been shown to persist after remission in a proportion of the patients with recurrent and remitted MDD (Van Den Eede et al., 2006, Vreeburg et al., 2009). However, we did not observe any significant differences in baseline HPA-axis activity between patients and control subjects, and both groups reacted similarly on the TSST. This may implicate an immune-specific reduced activation of the HPA-axis after inflammatory stress in remitted MDD, but this finding requires further investigation and replication in future studies.

While the vaccine without TSST did reduce mood in patients, the combined intervention (vaccine and TSST) did not. It can be hypothesized that the anti-inflammatory effect of the TSST negated the pro-inflammatory effect of the vaccine, though this cannot be clearly seen in the biomarker data of the combination intervention. An increase in IFN-γ was seen in patients only after combination treatment, but not after the single treatments. This indicates a synergistic effect of both stressors in patients, reflecting an earlier cross-sensitization, as we initially hypothesized. This difference was however not reflected in the behavioral measures. However, our study may have been underpowered to find small differences. Alternatively, it can be hypothesized that the mood-altering effects of these increases in cytokine levels appeared after the observation period of 6 hours.

This increased sensitivity to inflammation may be a trait that may increase MDD risk. In the present study, no effect of inflammatory stress on mood was found in controls; however, other studies (Strike et al., 2004, Wright et al., 2005, Harrison et al., 2009, Brydon et al., 2009a, Reichenberg et al., 2001, Eisenberger et al., 2009, Eisenberger et al., 2010), although not all (Paine et al., 2013), observed negative effects of inflammation in healthy controls. Interestingly, personality traits such as optimism protect against inflammation-induced mood decreases (Brydon et al., 2009b). This indicates a subgroup in the general population that is more sensitive to inflammation. Indeed, several risk factors for increased pro-inflammatory states are described in the literature, such as childhood maltreatment (Coelho et al., 2014, Levine et al., 2015), which is also associated with increased stress

responsivity and depression (Pariante and Lightman, 2008). However, our analysis controlled for these factors.

Strengths of the study are the studied population and the design. Most research is focused on patients during a major depressive episode. Selection of a population without active disease made it possible to observe if any disturbances persist after remission. The study was also designed to measure two different kinds of stressors, examining several disease facets. This is, to our knowledge, the first study to measure both inflammatory and psychosocial stress in a clinical population. However, some limitations have to be mentioned. First, the sample size was relatively small. Secondly, the cross-sectional design does not allow an examination of causality (predisposing factor in MDD or biological scar after recurrent depression). Third, the majority of patients took antidepressants, which can normalize HPA-axis disturbances and pro-inflammatory states (Raison and Miller, 2003, Kenis and Maes, 2002). Finally, the effects of the interventions were examined within a short time frame (6 h), although there may be additional and larger long-term effects.

In conclusion, patients with recurrent and remitted MDD were sensitive to the mood-lowering effects of inflammatory stress, contrary to controls. Moreover, the HPA-axis was not activated after inflammation in patients. Further research is needed to determine whether this is due to a trait that increases the risk for MDD or due to the consequences of multiple major depressive episodes. However, there was no increased sensitivity to psychosocial stress, suggesting that different types of stressors have different effects. While no synergistic effects of both stressors on mood were observed, the combination of both stressors had synergistic effects on inflammatory markers in the patient group. Overall, these findings corroborate previous reports that inflammatory processes are involved in MDD. In the present study, disturbances in the inflammatory system appear to persist after remission, which may play a role in recurrence. This increased sensitivity to inflammatory stress may be an interesting treatment target for the prevention of MDD recurrence.

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Supplementary tables and images

Table S1: Concomitant medication use

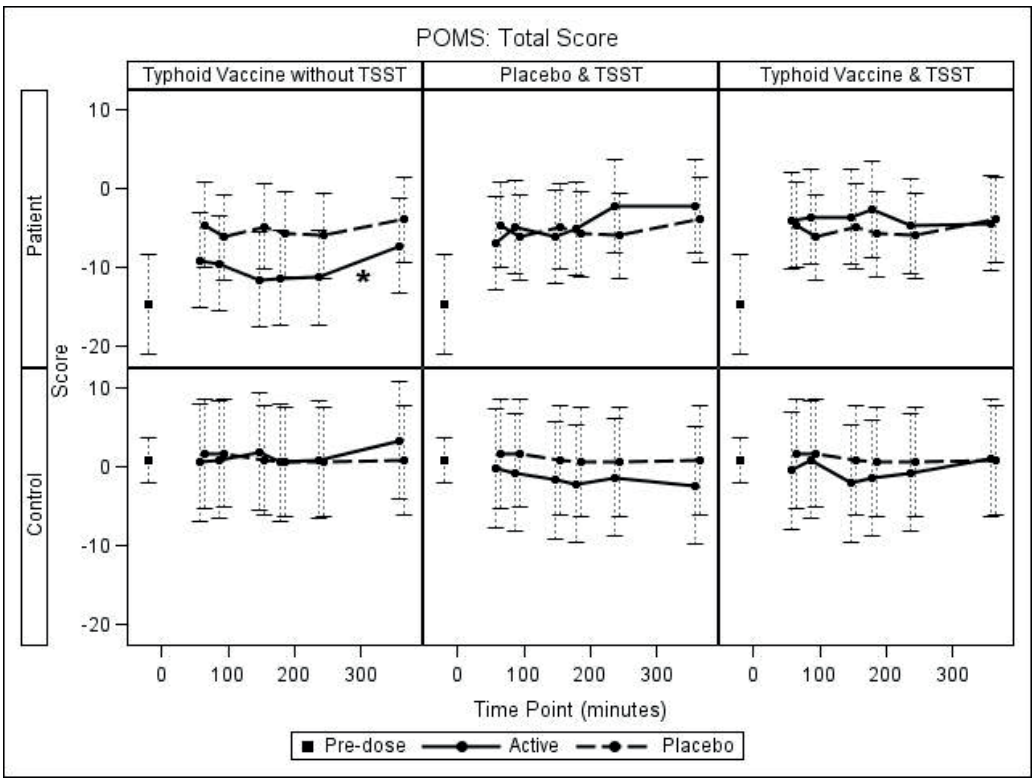
Medication	Patients (n = 21)	Controls (n = 18)
Alimentary Tract		
Loperamide	0%	5.56%
Omeprazole	4.76%	0%
Pantoprazole	4.76%	0%
Analgesics and Anti-Infectives		
Acetylsalicylic Acid *	4.76%	0%
Paracetamol **	4.76%	16.67%
Roxithromycin *	4.76%	0%
Blood and blood forming organs		
Enoxaparin sodium	0%	5.56%
Dermatological		
Calcipotriol/Betamethasone Dipropionate (topical)	0%	5.56%
Isotretinoin	4.76%	0%
Ketoconazole (topical)	4.76%	0%
Terbinafine (topical)	0%	5.56%
Anticonception		
Cyproterone Acetate	0%	5.56%
Cyptroterone Acetate/Ethinylestradiol	4.76%	11.11%
Desogestrel/Ethinylestradiol	9.52%	16.67%
Drospirenone/Ethinylestradiol	0%	11.11%
Estradiol/Nomegestrol Acetate	0%	5.56%
Ethinylestradiol	4.76%	0%
Ethinylestradiol/Etonogestrel (vaginal contraceptive ring)	4.76%	0%
Ethinylestradiol/Gestodene	4.76%	5.56%
Ethinylestradiol/Norgestimate	4.76%	0%
Levonorgestrel	14.29%	16.67%
Levonorgestrel (intrauterine contraceptive device)	0%	5.56%
Nervous System		
Alprazolam	4.76%	0%
Duloxetine	4.76%	0%
Escitalopram	14.29%	0%
Fluoxetine	4.76%	0%
Flurazepam	4.76%	0%
Lormetazepam	4.76%	0%
Meprobamate	4.76%	0%

Medication	Patients (n = 21)	Controls (n = 18)
Mirtazapine	4.76%	0%
Nortriptyline	4.76%	0%
Paroxetine	9.52%	0%
Quetiapine	14.29%	0%
Sertraline	9.52%	0%
Venlafaxine	19.05%	0%
Vitamins, Minerals, and Food supplements		
Vitamin B containing supplements	14.29%	5.56%
Iron containing supplements	9.52%	11.11%
Unspecified vitamins and minerals	4.76%	5.56%
Unspecified homeopathy and other food supplements	4.76%	5.56%

* This medication was used at screening but was discontinued before the start of the study.
** The occasional intake of paracetamol was permitted throughout the study provided no paracetamol was taken within 48 hours prior to the intervention

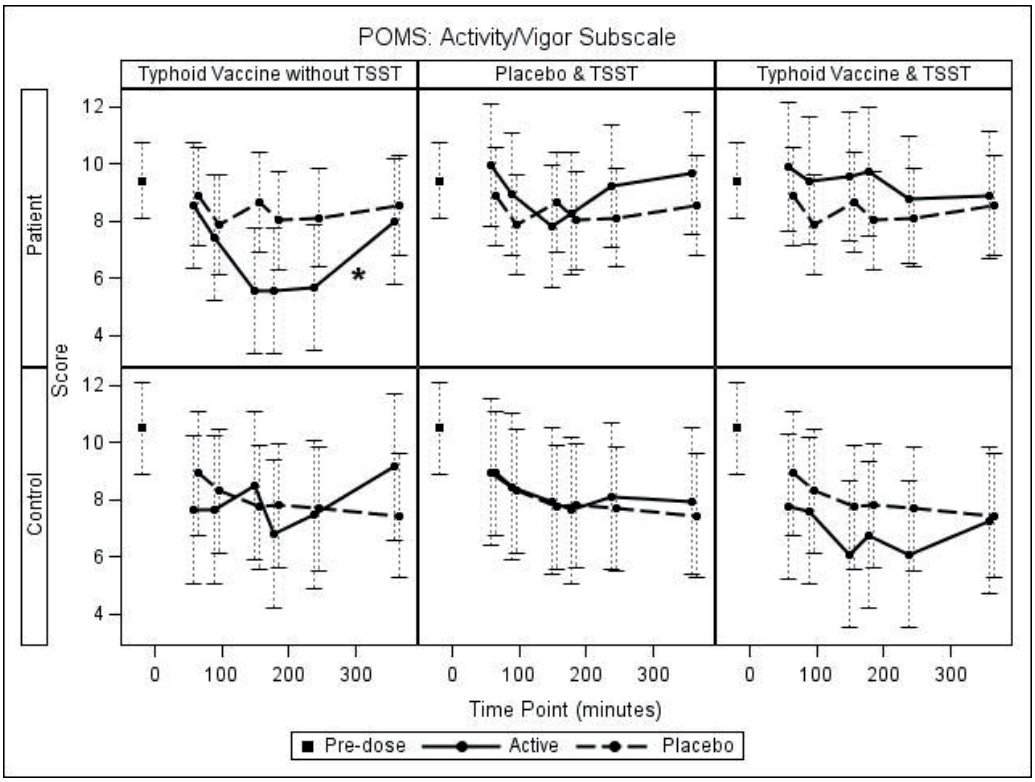
Results of the interventions on the Profile of Mood States (POMS)

Figure S1: POMS Total Score



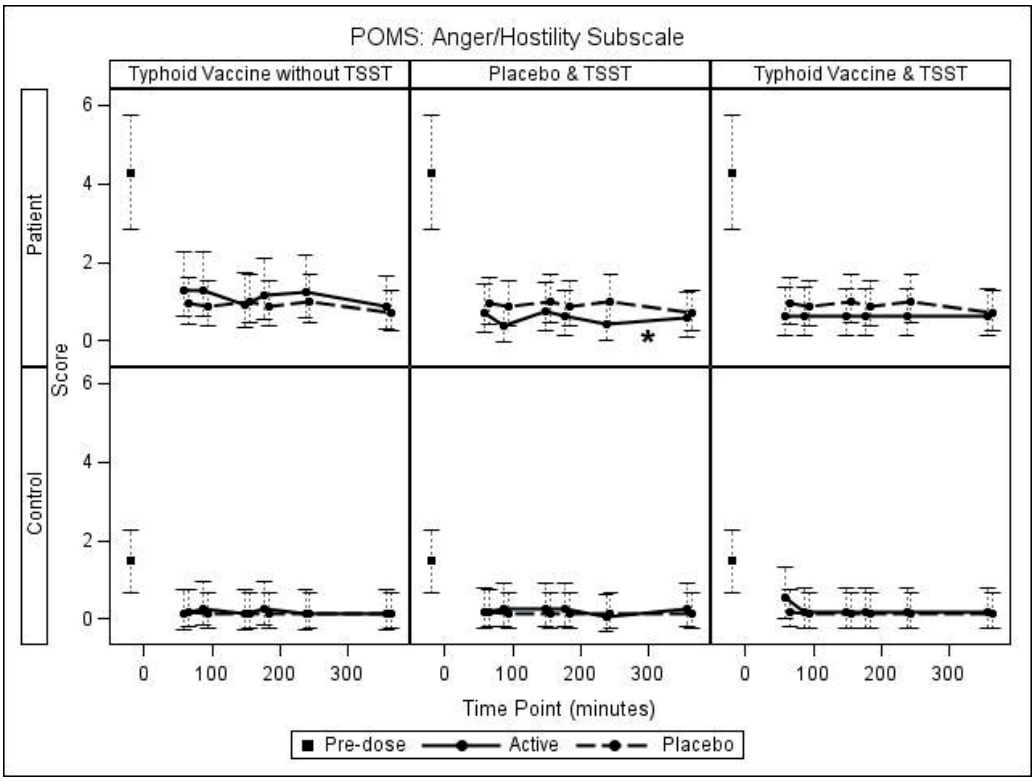
The least squares mean concentration with 95% confidence intervals are shown in this figure. Pre-dose concentration (mean concentration with 95% confidence interval of the whole group at 20 m before intervention) is also included.
*: $p < 0.05$ (on scores in general); TSST: Trier Social Stress Test

Figure S2: POMS Activity/Vigor Subscale



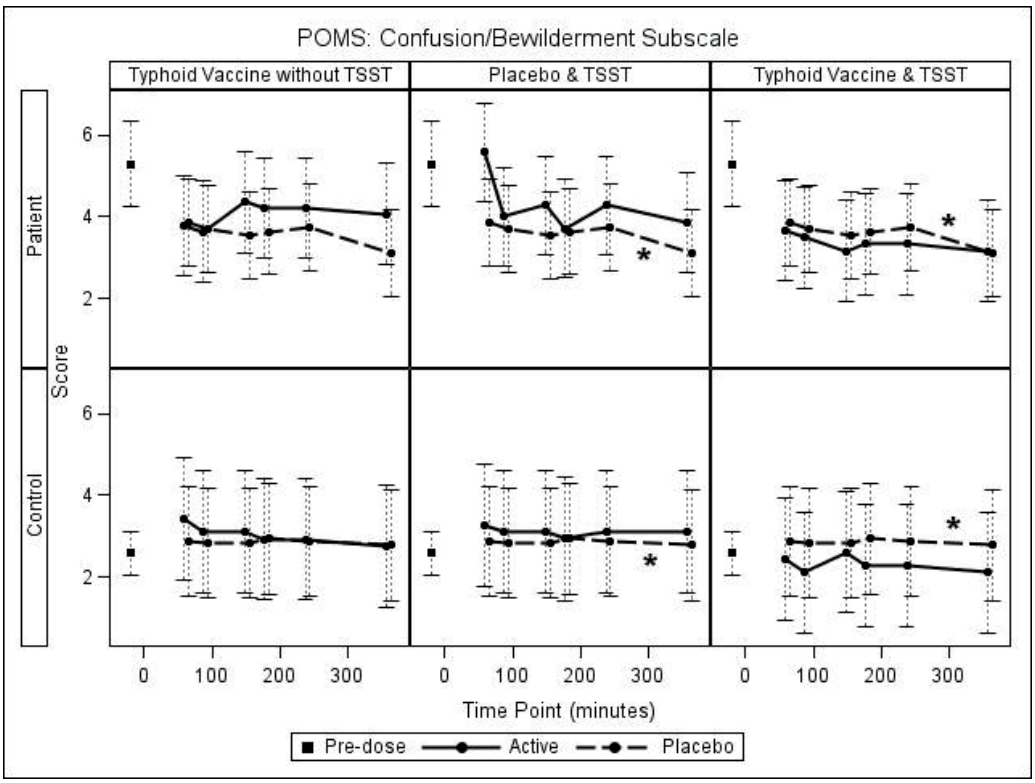
The least squares mean concentration with 95% confidence intervals are shown in this figure. Pre-dose concentration (mean concentration with 95% confidence interval of the whole group at 20 m before intervention) is also included.
*: $p < 0.05$ (on scores in general); TSST: Trier Social Stress Test

Figure S3: POMS Anger/Hostility Subscale



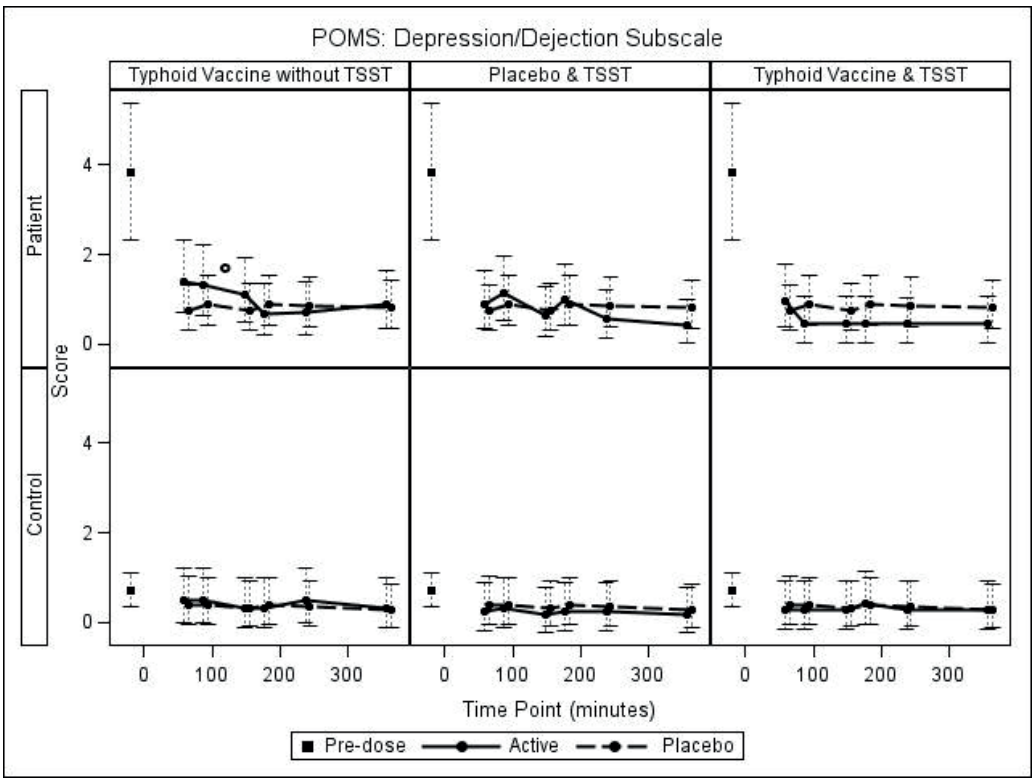
The least squares mean concentration with 95% confidence intervals are shown in this figure. Pre-dose concentration (mean concentration with 95% confidence interval of the whole group at 20 m before intervention) is also included.
*: $p < 0.05$ (on scores in general); TSST: Trier Social Stress Test

Figure S4: POMS Confusion/Bewilderment Subscale



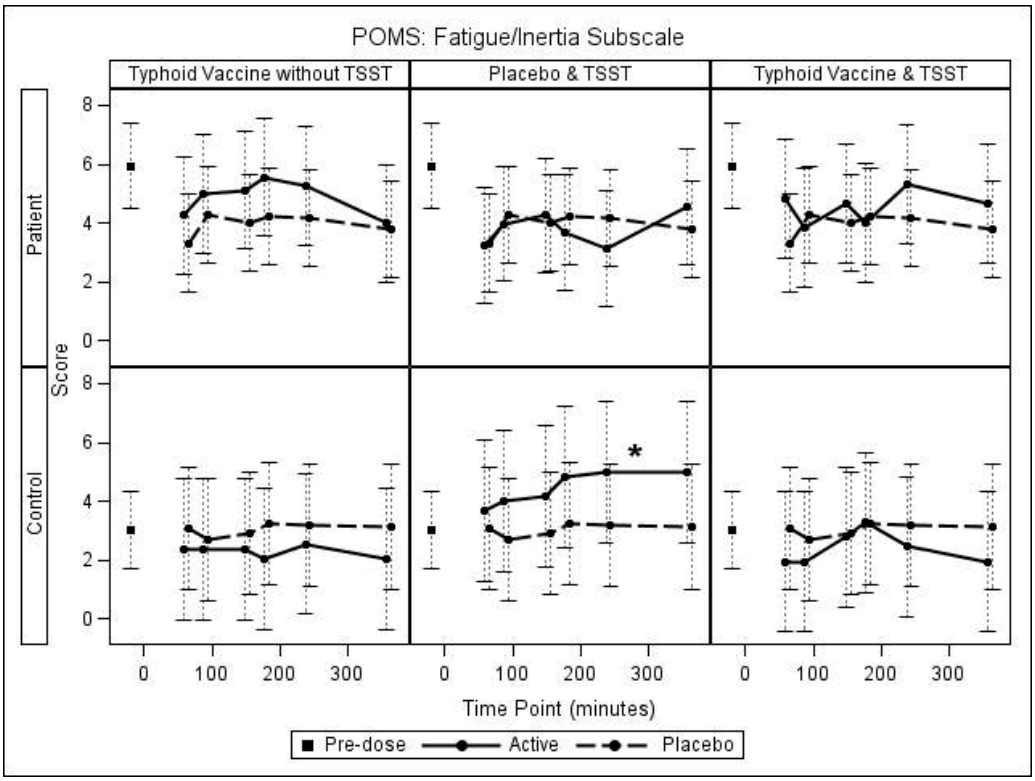
The least squares mean concentration with 95% confidence intervals are shown in this figure. Pre-dose concentration (mean concentration with 95% confidence interval of the whole group at 20 m before intervention) is also included.
*: $p < 0.05$ (on scores in general); TSST: Trier Social Stress Test

Figure S5: POMS Depression/Dejection Subscale



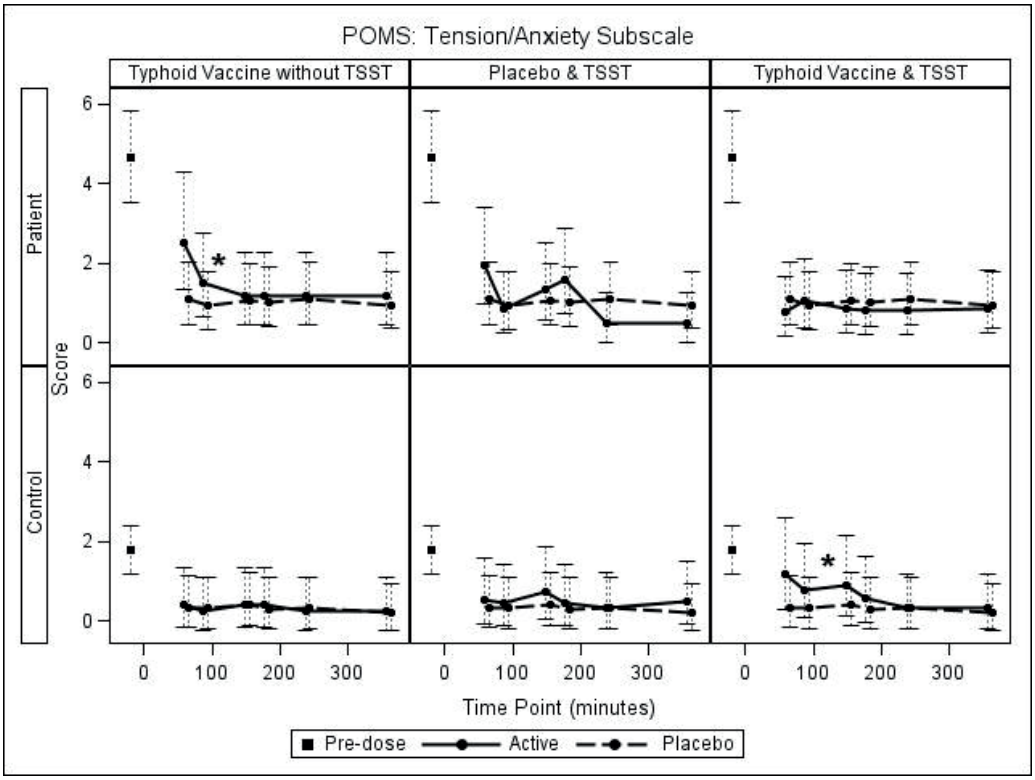
The least squares mean concentration with 95% confidence intervals are shown in this figure. Pre-dose concentration (mean concentration with 95% confidence interval of the whole group at 20 m before intervention) is also included.
°: $p < 0.1$ (on scores in general); TSST: Trier Social Stress Test

Figure S6: POMS Fatigue/Inertia Subscale



The least squares mean concentration with 95% confidence intervals are shown in this figure. Pre-dose concentration (mean concentration with 95% confidence interval of the whole group at 20 m before intervention) is also included.
*: $p < 0.05$ (on scores in general); TSST: Trier Social Stress Test

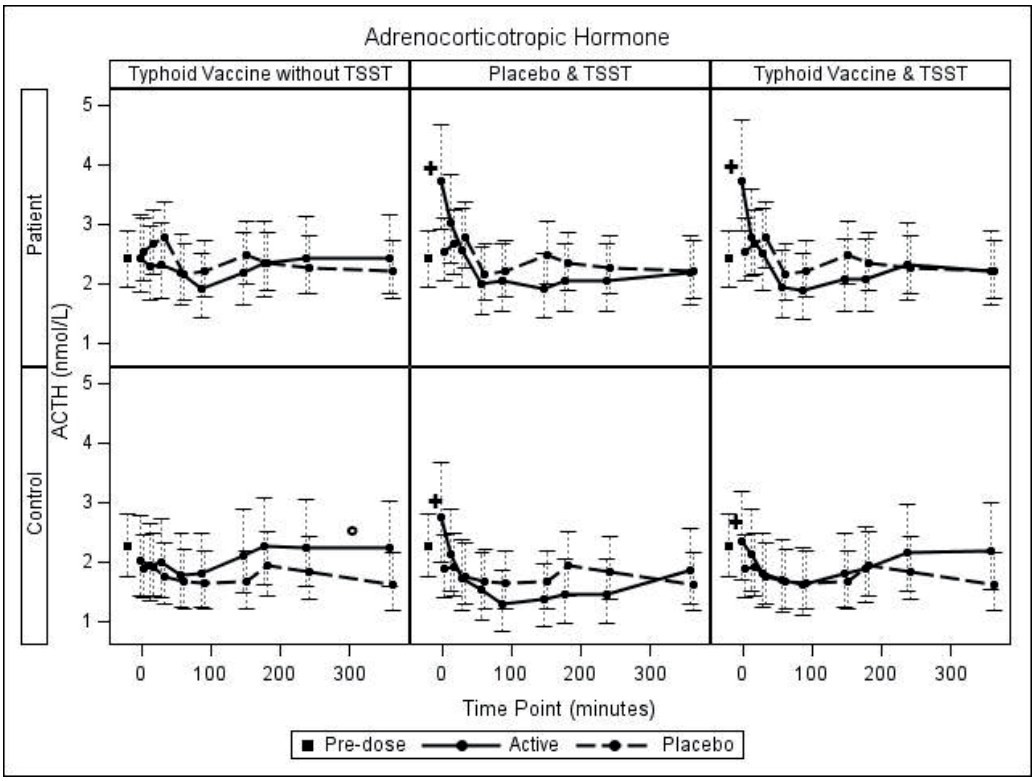
Figure S7: POMS Tension/Anxiety Subscale



The least squares mean concentration with 95% confidence intervals are shown in this figure. Pre-dose concentration (mean concentration with 95% confidence interval of the whole group at 20 m before intervention) is also included.
*: $p < 0.05$ (on scores in general); TSST: Trier Social Stress Test

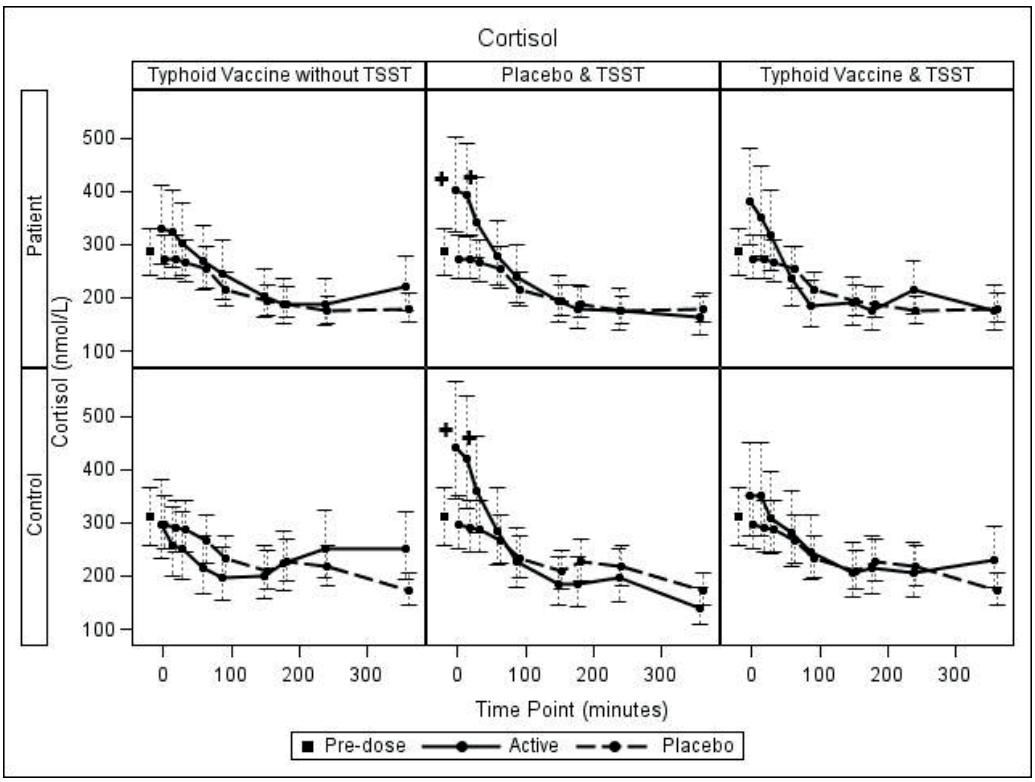
Results of the interventions on the biological measures

Figure S8: Adrenocorticotropic Hormone (ACTH)



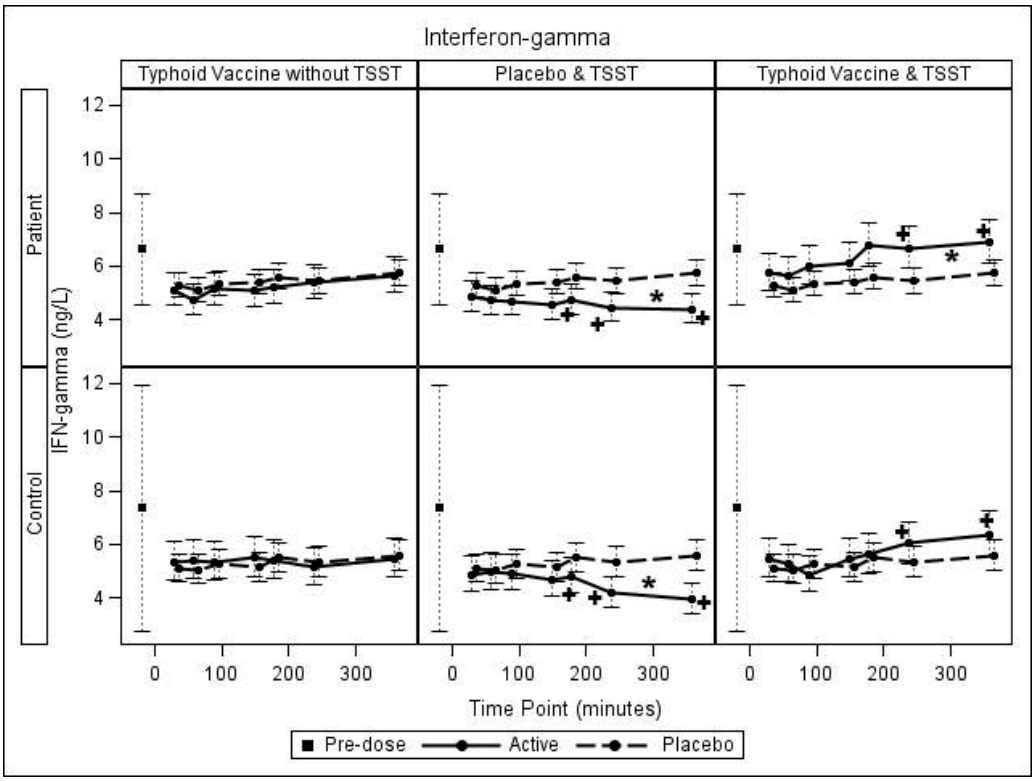
The least squares mean concentration with 95% confidence intervals are shown in this figure. Pre-dose concentration (mean concentration with 95% confidence interval of the whole group at 20 m before intervention) is also included. °: $p < 0.1$ (on blood concentration in general); $^{+}$: $p < 0.05$ (on specific time points); TSST: Trier Social Stress Test

Figure S9: Cortisol



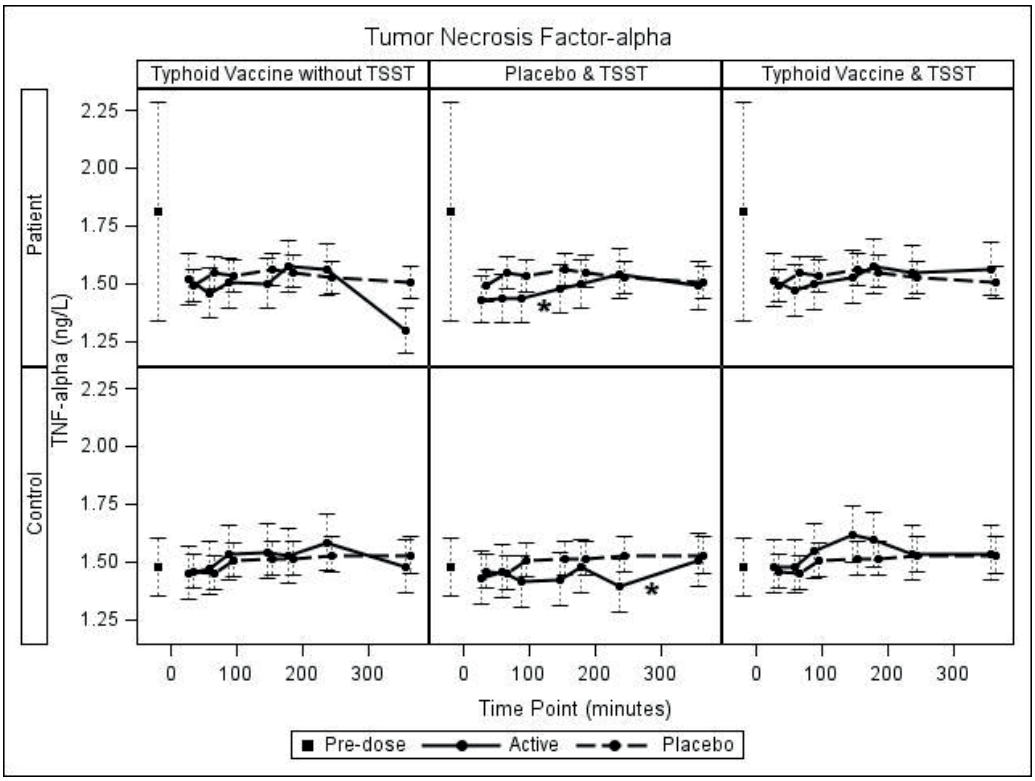
The least squares mean concentration with 95% confidence intervals are shown in this figure. Pre-dose concentration (mean concentration with 95% confidence interval of the whole group at 20 m before intervention) is also included.
$^{+}$: $p < 0.05$ (on specific time points); TSST: Trier Social Stress Test

Figure S10: Interferon-γ



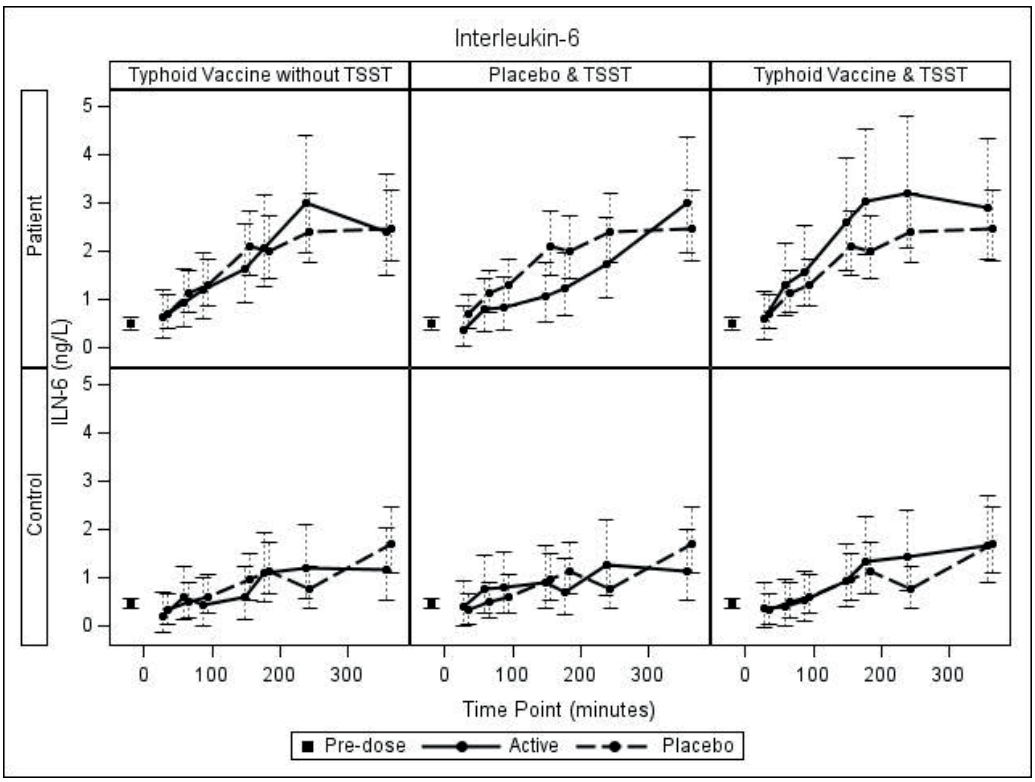
The least squares mean concentration with 95% confidence intervals are shown in this figure. Pre-dose concentration (mean concentration with 95% confidence interval of the whole group at 20 m before intervention) is also included. *: $p < 0.05$ (on blood concentration in general); $^{+}$: $p < 0.05$ (on specific time points); TSST: Trier Social Stress Test

Figure S11: Tumor Necrosis Factor-α

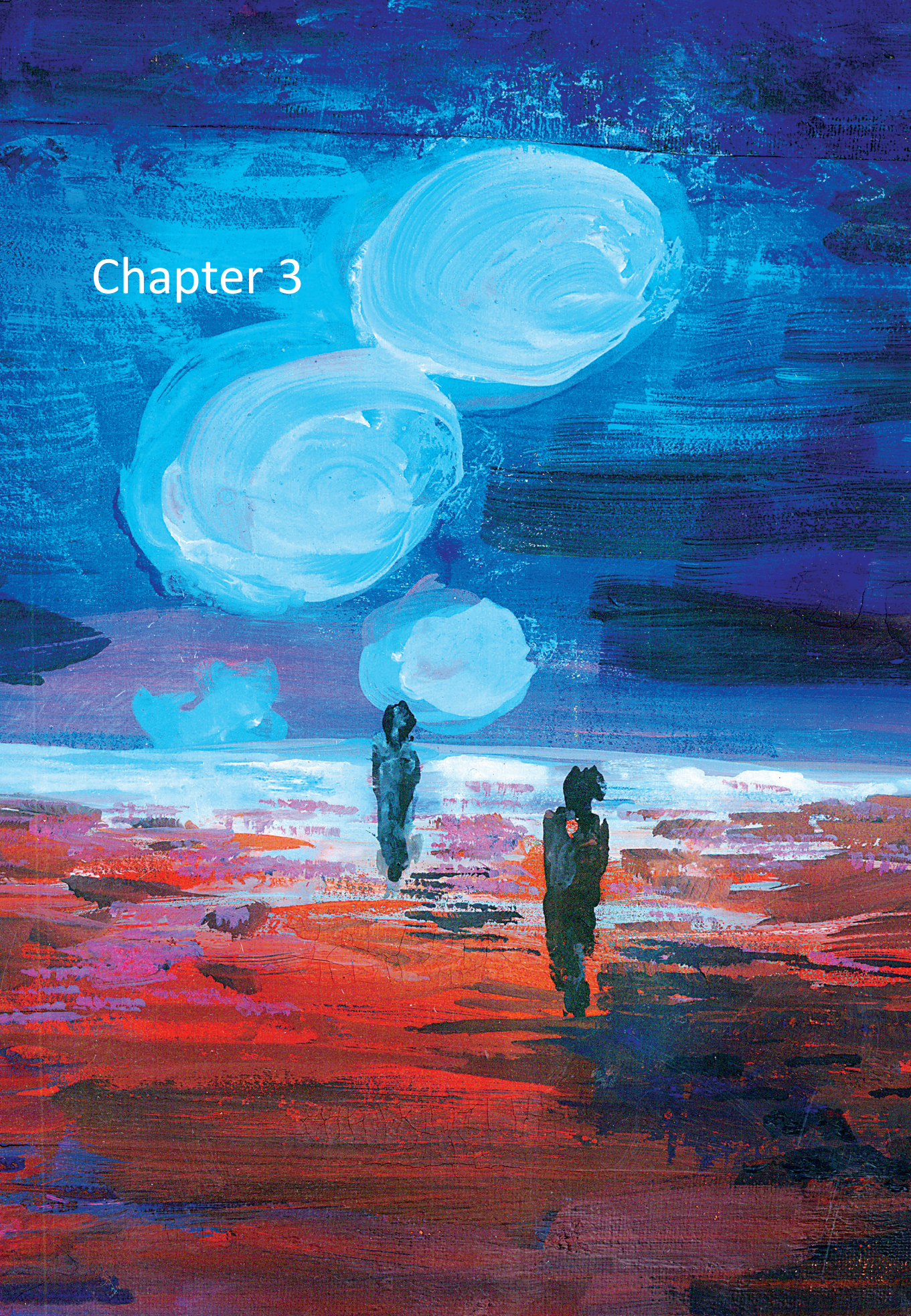


The least squares mean concentration with 95% confidence intervals are shown in this figure. Pre-dose concentration (mean concentration with 95% confidence interval of the whole group at 20 m before intervention) is also included.
*: $p < 0.05$ (on blood concentration in general); TSST: Trier Social Stress Test

Figure S12: Interleukin-6



The least squares mean concentration with 95% confidence intervals are shown in this figure. Pre-dose concentration (mean concentration with 95% confidence interval of the whole group at 20 m before intervention) is also included.
TSST: Trier Social Stress Test


Chapter 3

Digging Deeper in the Differential Effects of Inflammatory and Psychosocial Stressors in Remitted Depression: Effects on Cognitive Functioning

This chapter has been published as:
Niemegeers, P., de Boer, P., Schuermans, J., Dumont, G. J. H., Coppens, V., Spittaels, K., Claes, S., Sabbe, B. G. C. & Morrens, M. 2019. Digging deeper in the differential effects of inflammatory and psychosocial stressors in remitted depression: Effects on cognitive functioning. J Affect Disord, 245, 356-363.

Abstract

Background: Major Depressive Disorder (MDD) covers a wide spectrum of symptoms, including cognitive dysfunction, which can persist during remission. Both inflammatory states and psychosocial stress play a role in MDD pathogenesis.
Methods: The effects of inflammatory (i.e. *Salmonella typhi* vaccine) and psychosocial stressor (i.e. Trier Social Stress Test), as well as their combination were investigated on cognition in women (aged 25-45 years, n = 21) with (partially) remitted MDD and healthy controls (n = 18) in a single-blind placebo-controlled study. In a crossover design, patients received on the first day one of the aforementioned interventions and on the other day a placebo, or vice versa, with a washout period of 7-14 days. Short-term and verbal memory, working memory, attention, verbal fluency, information processing speed, psychomotor function, and measures of attentional bias to emotions were measured. Exploratory analyses were performed to assess the correlation between biomarkers of inflammation and the Hypothalamic-Pituitary-Adrenal axis and cognitive functioning.
Results: In patients, inflammatory stress decreased information processing speed and verbal memory, and increased working memory; after psychosocial stress, there was an increase in attention. There was also an increased negative attentional bias in patients after inflammatory stress. Neither stressor had any effect in controls.
Limitations: Limitations are the relatively small sample size and antidepressant use by a part of the participants. The effects of the stressors were also measured a relatively short period after administration.
Conclusion: Patients were sensitive to the cognitive effects of inflammation and psychosocial stress on cognition, while controls were not.

Introduction

Major depressive disorder (MDD) is a complex and heterogeneous syndrome that covers a wide spectrum of symptoms, including cognitive dysfunction in two-thirds of depressed patients (Afridi et al., 2011). Cognitive deficits have typically been identified in the areas of executive functioning, visual learning and memory, attention, and psychomotor speed; and have been shown to influence psychosocial functioning (Rock et al., 2014). However, while during remission clinically relevant symptoms of low mood are absent, cognitive shortfall can persist in many patients who had cognitive impairments while being depressed (Reppermund et al., 2009, Rock et al., 2014). Moreover, each recurrent depressive episode induces an additional decline in global cognitive function (Kessing, 1998) and importantly, some measures (such as psychomotor speed and cognitive inhibition) are possibly irreversibly declined (Halvorsen et al., 2012, Ardal and Hammar, 2011).

In recent years, preclinical and clinical findings have suggested the involvement of the immune system in the pathophysiology of depression. In MDD patients, increased levels of peripheral inflammatory markers such as Interleukin-6 (IL-6) and Tumor Necrosis Factor-Alpha (TNF-α) have been found compared to healthy controls (Liu et al., 2017). Moreover, MDD is a common side effect of immune stimulating treatments such interferon-α (IFN-α), with up to 40% developing MDD (Schafer et al., 2007). Additionally, chronic inflammatory diseases (*e.g.,* rheumatoid arthritis, inflammatory bowel disease, and others) have a high comorbidity of depression (Ambriz Murillo et al., 2015, Pryce and Fontana, 2017, D'Mello and Swain, 2017). Indeed, several studies suggest that induction of an inflammatory response can trigger depressive symptoms. As such, several intervention studies with healthy subjects demonstrated increases in depressive symptomatology upon administration of endotoxin (Strike et al., 2004, DellaGioia and Hannestad, 2010, Reichenberg et al., 2001, Eisenberger et al., 2009, Eisenberger et al., 2010, Benson et al., 2017, Kotulla et al., 2018) or the *Salmonella typhi* vaccine (Wright et al., 2005, Brydon et al., 2009, Harrison et al., 2009).

It has been shown that, in addition to inflammatory stimuli, prolonged psychological stress can also result in depressive symptoms (Anisman and Merali, 2003, Kendler et al., 1999, Yang et al., 2015). Interestingly, the detrimental effects of psychological stress on mood are suggested to be at least partially mediated through immunologic alterations (Glaser and Kiecolt-Glaser, 2005, Anisman and Merali, 2003, Morey et al., 2015). One potential mechanism underlying this phenomenon is stress-induced modulation of the hypothalamic-pituitary-adrenal (HPA) axis (Marques et al., 2009). Several components of this stress response pathway are known to enhance inflammatory stimuli (Sorrells et al., 2009). For instance, Corticotropin Releasing Hormone (CRH) stimulates the production of pro-inflammatory cytokines IL-6 and TNF-α (Angioni et al., 1993, Kato et al., 2013) and exposure

to glucocorticoids sensitizes the neuro-inflammatory response to endotoxins (Frank et al., 2010). Lastly, depression is associated with reduced glucocorticoid receptor functioning (Pariante, 2004, Anacker et al., 2011).

However, how inflammatory mediators and psychological stress interact to develop depressive episodes and cognitive deficits is not well understood. Moreover, it remains to be elucidated which specific cognitive domains are most sensitive to the effects of these stressors in subjects vulnerable for depressive disorders. We hypothesized that patients with MDD in remission would have a continued vulnerability, resulting in increased sensitivity to the effects of stress on cognition. Therefore, we investigated the effect of an inflammatory and psychosocial stressor, or the combination of both, on several domains of cognition in healthy controls and patients with (partially) remitted depression. A secondary objective of this study was whether several biomarkers levels had an effect on cognition.

Methods

Participants

Twenty-one women with (partially) remitted moderate to severe recurrent MDD and 18 female controls aged 25–45 years were recruited. For feasibility reasons, patients with partially remitted depression were also included; a score below 15 was required on the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). Inclusion criteria for both groups were being medically stable based on vital signs, clinical examination, and clinical laboratory tests (blood and urine sample); and having a body mass index (BMI) between 18–30 kg/m^2. Exclusion criteria were a current DSM-IV axis 1 diagnosis other than MDD, including substance abuse or dependence within the past 6 months (excluding nicotine and caffeine), treatment with more than one antidepressant or with drugs that compromise the immune system, acute suicidal behavior, a relevant medical history of disorders associated with increased inflammation, prior exposure to the psychosocial stress test, exposure to severe psychosocial stress within the past 6 months, and the administration of a typhoid vaccination within the last 5 years.

Study design

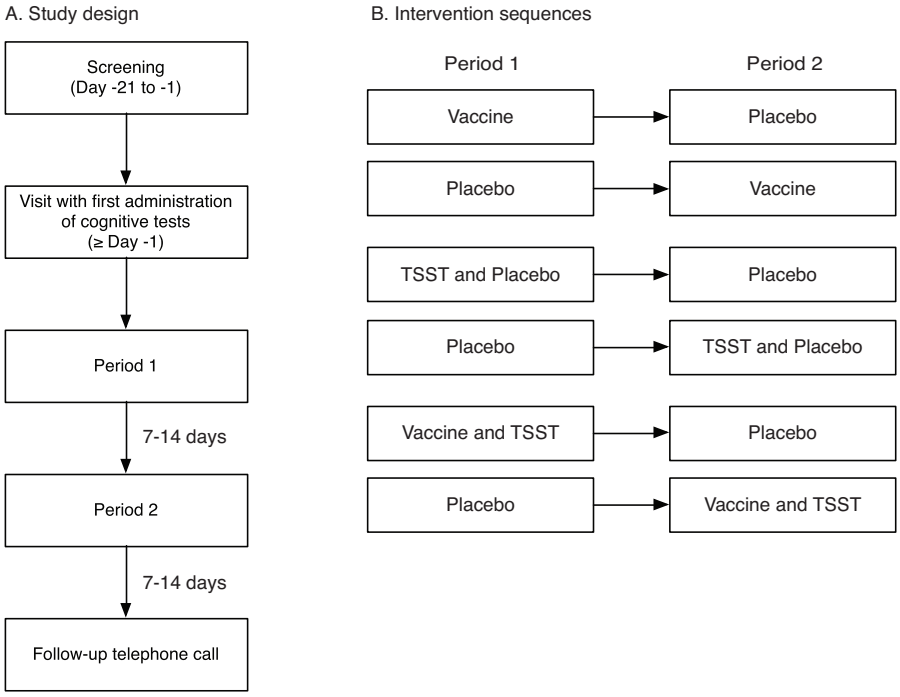
We conducted a two-way, randomized, single-blind, placebo-controlled crossover study to assess the effects of an inflammatory stressor, a psychosocial stressor, and their combination on cognition, as well as the relationship between cognition and markers of the HPA-axis and inflammation. This study was part of a larger study design, the results of which can be found in Niemegeers et al. (2016).

The study consisted of an eligibility screening examination, a run-in visit, two single-blinded intervention periods separated by a wash-out of 7-14 days, and a follow-up phone call 7-14 days after the last intervention day (**Figure 1A**). Before the first intervention period, the Childhood Trauma Questionnaire (CTQ), a retrospective questionnaire of childhood trauma, was administered (Bernstein and Fink, 1997). On the run-in visit, the cognitive test battery was administered to obtain a baseline measurement.

The participants were randomized by the sponsor using a computer-generated randomization sequence to receive on an intervention (the inflammatory stressor, the psychosocial stressor, or the combination of both). The *Salmonella typhi* vaccine was used as an inflammatory stressor and the Trier Social Stress Test (TSST) was used as a psychosocial stressor. The TSST was performed as described in Kirschbaum et al. (1993). On one day, the participants received the active intervention. On the other day they received the placebo. The possible intervention sequences are shown in **Figure 1B**.

At the start of each intervention period, an alcohol breath test, a urine drug and a pregnancy screening test were performed. In addition, the MADRS was administered by trained blinded staff. If applicable, the TSST was administered at 12:00h. At 12:20h, either the typhoid vaccine (0.5 mL containing 25 µg *Salmonella typhi* capsular polysaccharide; Typhim® Vi, Sanofi Pasteur MSD, Diegem, Belgium) or a placebo (0.5 mL NaCl 0.9%), both transferred to a similar looking syringe, were injected. Throughout the testing periods, vital signs were monitored regularly. The cognitive test battery consisted of two blocks, administered 3 and 4 h after the study drug administration, respectively. The participant left the study center 6 hours after administration of the intervention.

Figure 1: Study design and different intervention sequences



TSST: Trier Social Stress Test

Assessments

Cognition

The cognitive test battery was directed at the following cognitive domains: short-term and working memory, verbal fluency, verbal memory, sustained attention, psychomotor function, cognitive processing, and emotional interference on cognitive processing.

Block 1

The *Digit Span Forward and Backward* are tests of short-term and working memory, respectively (Wechsler, 1997). The subject is asked to repeat an increasing sequence of numbers either forward or backward. The outcome measure is the number of correctly repeated sequences.

In the *Controlled Oral Word Association Test (COWAT)*, the participant is asked to sum up as many words of a certain category (two trials) or with the same starting letter (three trials) in one minute. The outcome measure was the sum of the scores on the five trials (Lezak et al., 2004).

The *Continuous Performance Test* (CPT) is a measure of sustained attention, where stimuli (either numbers or shapes) were shown on a screen. When two identical stimuli were presented in a row, the subject had to respond. The main outcome measure of the CPT is *dprime* (*d'*), a measure of attentional capacity (Cornblatt et al., 1988, Niemegeers et al., 2014). A secondary outcome measure is the reaction time to hits, which can be interpreted as a measure of processing speed (Morrens et al., 2007).

Block 2

The *Hopkins Verbal Learning Test* (HVLT) is a test of verbal memory, consisting of a list of 12 words that should be memorized. Twenty minutes after three consecutive learning trials, the participant was asked to repeat the list. The number of correctly remembered words is the main outcome measure (Brandt and Benedict, 2001).

The *Symbol Digit Substitution Test* (SDST) is a measure of information-processing speed (Wechsler, 1981, Niemegeers et al., 2014). In this test, performed on a digitizing tablet, a series of symbols should be decoded as fast as possible, within a 90-s time limit, using a list of corresponding digit-symbol pairs (Morrens et al., 2006). Outcome measures are the number of correctly substituted digits, the matching time (i.e., time to find the corresponding digit) and the mean writing time (i.e., time to write the digit).

In the *Line Copying Test* (LCT), a straight line should be copied as quickly as possible from a computer screen to a form, which is placed on a digitizing tablet (Niemegeers et al., 2014, Docx et al., 2012, Morrens et al., 2008). The outcome measures are initiation time (i.e., the time to initiate the drawing) and movement time (i.e., the time to draw the line).

In the *Emotional Stroop*, the subject should name the color of the ink with which certain words are written as quickly as possible. Contrasting to the standard Stroop task, the words are either positive, neutral, or negative words. It has been well reported that depressed individuals show a negative bias towards negative stimuli (Clark et al., 2009, Roiser et al., 2012). The Emotional Stroop has been previously used to measure attentional bias (Dresler et al., 2009, Peckham et al., 2010). Ten negative, neutral and positive words were selected using a procedure based on Dresler et al. (2009). In a pilot study, 10 healthy volunteers were asked to rate the valence of a list of 300 words on a seven-point scale. The ten most negative words were selected, to which the ten most neutral and ten most positive words were matched taking word's frequency, function, length, and number of syllables into account, using data from the SUBTLEX-NL database (Keuleers et al., 2010). Ten rows of 10 words in the colors red, yellow, blue or green were printed on white paper. As such, there were 3 cards (a neutral, negative, and positive one). A practice card with only colors was administered first. The cards were presented in a randomized order and the subject

had to name the colors as quickly as possible. The outcome measure is the time needed to read the whole card.

Biological markers

Several biomarkers were evaluated. The pro-inflammatory markers interferon-γ [IFN-γ], TNF-α, and IL-6 were measured as previous research implicates these in the MDD (Dowlati et al., 2010, Pinto and Andrade, 2016, Janssen et al., 2010). Markers of the HPA-axis (*i.e.,* adrenocorticotropic hormone [ACTH] and cortisol) were also evaluated, as they are also implicated in MDD (Marques et al., 2009). The biomarkers were evaluated 5min before the intervention and before each testing block (*i.e.,* at 3h and 4h post-intervention). Cortisol and ACTH were analyzed using a Siemens® IMMULITE 2000 Immunoassay System at PRA International, Zuidlaren, the Netherlands, with following detection ranges: ACTH, 1.1 to 278 pmol/L; and cortisol, 28 to 1380 nmol/L. Inflammatory markers were analyzed at Janssen Biobank, Beerse, Belgium, using quantitative electrochemiluminescence immunoassays, namely the Meso Scale Discovery® V-PLEX Proinflammatory Panel 1 (human) kits, with following detection ranges: IFN-γ, 0.2-0.9 to 1060-1320 ng/L; TNF-α, 0.06-0.3 to 320-352 ng/L; and IL-6, 0.07-0.3 to 743-833 ng/L.

Statistics

Differences in demographics and baseline (i.e., cognitive performance on the run-in visit) between patients and controls were examined with an unpaired *Student's t*-test or the *Wilcoxon-Mann-Whitney*-test for non-normal data. The *chi-square* test was used for non-continuous variables.

The effect of the intervention was estimated using a linear mixed model. Both cohorts were analyzed separately. Dropouts were included in the analysis. The mixed model included as fixed effects administration of the typhoid vaccine (yes or no), TSST (yes or no), and the vaccine × TSST interaction. Baseline score of the run-in visit, treatment period, study center, body mass index, age, CTQ, pre-dose MADRS score, antidepressant use, and the number of education years were also included as fixed effects; subject was included as a random effect. A secondary analysis was performed to test any difference between groups. The same procedure was used in this secondary analysis, except that group (control or patient group) was also added as fixed effect with all the appropriate interactions. When a significant interaction was found, between-group comparisons were performed (e.g., between placebo and the three different treatments) using Bonferroni-correction. The estimated difference (β) between placebo and the intervention is reported with the 95% confidence interval (CI).

Exploratory analyses were performed to assess whether the effects of biomarker levels on cognitive performance were significantly different between the two groups. The Area Under the Curve (AUC) was calculated from the start of the measurements (pre-dose) until the time of the test (3h or 4h post-intervention). A linear mixed model was performed with the biomarker × group interaction as fixed effect, as well as biomarker, group, pre-dose biomarker concentration, baseline score of the run-in visit, treatment period, study center, body mass index, age, CTQ, pre-dose MADRS score, antidepressant use, and the number of education years. Subject was again included as a random effect. Only the biomarker × group interaction was examined. The estimated coefficient (β) is reported with the standard error and a t-test is done to examine if it significantly differs from zero.

Results

Eighteen participants in each group completed the study; 6 participants were included in each treatment group. In the patient group, three participants (two in the group with only typhoid vaccine and one in the placebo and TSST group) dropped out after period 1, due to pregnancy, recurrence of MDD, and difficulty taking blood samples on the second period.

The baseline demographic characteristics and the results of the cognitive tests on baseline are summarized in **Table 1**.

Effect of the interventions

The effects of the interventions on cognition are summarized in **Table 2**. In controls, none of the interventions had any significant effect.

No effects were observed on short-term memory (measured in the Digit Span Forward). After the vaccine, an improvement of working memory (Digit Span Backward) was observed. The group × vaccine interaction was significant ($p = 0.046$).

While there was no effect on main outcome measure of the attention task (i.e., the Continuous Performance Task) in patients after vaccine, their reaction time worsened after the vaccine. Conversely, after the TSST, both attention and reaction time improved in patients. There were no significant group × intervention interactions.

Table 1: Baseline demographic and clinical characteristics

Measure	Mean (SD), unless specified otherwise		
	Patients (n = 21)	**Controls (n = 18)**	**p-value**
Demographics			
Age	33.9 (7.02)	32.7 (6.65)	*n.s.*
BMI	24.0 (2.80)	22.4 (3.18)	*n.s.*
Education years	15.2 (2.40)	15.7 (2.97)	*n.s.*
Right-handedness (%)	85.0%	82.4%	*n.s.*
Antidepressant use (%)	66.7%	0.0%	< .001
Ethnicity (%):			*n.s.*
European descent	95.2%	88.9%	
Maghrebi descent	0.0%	11.1%	
African descent	4.8%	0.0%	
Clinical characteristics			
MADRS	6.38 (5.29)	0.64 (1.07)	< .001
Cognitive measures			
Digit Span:			
Forward	8.83 (1.948)	9.10 (2.189)	*n.s.*
Backward	6.72 (1.527)	6.76 (1.700)	*n.s.*
CPT:			
dprime	2.04 (0.862)	2.21 (0.794)	*n.s.*
Reaction Time (ms)	662 (85.3)	658 (78.4)	*n.s.*
COWAT			
HVLT	10.18 (1.704)	10.14 (1.493)	*n.s.*
SDST:			
Nr. Correct	63.53 (10.625)	61.81 (7.467)	*n.s.*
Matching Time (ms)	914 (216.1)	965 (171.6)	*n.s.*
Writing Time (ms)	471 (113.8)	491 (117.7)	*n.s.*
LCT:			
Initiation Time (ms)	712 (134.1)	746 (131.5)	*n.s.*
Movement Time (ms)	268 (73.3)	297 (164.7)	*n.s.*
Emotional Stroop:			
Neutral Words (s)	69.5 (10.26)	69.0 (14.53)	*n.s.*
Negative Words (s)	68.6 (10.82)	70.3 (14.66)	*n.s.*
Positive Words (s)	73.3 (11.49)	71.4 (16.92)	*n.s.*

BMI: body mass index; COWAT: Controlled Oral Word Association Test; CPT: Continuous Performance Test; HVLT: Hopkins Verbal Learning Test; LCT: Line Copying Test; MADRS: Montgomery-Åsberg Depression Rating Scale; *n.s.*: not significant; SDST: Symbol Digit Substitution Test.

Table 2: Results of the interventions

	Patient					Control				
	Vaccine		TSST		Vaccine × TSST	Vaccine		TSST		Vaccine × TSST
Measure	**β ± CI**	***p***	**β ± CI**	***p***	***p***	**β ± CI**	***p***	**β ± CI**	***p***	***p***
Digit Span										
Forward	-0.39 ± 0.90	*n.s.*	0.69 ± 0.90	*n.s.*	*n.s.*	0.60 ± 1.42	*n.s.*	0.69 ± 1.45	*n.s.*	*n.s.*
Backward	1.21 ± 0.96	0.016	-0.88 ± 0.95	0.069	*n.s.*	-0.40 ± 1.22	*n.s.*	0.65 ± 1.25	*n.s.*	*n.s.*
CPT										
dprime	-0.04 ± 0.41	*n.s.*	0.41 ± 0.41	0.049	*n.s.*	0.03 ± 0.46	*n.s.*	0.04 ± 0.48	*n.s.*	*n.s.*
reaction time	25.3 ± 21.8	0.026	-22.0 ± 10.2	0.049	*n.s.*	22.1 ± 34.0	*n.s.*	7.3 ± 34.5	*n.s.*	*n.s.*
COWAT	*	*	*	*	0.015	2.84 ± 8.01	*n.s.*	-4.15 ± 8.35	*n.s.*	*n.s.*
HVLT	-0.77 ± 0.77	0.049	0.08 ± 0.77	*n.s.*	*n.s.*	0.62 ± 1.18	*n.s.*	0.41 ± 1.23	*n.s.*	*n.s.*
SDST										
Nr. Correct	-3.02 ± 2.90	0.042	1.13 ± 2.87	*n.s.*	*n.s.*	0.50 ± 5.05	*n.s.*	-0.87 ± 5.07	*n.s.*	*n.s.*
Matching Time (ms)	53.8 ± 90.5	*n.s.*	17.4 ± 89.7	*n.s.*	*n.s.*	-28.3 ± 112.6	*n.s.*	-13.4 ± 119.0	*n.s.*	*n.s.*
Writing Time (ms)	22.3 ± 30.6	*n.s.*	-11.8 ± 30.9	*n.s.*	*n.s.*	-6.0 ± 49.5	*n.s.*	0.6 ± 51.1	*n.s.*	*n.s.*
LCT										
Initiation Time (ms)	15.9 ± 45.8	*n.s.*	-5.9 ± 46.0	*n.s.*	*n.s.*	13.7 ± 43.4	*n.s.*	-7.2 ± 44.8	*n.s.*	*n.s.*
Movement Time (ms)	-7.9 ± 40.4	*n.s.*	5.7 ± 40.9	*n.s.*	*n.s.*	-4.5 ± 39.5	*n.s.*	-8.4 ± 42.1	*n.s.*	*n.s.*
Emotional Stroop										
Neutral (s)	3.23 ± 5.52	*n.s.*	-2.82 ± 5.52	*n.s.*	*n.s.*	0.71 ± 3.84	*n.s.*	-3.01 ± 3.98	*n.s.*	*n.s.*
Negative (s)	5.51 ± 4.71	0.025	-3.47 ± 4.67	*n.s.*	*n.s.*	-0.32 ± 3.71	*n.s.*	3.56 ± 3.81	*n.s.*	*n.s.*
Positive (s)	0.01 ± 6.95	*n.s.*	-0.4 ± 6.93	*n.s.*	*n.s.*	-0.04 ± 5.73	*n.s.*	1.10 ± 5.91	*n.s.*	*n.s.*

*: if the vaccine × TSST interaction is significant, results of the single treatment groups have to be analyzed separately and are reported in the results section of the article

COWAT: Controlled Oral Word Association Test; CPT: Continuous Performance Test; HVLT: Hopkins Verbal Learning Test; LCT: Line Copying Test; *n.s.*: not significant; SDST: Symbol Digit Substitution Test.

There was a vaccine × TSST interaction on Verbal Fluency (measured in the Controlled Oral Word Association Task), with a non-significant lowering after both the vaccine (β ± 95% CI = -1.90 ± 9.06) and the TSST (β ± 95% CI = -9.26 ± 9.47), and a non-significant increase after the combination intervention (β ± 95% CI = 10.30 ± 10.18). While the group × vaccine × TSST interaction did not reach significance (p = 0.078), there was a significant group × TSST interaction (p = 0.039). Examination of the separate groups showed a significant increase in score in patients after the TSST (β ± 95% CI = 8.44 ± 7.32, p = 0.050) and a non-significant decrease in controls (β ± 95% CI = -2.57 ± 7.41). While this is a seemingly conflicting result, the increase after TSST in this analysis can be explained by the increase after the combination treatment in patients.

After the vaccine, a decrease in verbal memory was observed in patients, but not in controls. Patients reacted significantly different on the vaccine than controls (p = 0.045). The TSST had no effect.

Information processing (the number correct answers on the SDST) decreased in patients after the vaccination, though this effect was not seen in the matching time. The TSST had no effects and patients did not react significantly different on the intervention compared to controls. Neither the vaccine nor the TSST had any effect on psychomotor function (namely the LCT and the writing time of the SDST).

After the vaccine, there was an increase in time to read the colors of negative words in the Emotional Stroop, suggesting an increased interference of negative words after inflammatory stress. The group × vaccine interaction did not reach significance though (p = 0.089). No significant effects were seen in the neutral and positive words. While no significant reaction of the TSST were seen in both groups, there was a significant group × TSST interaction (p = 0.026) in the time to read the colors of negative words, reflecting a non-significant decrease in time in patients and a non-significant increase in controls.

Effect of biomarker levels on cognition

There were no significant biomarker × group interactions for Digit Span (forward and backward), CPT, COWAT, and HVLT.

There was a ACTH AUC × group interaction (p = 0.009) for the matching time of the SDST, with a significant relation between ACTH AUC in patients (β ± SE = 0.28 ± 0.09, p = 0.005) but not in controls (β ± SE = 0.28 ± 0.09, p = not significant [n.s.]). There were no significant interactions for the other biomarkers and the matching time. No biomarker × group interactions were observed in the other outcome variables of the SDST (number correct and writing time).

Although there was an ACTH AUC × group interaction for the initiation time of the LCT ($p = 0.046$), the estimated coefficients did not differ significantly from zero (patients, $\beta \pm SE = 0.06 \pm 0.05$, p = n.s.; controls, $\beta \pm SE = -0.12 \pm 0.09$, p = n.s.). A similar pattern is seen for the TNF-α × group interaction ($p = 0.041$), with none of the estimated coefficients significantly differing from zero (patients, $\beta \pm SE = 0.00 \pm 0.28$, p = n.s.; controls, $\beta \pm SE = -0.34 \pm 0.29$, p = n.s.). As such, both findings are of unclear significance. No interactions were observed for the other three biomarkers, neither was an interaction between any biomarker and the movement time of the LCT observed.

The interaction between IL-6 AUC and group was significant for the reading time of the negative words of the Emotional Stroop ($p = 0.047$). While the estimated coefficient was not significant in controls ($\beta \pm SE = -0.005 \pm 0.005$, p = n.s.), it was for patients ($\beta \pm SE = 0.007 \pm 0.003$, $p = 0.013$), suggesting and increased reading time with increasing IL-6 AUC. No interactions were found for the other biomarkers. No interaction between group and any biomarker was found for the reading time of the positive and neutral words.

Discussion

Numerous preclinical and clinical studies point towards the involvement of inflammatory mechanisms in the pathophysiology of depression (Liu et al., 2017). Besides affective symptoms, chronic inflammation is also associated with cognitive symptoms such as impaired memory, decreased motivation and confusion (Dantzer, 2009). This is in line with the findings of the current study, which shows a decrease in information processing and verbal memory following the administration of the typhoid vaccine, in (partially) remitted patients but not in healthy controls. Conversely, an improvement in working memory was also observed in the patient group after the vaccine. As remitted patients had comparable cognitive scores compared to controls, these results suggest that an induced pro-inflammatory state affects cognitive functions in patients that had previously suffered a depressive episode, but not in their healthy peers.

Previous studies suggest that healthy subjects who received a therapeutic dose of pro-inflammatory cytokines such as IFN-α or TNFα, reported neuropsychiatric side effects including impaired thought processing next to depressed mood (Licinio et al., 1998). Cancer and Hepatitis C patients receiving IFN-α therapy develop not only depression as a side effect but also cognitive dysfunction (Capuron and Miller, 2004, Scheibel et al., 2004). Although we did not find these cognitive alterations in our control sample, they were clearly observable in subjects who previously suffered a depressive episode currently in remission. The changes in verbal memory, attention and information speed in the remitted

patients in our study are in line with the findings in healthy controls of Krabbe et al. (2005) and Bollen et al. (2017) although these alterations were not always found (Bollen et al., 2017). This study suggests that, even when (partially) remitted, patients with MDD continue to have a vulnerability to the negative effects of stress. This vulnerability to stress was not observed in healthy controls.

A possible mechanism through which inflammatory stress alters cognition is through the *kynurenine-pathway*. Tryptophan is metabolized to serotonin and kynurenine (KYN). KYN is further metabolized into two different metabolites: quinolinic acid (QUIN) and kynurenic acid (KYNA). QUIN shows neurotoxic effects by increasing oxidative stress (through its metabolite 3-hydroxykynurenine) and by being an N-methyl-D-aspartate (NMDA) receptor agonist. KYNA, on the other hand, is an antagonist of both the NMDA-receptor and the α-7 nicotinic acetylcholine receptor (α7nAchR), both known to play an important role in the regulation of cognitive functioning. Pro-inflammatory cytokines, such as IFN-γ, stimulate a shift of tryptophan towards this pathway, with increased concentration of QUIN and KYNA, and decreased concentrations of serotonin. For a thorough review of the interaction between inflammation, the kynurenine-pathway, and cognition, we refer to Allison and Ditor (2014).

The finding that working memory was improved is of unclear significance. This effect was also observed by Cohen et al. (2003) and (Ofek et al., 2007). These authors suggest that a subgroup of patients react on inflammatory stress with reductions of the acetylcholine degrading enzyme Acetylcholine Esterase (AchE), reflecting an increase in acetylcholine associated with increased condition. On the other hand, a subgroup also had increased concentration of AchE, with reduced cognition. As such, this suggest that there are different types of response to inflammation, reflecting also different responses on several subdomains of cognition.

The inflammatory stressor leads to an increase in reading time of the colors of negative words in the Emotional Stroop test. This effect was not observed in the neutral and positive words. This suggests that there is an increased negative attentional bias in patients following inflammatory stress. While the response was not significantly different from controls, there was a trend toward a longer reading time in patients. Moreover, only in patients, there was a correlation between IL-6 and the time to read. This is in line with a previous study reporting a correlation between inflammation and negative emotional bias in breast cancer survivors (Boyle et al., 2017). It should be noted that the analyses of biomarkers and cognition were mainly exploratory, and confirmation is necessary. Previous studies showed effects of inflammation on social/emotional processing (namely: reduced perception of emotions, increased avoidance of punishment/loss experiences, and increased social disconnectedness) (Bollen et al., 2017). As depression is associated with negative emotional

bias (Baert et al., 2010), which is reversible by antidepressants (Godlewska et al., 2016), the observed effect of inflammation on negative attentional bias further confirms inflammatory processes play a significant part in the pathogenesis of MDD.

In our study, the TSST was associated with increased attention in patients, but not in controls. In previous studies on healthy controls, the effects of psychosocial stress on cognition are contradictory, with some studies (Smeets et al., 2006, Nater et al., 2007), but not all (Kuhlmann et al., 2005, Oei et al., 2006), reporting increased performance. In previous studies cortisol responses to the TSST (and as such, increased HPA axis activation) have indeed been associated with improvements in cognition (Nater et al., 2007, Plieger et al., 2017). In the study of Plieger et al. (2017) it is suggested that acute stress enhances selective attention as cognitive resources are limited and used optimally in stress situation. Indeed, acute psychosocial stress increased the attention in our sample. Interestingly, ACTH was negatively correlated to information processing, a more complex cognitive task, which may be in line with the notion of stress optimizing limited cognitive resources.

It should also be noted that the acute psychosocial stressor reduces pro-inflammatory cytokines in this study (Niemegeers et al., 2016). As such, this improvement may be due to a reduction of inflammation. The effects of psychosocial stress can also be interpreted as an arousal effect, leading to increased vigor and thus increasing performance on cognitive tasks. Indeed, the TSST increased wakefulness in another study (Kudielka et al., 2004), though this effect was not seen in the present study (Niemegeers et al., 2016).

As mentioned before, it has been shown that psychological stress results in negative mood symptoms in depressed patients (Hammen et al., 2009) as well as in healthy humans (Steptoe et al., 2007). Interestingly however, psychological stress exacerbated the deterioration of mood following administration of typhoid vaccine in healthy subjects, which suggests that inflammatory stress and psychological stress may have an accumulating effect on mood and possibly cognitive symptoms (Wright et al., 2005). In line with these findings, we investigated whether the combination of psychological and inflammatory stressors may have an accumulating effect on cognitive functioning. Although we demonstrated some mild effect of the combination of both stressors on verbal learning and memory which was not seen by either stressor alone, none of the other cognitive domains seemed to be affected by the combined stressors. Our findings thus partly argue against the hypothesis of accumulating effects of both stressors on cognitive functions in remitted subjects.

Our study has several limitations. The main limitation is the relatively small sample size. Although some of the mentioned effects are in line with previous observations in a healthy population in the literature, we observed them only in the patient group. This may reflect

that the study is possibly underpowered to find small effects in the control population, but it does suggest that the patient group is more sensitive to the effects of inflammatory and psychosocial stress, compared to controls.

Another confounding factor is that the majority of the patients took antidepressants, which are known to normalize pro-inflammatory states and reduce negative attentional bias (Kenis and Maes, 2002, Godlewska et al., 2016). Additionally, the effects of the interventions were only examined in a short time frame (6 hours), potentially masking other and stronger effects later in time. It is also possible that the 7-14-day period between the interventions is too short to recover from the effect of the stressors. Two thirds of the participants in the patient group took antidepressants. While this was controlled for in the statistical analysis, it should be noted that antidepressant therapy can have effects on inflammatory parameters and cognition (Kohler et al., 2018, Prado et al., 2018). Although a correlation between biomarkers and cognitive measures was found, it does not provide conclusive evidence that these biomarkers mediate direct changes in cognition. As expression levels of cytokine are highly correlated, it remains to be determined what their specific roles are.

In conclusion, patients were sensitive to the effect of both inflammatory and psychosocial stress. An inflammatory stressor reduced information processing speed and verbal memory, but improved working memory and a negative attentional bias. A psychosocial stressor, on the other hand, increased attention. In contrast, controls were not sensitive to the effects of both stressors.

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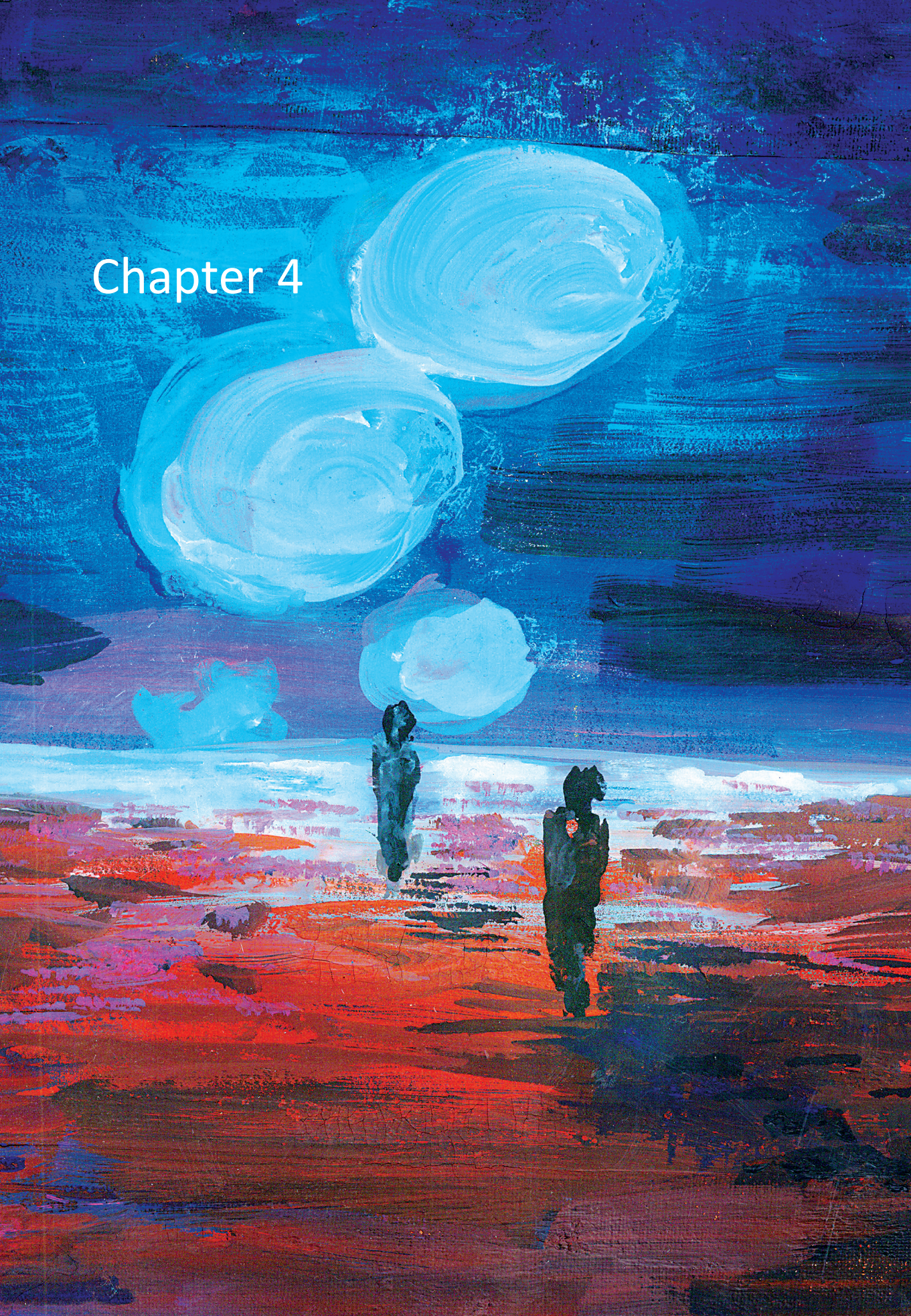

Chapter 4

The Effects of Nicotine are Dependent on Baseline Performance

This chapter has been published as:
Niemegeers, P., Dumont, G. J., Quisenaerts, C., Morrens, M., Boonzaier, J., Fransen, E., de Bruijn, E. R., Hulstijn, W. & Sabbe, B. G. C. 2014. The effects of nicotine on cognition are dependent on baseline performance. Eur Neuropsychopharmacol, 24, 1015-23.

Abstract

Since cholinergic neurotransmission plays a major role in cognition, stimulation of the nicotinic acetylcholine receptor may be a target for cognitive enhancement. While nicotine improves performance on several cognitive domains, results of individual studies vary. A possible explanation for these findings is that the effect of nicotine administration may be dependent on baseline cognitive function, where subjects with a suboptimal cognitive performance may benefit from nicotine, while subjects who already perform optimally may show a decline in performance after nicotinic stimulation. We conducted a double-blind randomised placebo-controlled crossover trial, examining the effects of placebo, 1, and 2 mg of nicotine on cognition in young (n=16, age 18-30 years) and healthy elderly (n=16, age 60-75 years) subjects. We hypothesised that the elderly would benefit more from nicotine compared to young subjects, as normal ageing is associated with decreases in cognitive function. Attention, working memory, visual memory, information-processing speed, psychomotor function, stereotypy, and emotion recognition were assessed. Compared to the young volunteers, the elderly performed significantly worse on psychomotor function and emotion recognition in the placebo condition. Nicotine had no effect in the young volunteers and decreased performance on working memory and visual memory in the elderly. Contrary to our hypothesis, the effect of nicotine was dependent on baseline performance in both groups, with subjects with lower baseline performance benefiting from nicotine administration, while those with higher baseline performance performed worse after nicotine administration. This suggests that, while nicotine generally had no or negative effects in our study, subjects with lower cognitive performance, irrespective of age, may benefit from nicotine.

Introduction

Cholinergic neurotransmission plays an important role in the peripheral and central nervous system. In the latter, it is an important modulator of cognition (Sarter and Parikh, 2005). Increased age is associated with a decreased availability of the nicotinic acetylcholine receptor (nAChR) (Mitsis et al., 2007, Mitsis et al., 2009), which may contribute to the decline of cognitive function (such as attention, executive function, memory, visuospatial function and cognitive speed) that is associated with normal ageing (Drag and Bieliauskas, 2010, Christensen, 2001). Decreases in nAChR's are also implicated in several pathological states associated with decreased cognitive functioning, such as neurodegenerative disorders (e.g. Alzheimer's disease) and schizophrenia (Dani and Bertrand, 2007, Quisenaerts et al., 2013b, Quisenaerts et al., 2013a). Stimulation of the cholinergic neurotransmission with cholinesterase inhibitors has been shown to ameliorate cognitive impairment in Alzheimer's disease (Birks, 2006, Rolinski et al., 2012), suggesting that the cholinergic system is a valid target for cognitive enhancement.

Nicotine, present in tobacco smoke, is an agonist of the nAChR, and as such may improve cognition (Heishman et al., 2010). Of the several subtypes of the nAchR, the α4β2 and the α7 nAchR appear to be the most important in cognitive functioning (Levin et al., 2006). In a meta-analysis of studies in healthy adult smokers and non-smokers, it was shown that nicotine improved attention, motor function, and short-term episodic memory (Heishman et al., 2010). Although the aforementioned meta-analysis showed that nicotine globally enhanced several domains of cognition, the results of individual studies are conflicting (Newhouse et al., 2004, Quisenaerts et al., 2014). Newhouse et al. (2004) suggest that the effects of nicotine may be dependent on baseline functioning, where the effect of nicotine is best described with an inverted U-shape, similar to the effects of stimulants (Cools and D'Esposito, 2011), where only those subjects with suboptimal cognitive performance may benefit from nicotine.

Following this line of thought, nicotine may be particularly effective in populations with decreased cognitive performance. Indeed, a study on patients with minimal cognitive impairment (MCI) showed that nicotine improved attention, memory, and psychomotor speed (Newhouse et al., 2012). So far, only two studies have addressed the effects of nicotine in a normal elderly population. White and Levin (2004) found that 10 mg of transdermal nicotine improved attention and clinical global impression score in patients with age-associated memory impairment, whereas another study in healthy elderly non-smokers, found that 5 mg transdermal nicotine improved verbal memory, but not short-term memory, concentration, and orientation (Min et al., 2001).

To assess the effects of nicotine on the cognitive performance of healthy elderly subjects, we conducted a clinical trial comparing the effect of the administration of 0, 1, and 2 mg oromucosal nicotine spray on several cognitive measures in healthy elderly and young volunteers. We hypothesised that the administration of nicotine would improve cognitive function in healthy elderly subjects, since we expected lower baseline cognitive functioning due to age-related decreases in cognitive performance. We expected that nicotine would have no or negative effects in healthy young subjects, since they already have an optimal cognitive performance relatively to elderly.

Experimental Procedures

Study Population

Healthy young (aged 18-30 years) and healthy elderly volunteers (aged 60-75 years) were eligible for the study. Additional inclusion criteria were: a body mass index between 18 and 30 kg/m^2 and the use of an effective contraceptive method by the female participants. The exclusion criteria were: smoking or the use of nicotine based products during the last 3 months, significant history of/or current psychiatric, somatic, or neurological illness, pregnancy or breast feeding, clinically significant abnormalities in lab values/physical examinations/vital signs/ECG, clinically significant recent or current acute illness, the use of any prescription irrespective of over-the-counter or herbal medication, and substance abuse. The consumption of alcohol, methylxanthine containing beverages or foods, quinine, grapefruit, grapefruit juice, Seville oranges, and any poppy seeds was not permitted from 48 hours before drug administration until discharge from the unit. Smoking was not allowed during the study and subjects were not allowed to do any strenuous exercise (from 7 days prior to the first study drug administration) until after study completion.

SGS Clinical Research Unit, Antwerp, Belgium, recruited the participants. A written informed consent form was obtained from every participant after full explanation of trial procedures. After screening each subject for eligibility, 16 young and 16 elderly healthy volunteers were included in the trial. The demographic variables are summarised in **Table 1**.

Table 1: Mean demographic and clinical variables (standard deviation)

Variable (unit)	Young	Elderly
Age (years)	22.6 (3.03)	62.9 (2.71)
Gender (male:female)	4:12	8:8
Education (years)	13.9 (1.03)	12.9 (1.89)
Education (level)		
- Low (%)	12.5%	18.75%
- Average (%)	62.5%	56.25%
- High (%)	25%	25%

Study Design

This was a double-blind, placebo-controlled, randomised three-way crossover study, which examined the effects of placebo, 1 and 2 mg of nicotine on the cognitive performance in healthy young and elderly volunteers. The study was conducted at the University Psychiatric Hospital Duffel, Belgium. Approval for the study was obtained from the local Ethics Committee and the Belgian Health Authorities. The study was conducted in compliance with the regulations of the participating institution, the International Conference on Harmonisation Good Clinical Practice guidelines, and the European Directive 2001/20/EC. The study was registered in the EudraCT database under the identifier *2009-010595-18* and in the ClinicalTrials.gov trial registry under the identifier *NCT01181934*. The study was funded by Janssen Pharmaceutica N.V., Belgium, and the Agency for Innovation by Science and Technology (IWT) of the regional government of Flanders, Belgium.

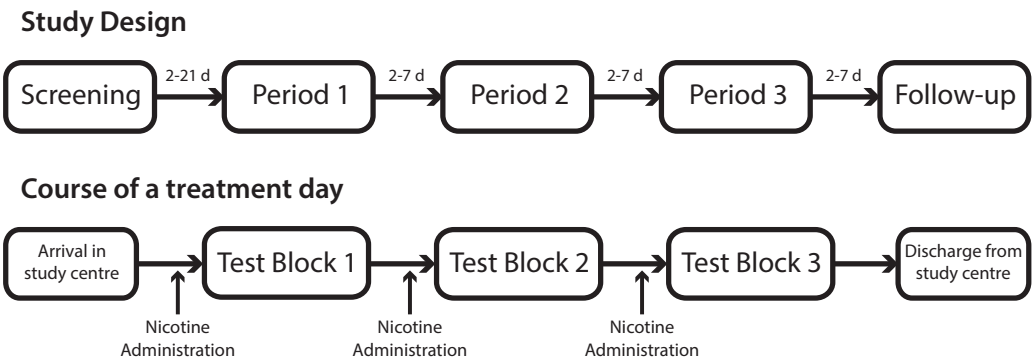
The study design is shown in **Figure 1**. It consisted of a screening visit, to determine subject eligibility, three treatment periods (separated by a washout of 2 to 7 days), and a follow-up examination. The screening consisted of a medical history and a physical and neurological examination performed by the research physician. During this visit, the following parameters of the participant were also recorded: weight, height, 12-lead electrocardiogram, vital signs (supine and standing blood pressure, and pulse), body temperature, alcohol breath test, and laboratory tests (haematology, serum chemistry, serology, urinalysis, urine drug screen, and urine pregnancy test for women of childbearing age).

On the treatment days, after an alcohol breath test and a urine drug and pregnancy screen, the subjects received placebo, 1, or 2 mg nicotine, three times daily with a dosing interval of 2.5 hours. There were three treatment days and each subject completed the three treatment conditions. Nicotine was administered using an oromucosal spray containing the pharmacologically active S-isomer of nicotine (Nicorette® mouth spray 1 mg/dose, McNeil AB, Sweden, kindly provided by the manufacturer). Two milligram of nicotine matches more or less half of the amount of nicotine found in a cigarette. As smoking one

cigarette results in almost complete occupancy of the α4β2 nAchR with blood nicotine concentrations of about 10ng/mL, and venous blood concentrations of nicotine of 0.87 ng/mL were already associated with 50% receptor occupancy, the doses of 1 and 2 mg nicotine were deemed sufficient to evaluate the cognitive effects of nicotine (Quisenaerts et al., 2014, Brody et al., 2006). The matching placebo spray contained capsaicin, to mimic the taste of nicotine and as such ensure the blinding of the participants. After each treatment administration, a 40-60 min block of cognitive tests was performed, with a total of three different testing blocks. The order in which the different testing blocks were administered, was for each participant the same on the three testing days. Between the participants, the order of the testing blocks was randomised and counterbalanced. The different treatment days (placebo, 1 mg, or 2 mg nicotine treatment) were done in a randomised and counterbalanced order, thus controlling for learning effects on the cognitive tests. Vital signs were measured before dosing and after each test block. Blood samples for pharmacokinetic analysis were taken before dosing, as well as 5 and 60 min after dosing.

On the follow-up visit (7-14 days after the last dose or early withdrawal), an abbreviated physical examination was performed, vital signs and blood pressure were measured, and laboratory tests (haematology, serum chemistry and urinalysis) and an ECG were performed.

Figure 1: Study Design



Cognitive Assessments

Three blocks of cognitive tests were performed on each testing day, measuring standard cognitive measures and social cognitive measures. Before the first treatment day, there was a practice session for all tests except for the Letter Number Sequencing, Symbol Digit Substitution Task, and Stereotypy Test Apparatus.

Continuous Performance Test – Identical Pairs version (CPT-IP)

The CPT-IP is a measure of sustained attention (Cornblatt et al., 1988). In this task, a series 4-digit numbers were shown on a computer screen at a rate of one per second. Each number was shown for only 50 milliseconds and was followed by a black screen. When two identical numbers were presented in a row, the subject was required to push a response button as fast as possible. There were also a number of "catch trials", where the number presented was similar to the previous one. From the 150 trials presented, there were 30 target trials and 30 catch trials. The primary outcome measure is the signal detection index *dprime* (*d'*), which is a measure of attentional capacity. Secondary outcome measures were the proportion of hits (correct responses), false alarms (responses to catch trials), and the mean reaction time to hits in milliseconds (ms).

Letter-number Sequencing (LNS)

The LNS is a test of working memory from the Wechsler Adult Intelligence Scale, 3rd version (Wechsler, 1997). A sequence of numbers and letters is read, each with an increasing sequence length (starting with 2 and ending with 7 characters). For each sequence length there are three trials. The subject is asked to repeat this sequence of letters and numbers, beginning with the numbers from low to high, followed by the letters in alphabetical order. When three consecutive trials with a particular sequence length are failed, the test is stopped. The outcome measure is the number of correctly repeated sequences.

Benton Visual Retention Test (BVRT)

The BVRT (Sivan, 1992) is a test of visual perception, visual memory and visuoconstructive skills, where 10 figures are shown for 10 seconds. The subject was asked to reproduce these images after a delay of 15 seconds. The outcome measure is the number of correctly drawn figures.

Symbol Digit Substitution Test (SDST)

The SDST is a measure of information-processing speed and is a variant of the Digit Symbol Substitution Test of the Wechsler Adult Intelligence Scale-Revised (Morrens et al., 2006b, Morrens et al., 2008, Wechsler, 1981). In this task, a series of symbols has to be decoded as fast as possible to its corresponding digit (ranging 1-9) using a list of corresponding digit-symbol pairs, within a time limit of 90 sec. The task was performed on a digitising tablet, using the procedure described in Morrens et al. (2006b). Outcome measures are the number of correctly substituted digits, the matching time (mean time needed by the subject to find the corresponding digit) and the mean writing time (mean time needed by the subject to write the digit), both measured in seconds (s). Erroneous digits were excluded from the calculation of these outcome measures.

Line Copying Task (LCT)

In the LCT, a line is shown on the computer screen, which the subject is asked to copy as fast as possible onto a sheet of paper divided into 3 by 4 cm squares, which is placed on a digitising tablet. The task is described in detail by Docx et al. (2012). The outcome measures are initiation time (i.e. the time [s] it takes to initiate the drawing of the line) and movement time (i.e. the time [s] it takes to draw the line).

Pointing Task

The pointing task is a task of fine motor control. The subject is asked to keep a pen above a small target on the digitising tablet for 1 min. The outcome measure is mean time in the target.

Pursuit Test

The Pursuit Test is a digital version of the classic rotor pursuit task (Ammons, 1951), and is a measure of visuospatial monitoring, sensorimotor speed and sensorimotor accuracy. Subjects had to follow a target (diameter 2 cm) on the computer screen, which moved with increasing speed on an invisible circular trajectory with a diameter of 15 cm, by moving a pen on the digitising tablet (Dumont et al., 2011). Thereafter, subjects had to do a similar task, but with a different, non-circular, trajectory, of about equal length of the circular trajectory. The outcome measure for both the circular and the non-circular trajectory was the percentage of the trajectory spent in the target.

Stereotypy Test Apparatus (STA)

The stereotypy test apparatus (Morrens et al., 2006a) is a device with nine randomly distributed buttons. The subject is asked to press one of the buttons, following an acoustic signal, in such a way that the order is as random as possible. There are 200 trials for the STA. The outcome measure is *Redundancy of Context*, which is a measure of stereotypy that reflects the chance of two consecutive presses within the total number of presses. The score lies between 0 and 1, with lower scores reflecting more random sequences.

Emotion Recognition/Matching (ERM)

This is a computerised task to measure emotion recognition. At the top of the computer screen a photograph is shown of a person expressing one of following six emotions: happy, sad, surprised, disgust, anxious or angry. At the bottom of the computer screen two photographs of another person is shown, one expressing the same emotion as the photograph at the top and the other one expressing a different emotion. The subject is asked to match the emotion at the bottom, with the corresponding emotion at the top of the screen. Thirty trials are shown. The outcome measure is the number of correct responses.

Reading the Mind in the Eyes test (RTME)

This is an advanced theory of mind and emotion recognition test. The subject is shown a series of photographs of the eye region that express certain emotional states. Along with each photograph, four adjectives describing possible states of mind (emotions) are presented, and the subject has to choose the adjective matching the mental state of the photograph (Vellante et al., 2012). The outcome measure is the number of correct responses.

Statistics

Since there is a possibility of accumulation of nicotine after each dosing, for each period of blood sampling (pre-dose, 5 min, and 1 h), a repeated measurements analysis was carried out to determine whether there is an interaction between dosing moment (1st, 2nd, or 3rd dosing) and plasma concentrations of nicotine. If this was statistically significant, a one-way ANOVA was carried out to compare the effect of testing moment (after the 1st, the 2nd, or the 3rd dose) and outcome measures of each cognitive test. In addition, mean outcome measures in the placebo condition were compared between the two groups (young and elderly) with a one-way ANOVA.

The effects of the dose (0, 1 or 2 mg) and the group (young and elderly) on the cognitive test outcomes were assessed. To determine whether the effect of dose was different between young and old individuals, a repeated measurements analysis was carried out testing for the significance of the interaction term. A significant interaction means that the effect of the dose on the outcome is significantly different between the two groups. If the interaction term is not significant, there may still be an effect of dose, but this effect does not differ significantly between the two groups. A repeated measurements analysis was also carried out for each group individually, to test the effect of dose within the respective groups. Pairwise comparisons between the different doses were performed as well, using Šidák-correction for multiple testing.

To assess whether the effects of nicotine were dependent on baseline cognitive performance, an exploratory analysis of the data was done. The difference between performance under 1 or 2 mg nicotine and baseline (i.e. placebo) was calculated, and for each cohort bivariate correlation with baseline performance was done. Data were tested for normality using the Shapiro-Wilk test. If the data of both the baseline and the difference between nicotine (1 mg or 2 mg) and baseline was normally distributed, Pearson correlation was used, if not, Spearman correlation was used.

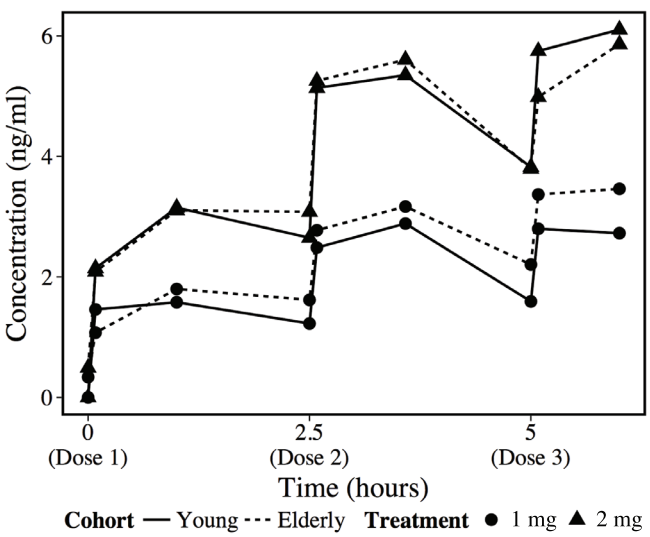
All analyses were carried out in IBM SPSS Statistics 22.0. Each cognitive test was analysed separately. In tests with multiple outcome measures, listwise deletion was used to handle missing data. Graphs were generated with the software package R (version 3.0.2) using the *ggplot2* package (version 0.9.3.1). Differences were considered significant at a p-value equal to or lower than 0.05.

Results

Pharmacokinetics

Since there was a significant effect ($p < 0.001$) of dosing moment on plasma levels of nicotine, a one-way ANOVA was carried out on the cognitive test results to see if there was an interaction between testing moment and outcome measures, which was not significant ($p>0.05$) for any of the outcome measures. One young subject was incorrectly dosed at the third dosing moment in the placebo condition and one elderly subject at the second dosing moment; all outcome measures after these doses were excluded from the analyses. Nicotine pharmacokinetic data are presented in **Figure 2**.

Figure 2: Pharmacokinetic data



Young vs. elderly volunteers

When comparing the two groups (young and elderly) on baseline (i.e. placebo) performance, the elderly performed significantly worse on measures of psychomotor function (SDST writing time ($p=0.004$), LCT initiation ($p=0.001$) and movement time ($p<0.001$), and time in target of both the rotations ($p<0.001$) and the non-circular trajectories ($p<0.001$) of the Pursuit Task). There were significantly less ($p=0.001$) correct numbers on the SDST. The elderly performed significantly worse on the RTME ($p=0.014$).

Effect of nicotine on cognitive measures

In the repeated measures analysis, Mauchly's test indicated a violation of the assumption of sphericity for the number of correct answers on the ERM in the elderly cohort and the writing time of the SDST in the young cohort. To compensate for the violation of sphericity in the Mauchly's test the degrees of freedom were corrected using Greenhouse-Geiser estimates of sphericity. The results of the young and elderly cohort are summarised in **Table 2**.

Effect of nicotine on young volunteers

There were no significant effects of nicotine (1 and 2 mg) on any of the measures in the young volunteers.

Effect of nicotine on elderly volunteers

Performance in the CPT (a measure for sustained attention) was unchanged on the primary outcome measure, dprime. There was a significant increase in hits (0 vs. 1 mg, $p=0.021$; other comparisons not significant [NS]), which was, however, paired with a significant increase in false alarms at the 1 mg dose (0 vs. 1 mg, $p=0.003$; 1 vs. 2 mg, $p=0.013$; 0 vs. 2 mg, NS). A significant ($p=0.041$) dose × group interaction was also observed for this increase in false alarms at the 1 mg dose. Reaction time decreased significantly after the administration of nicotine (0 vs. 1 mg, 0.026; 0 vs. 2 mg, $p=0.011$; 1 vs. 2 mg, NS).

Working memory (LNS) was significantly impaired after the administration of nicotine (0 vs. 2 mg, $p=0.009$; other comparisons NS), as well as visual memory (BVRT; 0 vs. 1 mg, 0.017; 0 vs. 2 mg, $p=0.016$; 1 vs. 2 mg, NS). Nicotine did not have any significant effects on information-processing speed, psychomotor function and emotion recognition.

Table 2: Results

		Young					Elderly				
		Mean (standard deviation)			Statistics		Mean (standard deviation)			Statistics	
Test	**Measure**	**0 mg**	**1 mg**	**2 mg**	**F-value**	**p-value**	**0 mg**	**1 mg**	**2 mg**	**F-value**	**p-value**
CPT	dprime	1.854 (0.909)	2.116 (0.933)	1.865 (0.851)	F=1.033	NS	1.791 (0.638)	1.666 (0.568)	1.801 (0.405)	F=0.785	NS
	hits	0.800 (0.120)	0.844 (0.126)	0.829 (0.101)	F=1.411	NS	0.751 (0.106)	0.824 (0.114)	0.800 (0.093)	F=5.508	p=0.010
	false alarms	0.216 (0.170)	0.218 (0.195)	0.238 (0.167)	F=0.234	NS	0.180 (0.159)	0.280 (0.160)	0.198 (0.119)	F=8.245	p=0.002
	reaction time (ms)	498.1 (58.5)	491.8 (73.1)	486.3 (69.6)	F=0.616	NS	516.6 (68.2)	484.9 (67.7)	479.5 (53.5)	F=7.685	p=0.002
LNS	nr. correct	11.00 (2.36)	10.80 (2.65)	10.67 (1.99)	F=0.207	NS	9.87 (1.6)	9.20 (1.47)	8.40 (1.84)	F=5.885	p=0.007
BVRT	nr. correct	8.81 (1.42)	8.81 (1.17)	8.50 (1.32)	F=0.338	NS	8.07 (1.1)	6.87 (1.55)	6.53 (1.36)	F=6.429	p=0.005
SDST	nr. correct	65.80 (9.19)	64.00 (8.55)	61.33 (7.58)	F=2.983	NS	54.53 (8.11)	54.13 (7.51)	52.07 (6.73)	F=2.410	NS
	matching time (s)	0.893 (0.200)	0.938 (0.204)	0.961 (0.225)	F=1.915	NS	1.027 (0.204)	1.074 (0.207)	1.121 (0.215)	F=3.040	NS
	writing time (s)	0.481 (0.079)	0.481 (0.116)	0.503 (0.121)	F=1.366	NS	0.634 (0.179)	0.600 (0.129)	0.602 (0.122)	F=1.162	NS
LCT	initiation time (s)	0.589 (0.097)	0.589 (0.095)	0.587 (0.081)	F=0.016	NS	0.742 (0.125)	0.724 (0.110)	0.743 (0.082)	F=0.546	NS
	movement time (s)	0.216 (0.048)	0.218 (0.051)	0.204 (0.040)	F=1.664	NS	0.328 (0.101)	0.332 (0.097)	0.341 (0.123)	F=0.184	NS
Pointing Task	duration out of target	6.25 (7.91)	3.94 (6.24)	5.39 (9.88)	F=0.404	NS	4.21 (3.78)	4.42 (5.08)	3.98 (5.99)	F=0.035	NS
Pursuit Test	percentage in target: rotation	61.19 (11.02)	55.38 (15.13)	57.38 (15.21)	F=1.276	NS	35.63 (17.18)	38.75 (17.98)	31.94 (14.87)	F=2.060	NS
	percentage in target: non-circular trajectory	82.69 (9.20)	81.56 (8.79)	81.13 (13.72)	F=0.130	NS	65.5 (14.38)	67.56 (12.84)	62.06 (12.7)	F=1.447	NS
STA	redundancy of context	0.204 (0.055)	0.200 (0.053)	0.196 (0.048)	F=0.255	NS	0.235 (0.098)	0.216 (0.075)	0.223 (0.082)	F=0.983	NS
ERM	nr. correct	28.25 (1.18)	28.63 (1.09)	27.63 (1.59)	F=3.025	NS	27.40 (1.72)	27.13 (1.85)	27.67 (2.16)	F=0.394	NS
RTME	nr. correct	24.67 (3.27)	25.40 (2.85)	24.87 (3.80)	F=0.522	NS	20.87 (4.58)	21.87 (3.62)	20.87 (3.96)	F=0.942	NS

NS=not significant

Effect of baseline performance on the effects of nicotine

The data of the correlation between baseline (i.e. placebo) performance and the difference between baseline performance and performance after nicotine administration, is summarised in **Table 3**.

Both in the young and elderly cohort, a significant effect of baseline performance was found for attention (CPT), working memory (LNS), information-processing speed (SDST number correct), psychomotor functioning (LCT, Pointing Task, Pursuit Task, and in the elderly SDST writing time), stereotypy (STA) and emotion recognition (RTME and ERM). In the young volunteers, a significant effect of baseline function was observed on the visual memory (BVRT). All significant correlation coefficients were negative, meaning that nicotine decreased performance more in those who performed better at baseline, and improved cognition more in those with lower baseline performance.

Table 3: Correlations between baseline functioning and the effects of nicotine

		Young				Elderly			
		Δ 1 mg		Δ 2 mg		Δ 1 mg		Δ 2 mg	
Test	**Measure**	**Pearson's r / Spearman's ρ**	**p-value**	**Pearson's r / Spearman's ρ**	**p-value**	**Pearson's r / Spearman's ρ**	**p-value**	**Pearson's r / Spearman's ρ**	**p-value**
CPT	dprime	r=-0.334	NS	r=-0.441	NS	r=-0.209	NS	r=-0.525	p=0.044
	hits	ρ=-0.426	NS	ρ=-0.533	p=0.041	r=-0.337	NS	r=-0.605	p=0.017
	false alarms	ρ=-0.169	NS	ρ=-0.447	NS	ρ=-0.281	NS	ρ=-0.801	p<0.001
	reaction time	r=0.023	NS	r=-0.095	NS	r=-0.308	NS	r=-0.621	p=0.014
LNS	nr. correct	r=-0.320	NS	r=-0.568	p=0.027	ρ=-0.642	p=0.010	ρ=-0.434	NS
BVRT	nr. correct	ρ =-0.674	p=0.004	ρ=-0.332	NS	r=-0.264	NS	r=-0.421	NS
SDST	nr. correct	ρ=-0.064	NS	r=-0.597	p=0.019	r=-0.567	p=0.028	r=-0.608	p=0.016
	matching time	r=-0.299	NS	r=-0.153	NS	r=-0.262	NS	r=-0.315	NS
	writing time	ρ=-0.136	NS	r=0.265	NS	ρ=-0.770	p=0.001*	ρ=-0.561	p=0.030
LCT	initiation time	r=-0.300	NS	r=-0.552	p=0.027	r=-0.483	p=0.058°	r=-0.759	p=0.001
	movement time	r=-0.191	NS	r=-0.592	p=0.016	r=-0.518	p=0.040*	r=-0.025	NS
Pointing Task	duration out of target	ρ=-0.609	p=0.012	ρ=-0.686	p=0.003	ρ=-0.571	p=0.021*	ρ=-0.624	p=0.010
Pursuit Test	percentage in target: rotation	r=-0.213	NS	r=-0.226	NS	r=-0.327	NS	r=-0.520	p=0.039
	percentage in target: non-circular trajectory	r=-0.671	p=0.004	r=-0.283	NS	r=-0.545	p=0.029	r=-0.598	p=0.014
STA	redundancy of context	r=-0.359	NS	r=-0.573	p=0.020	r=-0.673	p=0.004	r=-0.549	p=0.028
ERM	nr. correct	r=-0.834	p<0.001	ρ=-0.270	NS	r=-0.462	NS	r=-0.710	p=0.003
RTME	nr. correct	r=-0.575	p=0.025	r=-0.214	NS	r=-0.612	p=0.015	r=-0.569	p=0.027

NS=not significant; a significant correlation indicates that the effect of nicotine is dependent on baseline

Discussion

This study examined the effects of two doses of nicotine (1 and 2 mg of oromucosal nicotine spray) on several cognitive measures in healthy young and elderly volunteers. Our results corroborate previous findings that the elderly generally perform less well compared to the younger subjects on the domains of psychomotor functioning and information processing under placebo conditions. Contrary to our hypothesis, nicotine had a negative effect on working memory and short-term visual memory in the elderly. No effects were found on the primary outcome measure (i.e. dprime) of the attentional task (CPT). However, reaction time decreased and the number of correct hits increased. On the other hand, the latter was paired with an increase in false alarms. These results collectively suggest an increased tendency to respond rather than improved performance. The elderly also performed worse compared to the young on the theory-of-mind task (RTME). As previous research yielded conflicting results for the effect of aging on the RTME (Castelli et al., 2010, Baglio et al., 2012, Pardini and Nichelli, 2009), our results may provide further evidence for an age-related decline in theory-of-mind skills. To conclude, the performance under nicotine was generally either unchanged or worse in the elderly.

We also assessed whether the effects of nicotine on cognitive performance are dependent on baseline performance. A significant correlation between baseline function and nicotine effects was found in both the young and the elderly. In those having a baseline performance below average, nicotine improved performance, and in those whose baseline performance was above average, it decreased performance. These findings suggest that the cognition-enhancing effects of nicotine follow an inverted U-curve, which is comparable to the effects of stimulants (Cools and D'Esposito, 2011). As stimulation of the nAChR induces dopamine release (Jasinska et al., 2013), a key feature of stimulants, a dopaminergic effect may provide a common neurobiological substrate for this inversed U-curve.

When the effects of nicotine were averaged, this resulted in unchanged performance under nicotine in the young. In the elderly, nicotine decreased performance on average in several cognitive domains, which may suggest that the elderly are more sensitive to overstimulation of the nAchR, in line with findings that increased age is associated with a decreased availability of the nicotinic acetylcholine receptor (nAChR) (Mitsis et al., 2007, Mitsis et al., 2009).

However, limitations should be noted. This study was not primarily designed to assess the effect of baseline function on the cognitive effects of nicotine. Another limitation is that the sample size was relatively small. As such, these results should be considered preliminary. For some measures, namely the CPT (attention) and ERM (emotion recognition), the findings could be explained by ceiling effects, meaning that since baseline function was

near perfect in certain subjects, there was less room for improvement. However, other measures, which were devoid of ceiling effects, also showed significant correlations between baseline performance and nicotine effects, making it unlikely that ceiling effects account for the observed correlations. It should also be noted that the negative effects on visual and working memory were seen at the 2 mg dose, the effects on the CPT (hits and false alarms) were seen at the 1 mg dose, and the effects on reaction time in the CPT were seen at both doses. This suggests that nicotine differentially modulates different cognitive domains. Future research should address the dose-effect relationship of nicotine on different cognitive domains.

In conclusion, healthy elderly subjects show impaired cognitive performance compared to young healthy subjects on measures of information-processing speed and psychomotor function. In young healthy volunteers, nicotine did not affect cognitive function, while in the healthy elderly, cognition was generally decreased or unaffected. An exploratory analysis revealed that subjects with lower baseline functioning benefited from nicotine administration. Although these results are preliminary and should be replicated, this suggests that there may be a subgroup in the population that benefits cognitively from nicotine, independent of age.

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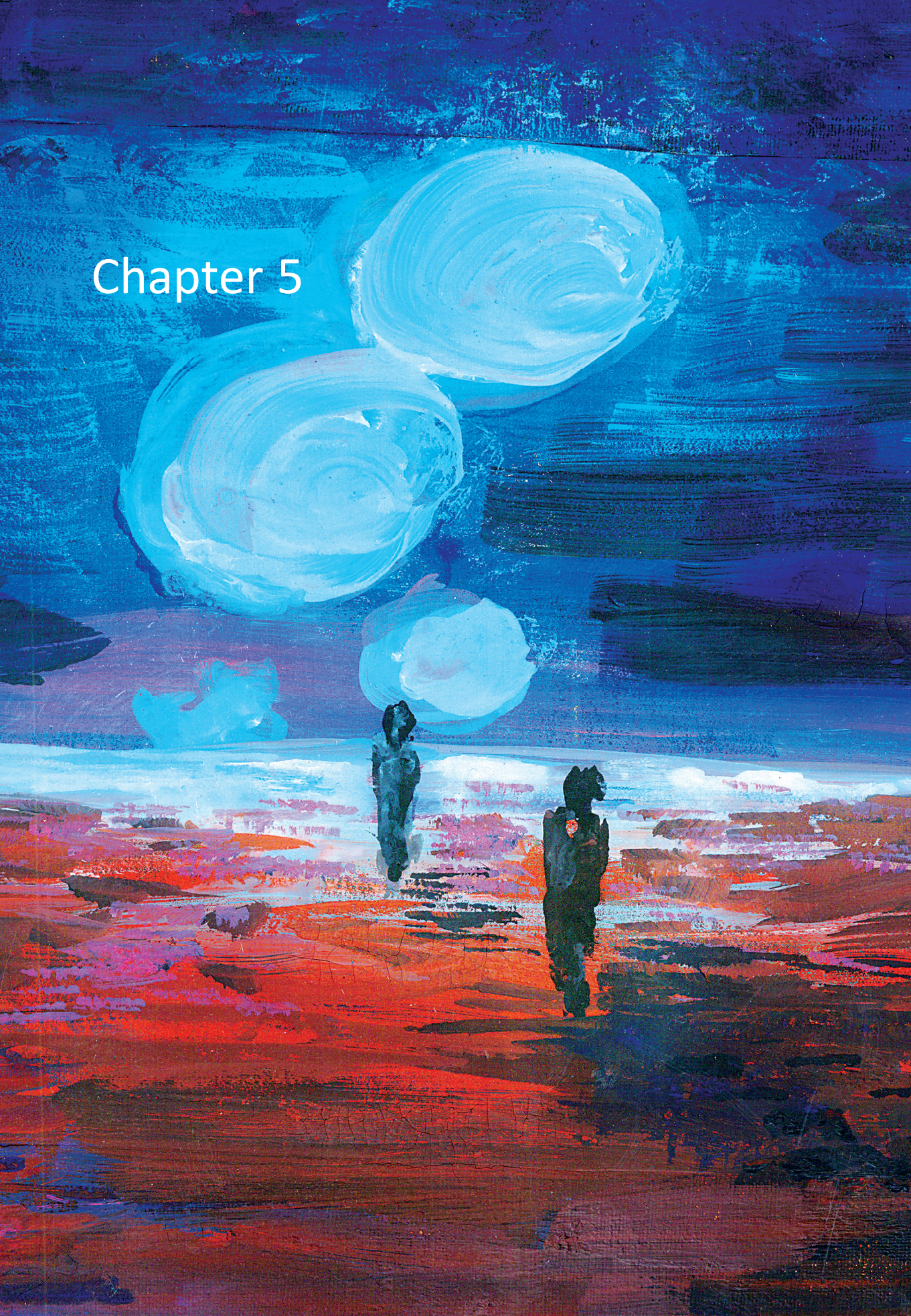
Chapter 5

Remission of Treatment-Resistant Depression with Electroconvulsive Therapy and Ketamine: a case report

This chapter has been published as:
Niemegeers, P., Schrijvers, D., Madani, Y. & Sabbe, B. G. C. 2014. Remission of treatment-resistant depression with electroconvulsive therapy and ketamine. J ECT, 30, e31-2.

Electroconvulsive therapy (ECT) is a highly efficacious treatment for treatment-resistant depression. However, some patients do not or just poorly respond. Since ECT has a high success rate, limited evidence is available for standard practice or augmentation strategies for ECT-resistant patients.

We present a case of ECT-resistant depression that responded by using ketamine for anesthesia induction. A 75-year-old woman was hospitalized due to a severe major depressive episode with psychotic features, already lasting almost a year. The patient experienced low mood, psychomotor retardation, decreased appetite and energy, hopelessness, paranoid and somatic delusions, and suicidal ideation. During her life, she already suffered from at least five depressive episodes, with the first one at the age of 21.

Previously, she had been adequately treated with courses of several tricyclic antidepressants, without clinical improvement but with substantially impairing side effects. Addition of several antipsychotics (haloperidol, olanzapine, risperidone, flupentixol, and pipamperone) had no effect. Given the serious physical and mental deterioration, ECT was started. Routine examinations before the start of ECT (i.e. blood examination, electroencephalogram, and computed tomography scan of the head) did not reveal any relevant abnormalities. The patient scored 34 on the Hamilton Depression Rating Scale (HDRS), indicating severe depression, and 9 on the Bush-Francis Catatonia Rating Scale (with a score of 3 for mutism, stupor, and withdrawal). Her score on the Mini Mental State Examination (MMSE) was 28/30.

At the start of ECT treatment, the patient took amitriptyline 25 mg daily, lorazepam 1 mg daily, and pipamperone 60 mg daily. After the second ECT, due to persisting agitation and suicidal ideation, clozapine was started and titrated up to 150 mg. Since neither lorazepam nor pimpamperone had any positive effect, both were discontinued. During the ECT course, amitriptyline was increased to 50 mg and aripiprazole 10 mg was added. From session 17, the medication scheme was unchanged.

Initially, bifrontal electrode placement was chosen at a frequency of two stimulations per week. A constant-current Thymatron System IV device (Somatics LLC, Lake Bluff, IL) was used. Induction and modification were achieved with propofol 80 mg (1.5 mg/kg) and succinylcholine 25 mg (0.5 mg/kg), before each treatment. Dosing was age-based and stimulus parameters were energy, 35%; pulse width, 0.5 milliseconds; frequency, 30 Hz; and stimulus duration, 6.52 seconds. Adequate seizures were obtained ranging from 44 to 55 seconds.

As no clinical improvement occurred after 8 sessions, propofol was switched to etomidate (20mg, 0.4 mg/kg), and bitemporal stimulation was started with stimulus parameters ranging between 35% and 40% energy (pulse width, 0.5 milliseconds; frequency, 30 Hz; and stimulus duration, 6.52-7.45 seconds), without any improvement after 10 sessions. Due to cognitive side effects, bitemporal electrode placement was switched back to bifrontal placement at the 19th session, and racemic ketamine was used for induction (40 mg, 0.7 mg/kg), resulting in adequate seizures. After four sessions, a spectacular improvement was observed, with a decrease of HDRS score to 8, and a resolution of psychotic symptoms.

Afterwards, treatment was continued at a rate of one ECT per week, and right unilateral electrode placement was started at session 25, due to the cognitive side effects (MMSE 21/30). Since then, HDRS scores remain relatively stable, but the MMSE-score remained 21/30. When the patient was stable for several weeks, she was discharged to home, and continuation ECT at tapering frequencies was started.

In the current case, we used ketamine as an augmentation option in a patient that was ECT-resistant. Recently, more and more studies are published, which compare the use of ketamine with other anesthetic agents during ECT practice. In a double-blind randomized controlled trial (RCT) (Loo et al., 2012), ketamine plus thiopentone was compared with placebo plus thiopentone in patients who were referred for ECT. The ECT-ketamine-group was modestly superior at week 1 and the one-week follow-up, but not at the end of the treatment course and the one-month follow-up. This suggests that ketamine speeded up the response to ECT, but did not increase efficacy. These results were further substantiated by a double-blind RCT by Yoosefi et al., 2013 (Yoosefi et al., 2013), comparing ketamine-anesthesia to thiopental-anesthesia in 31 patients. Patients in the ketamine group responded faster, but at the end of the study, both treatments were equal.

However, two studies compared the use of thiopental (Abdallah et al., 2012) or propofol (Järventausta et al., 2013) alone with the use of these agents in combination with ketamine or S-ketamine, respectively. Both failed to demonstrate any enhanced antidepressant effects, and increased post-treatment disorientation and restlessness in the propofol-S-ketamine-group, were found. It can thus be concluded that the available data do not unequivocally support the use of ketamine as augmentation for ECT for the treatment of severe major depressive disorder.

Our case is different, in that we used ketamine as an augmentation strategy of the ECT treatment scheme because our patient did not react on a change of electrode sites, and change of anesthetic agents. Before the use of ketamine as anesthetic agent, good and adequate seizures were also elicited, but without clinical improvement.

In contrast, the previously mentioned studies included patients without ECT-resistance. It may be possible that ketamine may either augment the ECT, or may either be effective on its own in ECT-resistant patients. This last possibility is in line with the results of Ibrahim et al., 2010 (Ibrahim et al., 2011), who found that even in patients with ECT-resistance, one dose of ketamine induced a fast but transient decrease in depressive symptoms, though less so than in patients who were not ECT-resistant. Another possibility is that the administration of ketamine led to the previously described rapid acting though short lasting antidepressant effect, but that ECT consolidated this improvement in mood symptoms. However, we did not see an immediate response after the first administration of ketamine, but only an improvement after session 3.

Despite high remission rates of ECT, a significant minority of patients is ECT-resistant. For this population, evidence-based guidelines are lacking. Ketamine may be useful either as primary treatment or as an augmentation strategy that can be safely combined with ECT to enhance its efficacy or provide more rapid relief.

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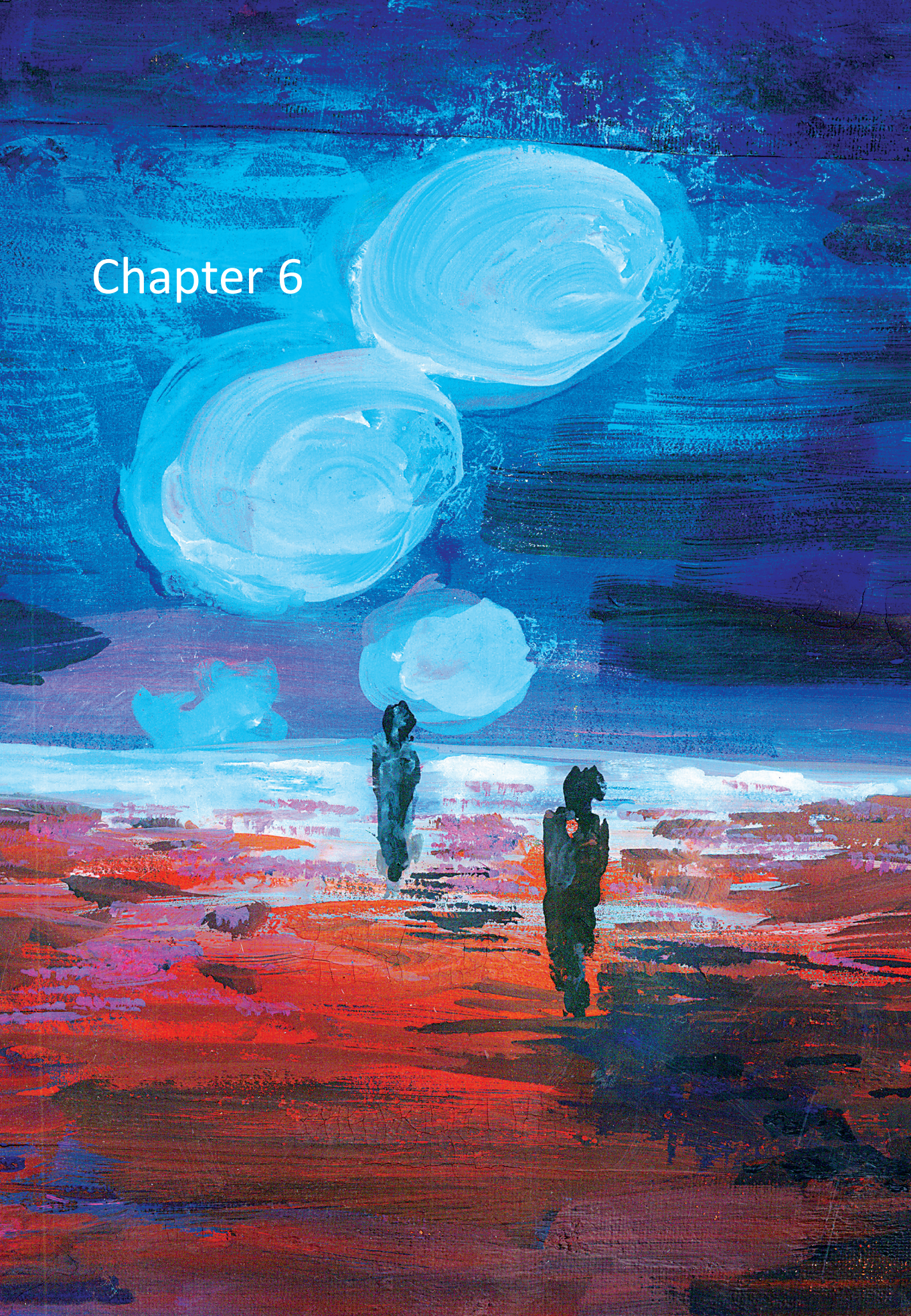

Chapter 6

Bupropion for the Treatment of Seasonal Affective Disorder

This chapter has been published as:
Niemegeers, P., Dumont, G. J., Patteet, L., Neels, H. & Sabbe, B. G. C. 2013. Bupropion for the treatment of seasonal affective disorder. Expert Opin Drug Metab Toxicol, 9, 1229-40.

Abstract

Introduction: Seasonal affective disorder (SAD) is a psychiatric illness with recurring depressive episodes during particular seasons, mostly winter. Bupropion is effective in the preventive treatment of SAD and is probably also effective in the acute treatment of SAD.

Areas covered: This review covers the pharmacokinetics and pharmacodynamics of bupropion. The authors also evaluate bupropion's clinical efficacy as well as its safety and tolerability.

Expert opinion: Bupropion is available in an immediate release formulation, as well as a sustained release formulation and an extended release (XR) formulation. The XR formulation is recommended for SAD due to its ease of use and is the only formulation currently used as a therapy. Due to the predictable nature of SAD, the use of bupropion XR is considered a relevant treatment option. Bupropion's efficacy is shown in three trials that started in autumn at a time when SAD symptoms were not yet present although treatment effects were relatively small compared with a placebo. Bupropion was also shown to have efficacy in an open-label study. That being said, in order to reach definitive conclusions about its efficacy with acute treatment of SAD, more placebo-controlled trials are needed.

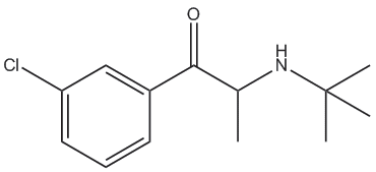
Introduction

Seasonal affective disorder (SAD) is a psychiatric illness in which depressive episodes occur during particular times of the year, while the patient does not have any symptoms for the remainder of the year (Partonen and Lonnqvist, 1998). Usually, the onset of the episodes is in fall or winter with remission in spring; recurrent depressive episodes during summer are much less common (Partonen and Lonnqvist, 1998). Patients with winter depression are more likely to have reverse vegetative symptoms (increased appetite and hypersomnia), while patients with summer depression are more likely to have decreased appetite and insomnia (Wehr et al., 1991).

In the Diagnostic and Statistical Manual of Mental Disorders, 4th version, SAD is included as a "seasonal pattern specifier", which can be applied to recurrent major depressive disorder, bipolar I, and II disorder (American Psychiatric Association, 1994). Using the DSM-IV criteria, the prevalence in the United States and Canada is 1-2% and 2%, respectively (Kurlansik and Ibay, 2012). SAD is associated with disturbances in circadian rhythms during the winter months and disturbances in monoamine neurotransmitters. For a thorough review, we refer to Levitan (2007). As SAD with depressive episodes in the winter is more common, the remainder of the article will refer to this subtype simply with SAD.

This paper provides an evaluation of the clinical usefulness of bupropion (**Table 1**) for the treatment of seasonal affective disorder. A Medline search was performed using the search terms 'bupropion' and 'seasonal affective disorder', 'winter depression', 'pharmacokinetics', 'metabolism', 'elimination', 'safety', or 'tolerability'. The titles and abstracts of the found references were examined for relevance (i.e. papers about treatment of SAD with bupropion, and papers concerning the pharmacokinetics and safety of bupropion). A search of the U.S. National Institute of Health clinical trial registry was performed using the same search terms, to identify previous and ongoing clinical trials of bupropion in the treatment of seasonal affective disorder that have not been published. All bupropion trials in the clinical study registry of, the original manufacturer of bupropion, were examined, and are also considered in this review. The reference lists of identified publications were also examined for relevant publications.

Table 1: Drug summary

Drug name	Bupropion
Phase	Phase IV
Indication	Prevention of Seasonal Affective Disorder
Pharmacology description/ mechanism of action	Antidepressant which acts as a norepinephrine and dopamine reuptake inhibitor
Route of administration	Oral
Chemical Structure	
Pivotal Trials	A 7-Month Multicenter, Parallel, Double-Blind, Placebo-Controlled Comparison of 150-300mg/day of Extended-release Bupropion Hydrochloride and Placebo for the Prevention of Seasonal Depressive Episodes in Subjects with a History of Seasonal Affective Disorder Followed by an 8-week Observational Follow-up Phase (Modell et al., 2005) [NCT00069459/WELL 100006 (GlaxoSmithKline, 2003), NCT00046241/WELL AK130930 (GlaxoSmithKline, 2002b), and WELL AK130936 (GlaxoSmithKline, 2002c)]

Overview of the market

Several pharmacological as well as non-pharmacological treatment options are available for the treatment of SAD. Light therapy is an established treatment for SAD and can be used for the acute or preventive treatment of SAD (Ravindran et al., 2009, Golden et al., 2005, Partonen and Lonnqvist, 1996b). It consists of daily exposure to bright light, usually with an intensity of 10,000 lux for 30 min, administered early in the morning (Ravindran et al., 2009). There might be a positive effect of high-density negative air ionization, though results are conflicting (Terman and Terman, 1995, Terman and Terman, 2006, Flory et al., 2010). Dawn simulation (i.e. gradually increasing light intensity during early morning before wake-up simulating sunrise) may also be effective (Terman and Terman, 2006, Avery et al., 2001). Cognitive Behavioural Therapy alone, bright light therapy alone, or the combination of both was compared to a waiting list in the acute treatment of SAD in one trial (n=61) (Rohan et al., 2007). All treatments significantly improved depression severity, and the combination treatment had a significant higher remission rate versus the waiting list.

In the acute treatment of SAD, antidepressants are probably effective (**Table 2**). Sertraline was significantly superior to placebo in one 8-week double-blind randomised placebo-controlled trial (n=187) (Moscovitch et al., 2004). One randomised controlled trial (n=68) failed to show significant differences between fluoxetine and placebo in depression scores

on the continuous measure, a modified *Hamilton Depression Rating Scale* (HDRS), which, besides the regular items of the HDRS, also includes items of hypersomnia, increased appetite, carbohydrate craving, and weight gain (Lam et al., 1995). When cut-off values for response were used (i.e. a reduction on the modified HDRS score of more than 50%), there were significantly more responders in the fluoxetine group than in the placebo group. In two other double-blind randomised controlled trials (n=40 and n=96), 10,000 lux light therapy was equally effective as fluoxetine, but no placebo arm was included (Lam et al., 2006, Ruhrmann et al., 1998). Moclobemide was not significantly better than placebo in one controlled trial (n=34), but equally effective than fluoxetine in another trial (n=32) (Partonen and Lonnqvist, 1996a, Lingjaerde et al., 1993). Several open-label trials showed efficacy for escitalopram, duloxetine, agomelatine, reboxetine, nefazodone, bupropion, tranylcypromine, and mirtazapine (Pjrek et al., 2007b, Pjrek et al., 2008, Pjrek et al., 2007a, Hilger et al., 2001, Shen et al., 2005, Dilsaver and Jaeckle, 1990, Dilsaver et al., 1992, Hesselmann et al., 1999), though sample sizes were small (ranging from 8 to 37) and no placebo arm was included in these trials. In one small trial (n=8), citalopram combined with light therapy was more effective than light therapy combined with placebo in the acute treatment of SAD (Thorell et al., 1999). Hypericum extract (St John's Worth) was effective in three open-label studies (Kasper, 1997, Martinez et al., 1994, Wheatley, 1999). L-tryptophan, a rate limiting precursor in the synthesis of serotonin, was superior to placebo and equal to bright light treatment in a small (n=13) trial (McGrath et al., 1990).

Several antidepressants were also shown to be effective in the prevention of SAD (**Table 2**). Bupropion was significantly superior to placebo in three double-blind randomised controlled trials as a prophylactic treatment for depressive episodes associated with SAD, when started in autumn, before the onset of symptoms, and continued until spring (Modell et al., 2005). Citalopram was evaluated for the prevention of relapse of SAD after successful bright light treatment in a 15-week placebo-controlled study (n=282) (Martiny et al., 2004). Citalopram only separated from placebo on two secondary outcome measures (a 6-item depression subscale of the HDRS and the Melancholia Scale), but not on the primary outcome measure (the 17-item HDRS).

Table 2: Overview of antidepressant trials in the acute and preventive treatment of SAD

Author, Year [Reference]	Method	N	Duration	Treatments	Findings
Acute Treatment					
Pjrek et al. (2007a)	Open-label	37	14 weeks	Agomelatine 25mg	A significant decrease in Structured Interview Guide for the Hamilton Depression Rating Scale SAD-version (SIGH-SAD), Clinical Global Impression of Severity (CGI-S) and Improvement (CGI-I). Response rate (SIGH-SAD<50% of baseline) and remission rates (SIGH-SAD≤8) were 75.7% and 70.3%, respectively.
Dilsaver et al. (1992)	Open-label	15	5 weeks	Bupropion IR 200-400mg	33,3% partical response (modified Hamilton Depression Rating Scale (HDRS)=6-10) and 66,6% remission (modified HDRS≤5)
Pjrek et al. (2008)	Open-label	26	8 weeks	Duloxetine 60-120mg	Significant decrease in SIGH-SAD, CGI-S, Social Adaptation Self Evaluation Scale (SASS), and the Sheehan Disability Scale (SDS). Response rate (SIGH-SAD<50% of baseline) and remission rates (SIGH-SAD≤8) were 80.8% and 76.9%, respectively.
Pjrek et al. (2007b)	Open-label	20	8 weeks	Escitalopram 10-20mg	Significant decrease in SIGH-SAD, CGI-S, and SASS. Response rate (SIGH-SAD<50% of baseline) and remission rates (SIGH-SAD≤7) were 95% and 85%, respectively.
Lam et al., 1995Lam et al. (1995)	Double-blind RCT	68	5 weeks	Fluoxetine 20mg vs. placebo	Fluoxetine was nog significantly superior on the continuous measure (modified HDRS), but there were significantly more responders (i.e. a reduction of ≥50% on the modified HDRS) in the fluoxetine than in the placebo group (59% vs. 34%).
Partonen and Lonnqvist (1996a)	Double-blind RCT	32	6 weeks	Fluoxetine 20-40mg vs. Moclobemide 300-450mg	No significant differences between the two treatments.
Ruhrmann et al. (1998)	Double-blind RCT with 1-week placebo run-in	40	5 weeks	Bright (3000-lux) light + placebo vs. dim light + fluoxetine 20mg	No significant differences between the two treatments.
Lam et al. (2006)	Double-blind RCT	96	8 weeks	10,000-lux light treatment + placebo vs. 100-lux light treatment + fluoxetine 20mg	No significant differences between the two treatments.

Author, Year [Reference]	Method	N	Duration	Treatments	Findings
Martinez et al. (1994)	Single-blind controlled trial	20	4 weeks	Hypericum 900mg + dim light vs. hypericum 900mg + bright light (3,000 lux)	Significant reduction in HDRS but no significant differences between the two treatments.
Wheatley (1999)	Postal survey	301	8 weeks	Hypericum vs. hypericum + bright light treatment	No significant differences between the two treatments.
Hesselmann et al. (1999)	Open-label	8	4 weeks	Mirtazapine 30mg	Mirtazapine was effective in the treatment of seasonal affective disorder.
Lingjaerde et al. (1993)	Double-blind RCT	34	14 weeks	Moclobemide 400mg vs. placebo	No significant differences between the moclobemide and placebo.
Shen et al. (2005)	Open-label	12	8 weeks	Nefazodone 400mg	Significant improvements in HDRS, Hamilton Rating Scale for Anxiety (HAM-A), sleep latency, and sleep efficiency.
Hilger et al. (2001)	Open-label	16	6 weeks	Reboxetine 8mg	Significant decrease in SIGH-SAD. 68,75% experienced positive response (SIGH-SAD ≤12 and SIGH-SAD<50% of baseline value).
Moscovitch et al. (2004)	Double-blind RCT	187	8 weeks	Sertraline 50-200mg vs. placebo	Sertraline was significantly better than placebo on the SIGH-SAD, HDRS, CGI-S, CGI-I, HAM-A, and the Hospital Anxiety and Depression scale.
Dilsaver and Jaeckle (1990)	Open-label	14	4 months	Tranylcypromine	SAD responds to tranylcypromine
McGrath et al. (1990)	Cross-over trial	13	1 week for each treatment condition	L-tryptophan vs bright light treatment vs placebo	L-tryptophan and bright light were better than placebo. There was no difference between L-tryptophan and bright light.
Preventive treatment					
Modell et al. (2005)	3 Double-blind RCT's	277, 311, and 473	7 months	Bupropion XR 150-300mg vs. placebo	In all studies significantly increased depression-free rates in the bupropion group.
Martiny et al. (2004)	Double-blind RCT	282	15 weeks	Citalopram 20-60mg vs. placebo after succesful bright light treatment	Citalopram was only significantly suprior to placebo on the 6-item HDRS and the Melancholia scale

Introduction to the compound

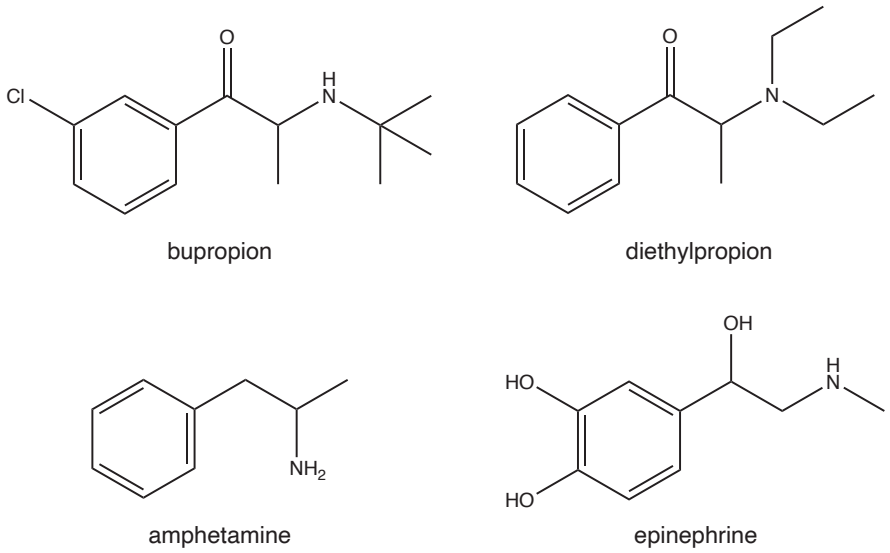
Bupropion is on the market as its hydrochloride and hydrobromide salt (GlaxoSmithKline, 2011b, sanofi-aventis U.S. LLC, 2012). Bupropion hydrochloride is available in an immediate release (IR), requiring thrice daily dosing, a sustained release (SR) formulation, requiring twice daily dosing, and an extended release (XR) formulation, which has to be administered once daily (GlaxoSmithKline, 2011b, GlaxoSmithKline, 2011a, GlaxoSmithKline, 2012, BTA Pharmaceuticals, 2011). The hydrobromide formulation is only available as an extended release formulation and is taken once daily (sanofi-aventis U.S. LLC, 2012).

In the U.S. and Canada, the recommended dosage for the treatment of major depressive disorder is 300-450mg daily given in 3 doses of 75-150mg for bupropion IR, in 2 doses of 100-200mg for Bupropion SR, or in one dose of bupropion XR (GlaxoSmithKline, 2011b, GlaxoSmithKline, 2011a, BTA Pharmaceuticals, 2011). In most EU countries, the maximal dosage is only 300mg. The recommended dose for smoking cessation is 300mg bupropion SR daily in 2 doses and for seasonal affective disorder 300mg bupropion XR daily in 1 dose (GlaxoSmithKline, 2011b, GlaxoSmithKline, 2011a, BTA Pharmaceuticals, 2011). The recommended dose of bupropion hydrobromide XR for major depressive disorder is 348-522mg daily, for SAD 348mg, both in 1 dose (sanofi-aventis U.S. LLC, 2012). These increased dosages are due to the higher molecular weight of bupropion hydrobromide compared to bupropion hydrochloride, and are comparable to 300-450mg bupropion hydrochloride. Bromide is known to have sedative and anticonvulsive properties and can also be toxic in high dosages (Bowers and Onoroski, 1990). The available bupropion hydrobromide dosages, i.e. 174 mg, 348 mg, and 522 mg, contain 44 mg, 87 mg, and 130 mg bromide ion, respectively, which is below the presumed no-effect level (NOEL) of bromide (4 mg Br^- per kg body weight per day, i.e. 240 mg/day) (van Gelderen et al., 1993). However, this is higher than the acceptable daily intake (ADI) of 0.4 mg Br^- per kg body weight per day, i.e. 24 mg/day, as was determined by the European Medicines Agency, calculated by application of a safety factor of 10 to the NOEL (Commitee for veterinary medicinal products, March 1997).

Chemistry

Bupropion [(±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone] is an antidepressant structurally unrelated to other known antidepressants. It has one chiral centre and is marketed as its racemate (GlaxoSmithKline, 2011b). It is structurally similar to diethylpropion and related to phenylethylamines (**Figure 1**) (GlaxoSmithKline, 2011b). It is a white crystalline powder, which is very soluble in water (GlaxoSmithKline, 2011b).

Figure 1: The structure of bupropion and several structurally related compounds



Pharmacodynamics

Bupropion's mechanism of action is inhibition of the neuronal reuptake of norepinephrine and dopamine (Stahl et al., 2004, Learned-Coughlin et al., 2003). It has, unlike most other antidepressants, no effect on serotonin. It is also an inhibitor of the nicotinic acetylcholine receptor (Arias, 2009). Neither bupropion nor its metabolites have affinity for postsynaptic histamine, α- or β-adrenergic, serotonin, dopamine or muscarinic acetylcholine receptors (Stahl et al., 2004).

Bupropion is not a controlled substance in the United States and is generally considered to have low abuse potential, when used in recommended doses (Miller and Griffith, 1983, Griffith et al., 1983). However, as bupropion increases dopamine concentrations in the synapse, albeit with a rather modest potency (Stahl et al., 2004), it may have some abuse potential in higher dosages. Studies in several animal models suggested this (GlaxoSmithKline, 2011b), and there are several case reports of bupropion abuse (McCormick, 2002, Khurshid and Decker, 2004, Hill et al., 2007, Kim and Steinhart, 2010), mainly through nasal insufflation.

Pharmacokinetics and metabolism

Bupropion IR reaches the maximum plasma concentration (Cmax) within 2 hours (Findlay et al., 1981, GlaxoSmithKline, 2011b). The SR and the XR formulation reach Cmax in approximately 3 hours and 5 hours, respectively (Jefferson et al., 2005, BTA Pharmaceuticals, 2011). The SR and XR formulations were shown to be bioequivalent to the IR formulation in steady state (GlaxoSmithKline, 1991, GlaxoSmithKline, 1992, GlaxoSmithKline, 2001) and the XR formulation was shown to be bioequivalent to the SR formulation in steady state (GlaxoSmithKline, 2002a). Steady-state plasma concentrations are reached in about 8 days (GlaxoSmithKline, 2011b). Bupropion showed linear pharmacokinetics between daily doses of 300 to 450mg (GlaxoSmithKline, 2011b).

While there appears to be no effect of food intake on the absorption of the IR and XR formulation (GlaxoSmithKline, 2011b, BTA Pharmaceuticals, 2011), there is an increase of 11-35% in Cmax and 16-19% in area under the curve (AUC) when bupropion SR is taken with food, which is not considered clinically significant (GlaxoSmithKline, 2011a). Smoking has no effect on the pharmacokinetics of bupropion (GlaxoSmithKline, 2011b, Hsyu et al., 1997). There is mildly higher exposure of bupropion in women, but the clinical significance of this is unclear (Kokras et al., 2011).

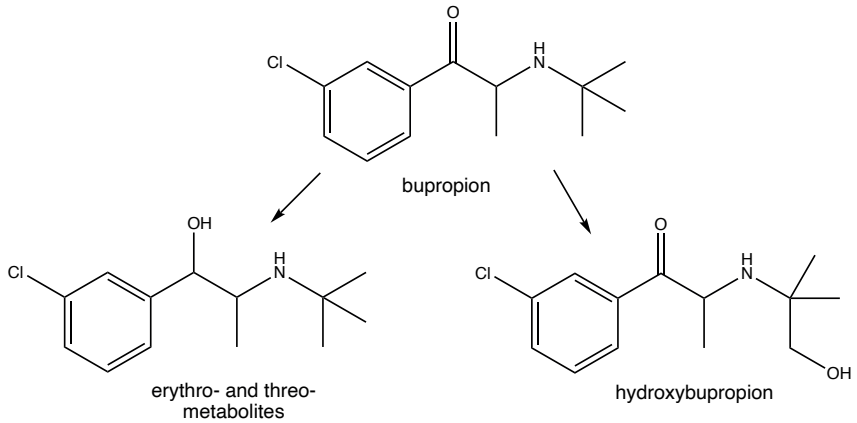
The mean volume of distribution at steady state is 19L/kg (Findlay et al., 1981). Based on in vitro tests, the binding to plasma proteins is about 85% in concentrations up to 200 mcg/mL (Schroeder, 1983).

Bupropion IR is eliminated with a mean half-life of 21±9 hours (GlaxoSmithKline, 2011b). It is extensively metabolized by the liver (Schroeder, 1983). There are three active metabolites: hydroxybupropion, formed by hydroxylation of the tert-butyl group, threohydrobupropion and erythrohydrobupropion, which are both amino-alcohol isomers formed by reduction of the carbonyl group (**Figure 2**) (GlaxoSmithKline, 2011b). Compared to bupropion, hydroxybupropion was about half as potent and threo- and erythrohydrobupropion were five-fold less potent in a mouse model of depression (Jefferson et al., 2005, GlaxoSmithKline, 2011b, Schroeder, 1983). As hydroxybupropion has two chiral centres, there are 4 possible enantiomers. However, only (R,R)-hydroxybupropion and (S,S)-hydroxybupropion are found in human plasma (Coles and Kharasch, 2008).

Hydroxybupropion, threohydrobupropion and erythrohydrobupropion reach their peak concentration 3 hours after administration, their half-lives are 20±5, 33±10 and 37±13 hours, respectively (GlaxoSmithKline, 2011b). The AUC values at steady state are respectively 17, 1.5 and 7 times that of bupropion (GlaxoSmithKline, 2011b). Unchanged

bupropion accounts for only 10-12% of the plasma concentration, and less than 1% of the dose was found unchanged in urine and faeces (Schroeder, 1983).

Figure 2: Metabolism of bupropion



Bupropion is primarily metabolized to hydroxybupropion by the cytochrome P450 (CYP) 2B6 isoenzym (Hesse et al., 2000). The metabolism of bupropion by the CYP2B6 enzym is stereoselective, with (S)-bupropion being metabolised thrice the rate of (R)-bupropion (Coles and Kharasch, 2008). The cythochrome P450 enzymes are not involved in the formation of threohydrobupropion and erythrohydrobupropion. Thus, interactions are possible with medicines that influence CYP2B6, such as clopidogrel and ticlopidine, inhibitors of CYP2B6 (Turpeinen et al., 2005), which reduced the AUC of hydroxybupropion by 52% and 84%, respectively, and increased the AUC of bupropion by 68% and 90%, respectively. This increase in bupropion plasma concentration may lead to increased side effects. A decrease of 57% in the AUC of bupropion itself and a 50% increase in the AUC of hydroxybupropion are documented when bupropion was co-administered with ritonavir and efavirenz, which are known CYP2B6 inductors (GlaxoSmithKline, 2011b, Hogeland et al., 2007). When using ritonavir, the interaction appears only of clinical significance when using high doses (e.g. 600mg b.i.d. decreased the AUC of bupropion by 62-67%), but not in lower doses (e.g. 100mg b.i.d. reduced AUC of bupropion by 21-22%) (Hesse et al., 2006, Park et al., 2010). Induction of bupropion metabolism is also documented with carbamazepine, with carbamazepine reducing the AUC of bupropion, threohydrobupropion, and erythrohydrobupropion by 90%, 86%, and 96%, respectively, and increasing the AUC of hydroxybupropion by 94%, and hypericum decreasing the AUC of bupropion by 14% and increasing the oral clearance of bupropion by 20% (Ketter et al., 1995). Co-administration of bupropion with inducers of CYP2B6 will likely lead to sub-optimal plasma concentrations of bupropion and may lead to treatment failure and should thus be avoided whenever possible.

Bupropion is itself a potent inhibitor of the CYP2D6 enzyme (GlaxoSmithKline, 2011b), leading to interactions with numerous compounds that are metabolised by CYP2D6, such as antidepressants (e.g. tricyclic antidepressants, fluoxetine, sertraline, paroxetine) (Reese et al., 2008), some antipsychotics (e.g. aripiprazole, haloperidol, risperidone, sertindole), beta-blockers, type 1C antiarrhythmics, and tamoxifen (Desmarais and Looper, 2009). Plasma concentrations of the aforementioned compounds will rise if bupropion is co-administered, with possible side effects as a consequence, as evidenced by several case reports (Weintraub, 2001, Shad and Preskorn, 1997).

As bupropion is primarily metabolized by the liver, changes in the pharmacokinetics of bupropion in patients with liver disease are expected (DeVane et al., 1990). A significant increase in t1/2 (from 21.1±4.9 to 32.2±13.5h), of hydroxybupropion was seen in patients with alcoholic liver disease. In patients with severe liver cirrhosis, a significant increase in Cmax and AUC of bupropion was seen, and a significant decrease in Cmax and increase in Tmax and t1/2 of hydroxybupropion. AUC, tmax and t1/2 of threohydrobupropion were also significantly increased. There were no significant differences in mild to moderate liver cirrhosis (GlaxoSmithKline, 2011b, GlaxoSmithKline, 1997). Thus, when bupropion is considered in patients with liver dysfunction, caution should be used, and the dose may have to be lowered. This is most relevant in patients with severe liver dysfunction, where the product insert recommends that dosages should not exceed bupropion IR or SR 75mg daily or 150mg of bupropion XR every other day (GlaxoSmithKline, 2011b, BTA Pharmaceuticals, 2011).

Bupropion is transferred from the maternal circulation to the fetal circulation (Earhart et al., 2010). Bupropion is a FDA Pregnancy Category C substance, and is possibly associated with a small increase in risk for congenital cardiac malformations, when used in the first trimester of the pregnancy (Alwan et al., 2010, Thyagarajan et al., 2012). The risk is however small in absolute terms, and the decision to continue bupropion therapy during pregnancy should be made on a case by case basis.

Renal function also has an effect on the kinetics of bupropion. In 8 smoking haemodialysis patients, pharmacokinetics were studied after a single dose of 150mg bupropion SR, and compared to existing pharmacokinetic data of healthy volunteers (Worrall et al., 2004). There was no change in bupropion pharmacokinetics, but there was an increase in Cmax (20% higher), tmax (two-fold increase), AUC (136% increase) and t1/2 (73% increase) of hydroxybupropion, and a three-fold increase of AUC and tmax of threohydrobupropion, and a 16% and 17% increase of Cmax and t1/2 of threohydrobupropion, respectively. In a study with patients with impaired renal function, AUC, Cmax and t1/2 of bupropion were 126%, 86%, and 140% higher, respectively. There was little effect on the metabolites

(Turpeinen et al., 2007). Although renal function has a moderate impact on the pharmacokinetics of bupropion, these are not considered clinically relevant.

The pharmacokinetics of bupropion in elderly were similar to younger patients, but an increase in the Cmax of bupropion and threohydrobupropion, and an increase in the Tmax of hydroxbupropion was reported, next to a decrease in t1/2 of threohydrobupropion (GlaxoSmithKline, 1984). There may be a risk of accumulation of bupropion metabolites in some elderly, but it is unclear which patients are at risk (Sweet et al., 1995). Thus, when used in this population, side effects should be thoroughly monitored.

Clinical Efficacy

In the acute treatment of SAD, bupropion is only evaluated in one open-label trial (Dilsaver et al., 1992). 15 patients with SAD were treated for up to 5 weeks with bupropion IR 200-400 mg/day. The outcome measure was a modified version of the *Hamilton Rating Depression Scale* (HDRS), which consisted of the usual items of the HADRS and ratings of hypersomnia, increased appetite and carbohydrate craving, and weight gain. The mean modified HDRS score ± SD was 25.5±6.4 before treatment, and 4.1±3.1 after treatment. 10 subjects went into remission (modified HDRS score < 5) and 5 subjects had partial response (modified HDRS score = 6-10). This report shows that bupropion is efficacious in the acute treatment of SAD, but since there was no placebo arm, and the sample size was rather small, these findings should be considered preliminary until replicated.

For the prevention of SAD, Bupropion XR was evaluated in three similarly designed double blind randomized placebo-controlled trials, all reported by Modell et al. (2005). We will refer to these studies as Study A (GlaxoSmithKline, 2002b), Study B (GlaxoSmithKline, 2002c), and Study C (GlaxoSmithKline, 2003). Patients with a history of a DSM-IV diagnosis of recurrent major depressive disorder with seasonal pattern, diagnosed using the *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)*, were randomized to treatment with bupropion XR or a matching placebo. Treatment with bupropion XR 150mg (or placebo) was initiated in the autumn, with an increase to 300mg after 7 days, if tolerated. 80% of the participants remained on the higher dose of 300mg daily throughout the trial. Treatment with bupropion was continued until the first week of spring, after which the dose was reduced to 150mg for 2 weeks, and then discontinued. There was an 8-week follow-up assessment after discontinuation. Use of light therapy or travel to sunny destinations for more than 5 days (Study A and B) or 7 days (Study C) was not allowed.

Depressive symptoms were measured using the *Structured Interview Guide of the Hamilton Depression Rating Scale, SAD version (SIGH-SAD)*, which is a 24-item inventory consisting of the 17 items of the *Hamilton Depression Rating Scale* and 7 items measuring atypical depressive symptoms. If a patient scored ≥20 on the SIGH-SAD, he or she was evaluated one week later, and if the score was still ≥20, the patient was considered to be relapsed.

Outcome measures were end-of-treatment depression-free rates and survival distributions of onset of depressive episodes, analysed using the Cochran-Mantel-Haenszel statistic and the Kaplan-Meier method, respectively.

277, 311 and 473 patients were randomised in study A, B and C, respectively. 272, 306 and 464 were included in the intent-to-treat analysis. In study A, 19% experienced a depressive episode versus 30% in the placebo group ($p<0.05$). In study B, 13% had a recurrence of a depressive episode with bupropion versus 21% on placebo ($p<0.05$), and in study C, 16% had a recurrence of a depressive episode with bupropion versus 31% on placebo ($p<0.001$). With Kaplan-Meier survival analysis, there was a trend favouring bupropion in study A and B ($p<0.1$), while in study C, bupropion was significantly ($p<0.001$) better than placebo. Adverse events led to discontinuation in 9% of bupropion treated patients, versus 5% in the placebo group. Most common adverse events were dry mouth (bupropion 26% vs. placebo 15%), nausea (13% vs. 8%), constipation (9% vs. 2%), and flatulence (6% vs. 3%). There was a significant increase in mean heart rate (1.6 beats per minute) and systolic blood pressure (1.2 mmHg), and a significant decrease in mean weight (-0.9kg) vs. placebo (+0.8kg). During the taper phase, incidence of adverse events was 14% in the bupropion group and 18% in the placebo group.

Safety and tolerability

Bupropion is generally well tolerated. The most common side effects of bupropion IR reported in the product insert are agitation (31,9%), constipation (26%), insomnia (18,6%), dry mouth (27,6%), headache (25,7%), nausea and vomiting (22,9%), and tremor (21,1%) (GlaxoSmithKline, 2011b). Rates of agitation, anxiety, and insomnia in the treatment of SAD with bupropion XR were 2%, 7%, and 20%, respectively (BTA Pharmaceuticals, 2011). Contrary to serotonergic antidepressants, there is little effect on sexual functioning (Serretti and Chiesa, 2009). Due to its effect on the dopamine system, there are concerns that it might induce or worsen psychosis (Kumar et al., 2011), although the risk appears to be rather low. The risk seems to increase with increasing dosages, pre-existing psychotic symptoms, substance abuse, and the use of concomitant medication interacting with bupropion metabolism (Kumar et al., 2011). Bupropion overdose is associated with seizures

in one third of the reported cases, and can also cause hallucinations, loss of consciousness, cardiac disturbances, and rarely death (GlaxoSmithKline, 2011b).

Bupropion is associated with a dose-dependent increased risk for seizures, and is contraindicated in patients with a seizure disorder (GlaxoSmithKline, 2011b). The seizure rate with bupropion IR is about 0,4% in doses up to 450 mg per day (Johnston et al., 1991). The seizure rate with bupropion SR up to 400 mg is about 0,1%, which is similar to other antidepressants (Dunner et al., 1998, Montgomery, 2005). As the risk of seizure is dose-dependent, bupropion SR and bupropion XR, which have lower peak concentrations than bupropion IR (GlaxoSmithKline, 2011a, Dunner et al., 1998, Jefferson et al., 2005), should theoretically have a reduced risk of seizures, though no head-to-head trials assessing the seizure risk of different formulations of bupropion were found. Seizure risk is increased in patients with bulimia and benzodiazepine withdrawal, and bupropion is thus contraindicated in these populations (GlaxoSmithKline, 2011b).

As with every antidepressant, bupropion carries a black box warning for an increased risk for suicidal ideation and suicidality in children, adolescents, and young adults. In a meta-analysis of Wightman et al., there was a trend of increased suicidality in young adults (<25 years) compared to placebo, but statistical significance was not reached ($p = 0.07$) (Wightman et al., 2010). In a meta-analysis of double blind randomised controlled trials of 12 marketed antidepressants, including bupropion, conducted by the U.S. Food and Drug Administration, the risk of suicidality in young adults (<25 years) was also significantly increased (Stone et al., 2009). A cohort study, including 287,543 patients, which compared different antidepressants (bupropion not included) showed an equal risk for suicidality between these antidepressants (Schneeweiss et al., 2010). Therefore it can be concluded that while there may be an increased risk for suicidality when bupropion is used in young adults, this appears to be a class effect and not limited to bupropion.

As bupropion stimulates the noradrenergic system, it is associated with an increase in blood pressure, and in some cases hypertension, and caution should be used in patients with cardiovascular disease (GlaxoSmithKline, 2011b, Thase et al., 2008). However, in trials of bupropion SR for smoking cessation, it was shown to be safe in populations with cardiovascular disease (Tonstad et al., 2003, Rigotti et al., 2006). Based on this data, it seems reasonably safe to use bupropion in patients with stable cardiovascular disease. Treatment emergent adverse events should of course be carefully monitored.

Regulatory affairs

The U.S. Food and Drug Administration has approved bupropion for the treatment of major depressive disorder, seasonal affective disorder and smoking cessation (GlaxoSmithKline, 2011b, GlaxoSmithKline, 2011a, BTA Pharmaceuticals, 2011, GlaxoSmithKline, 2012). Bupropion is not categorized as a controlled substance by the Drug Enforcement Administration (GlaxoSmithKline, 2011b).The immediate release formulation is approved in the United States for the treatment of major depressive disorder, the sustained release formulation is approved in the United States and Canada (Health Canada, 2013) for the treatment of major depressive disorder and smoking cessation, and the extended release is approved in the United States and Canada for the treatment of major depressive disorder and SAD (BTA Pharmaceuticals, 2011). The trade name Wellbutrin® is used in the treatment of depression, the trade name Zyban® is used for smoking cessation. Bupropion hydrobromide is commercialized as Aplenzin®.

As bupropion is not centrally approved by the European Medicines Agency, availability of bupropion was separately examined in the countries of the European Union, as well as Iceland, Norway, Switzerland, and the United Kingdom. on the websites of the national competent authorities or the local site of the manufacturer (for Italy). A full list of references is included in supplementary table. In none of the countries was bupropion approved of the prevention of SAD. Bupropion IR and bupropion hydrobromide were nowhere registered. Bupropion SR is registered for depression only in Latvia and the Czech Republic. For the treatment of smoking cessation, bupropion SR was registered in all countries, except Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, and Slovakia. Bupropion XR is registered for depression in all countries, except Bulgaria, France, Latvia, Ireland, and the United Kingdom. Used trade names for depression treatment are Elontril®, Magerion®, Wellbutrin®, or Voxra®; trade names for smoking cessation were Zyban® or Zyntabac®.

Conclusion

Seasonal Affective Disorder is a psychiatric illness in which depressive episodes occur during a particular season (mostly in winter). Since the occurrence of depressive episodes is highly predictable, preventive measures can be taken. Bupropion XR has been shown to be a safe and effective prophylactic for depressive episodes during the winter months associated with SAD. One non-placebo-controlled open-label trial suggested bupropion is also effective in the acute treatment of depressive episodes associated with SAD.

Expert opinion

While seasonal affective disorder is a frequently occurring mental health problem with a prevalence of 1-2% in the United States and 2% in Canada (using DSM-IV criteria), many available antidepressant treatments are not adequately researched. The predictability of the depressive episodes makes preventive treatment with antidepressants, taken only in the winter months, possible. This treatment may reduce the burden that comes with a depressive episode. Since bupropion is the only antidepressant with a proven efficacy for this indication, it is the first choice when antidepressant prophylaxis for SAD is considered. However, we assume that other antidepressants or light therapy may also be a worthwhile treatment option, particularly if patients have responded favourably to such an alternative treatment option during a previous depressive episode. Citalopram for example has been shown to be significantly better than placebo to sustain response, induced by 1-week light treatment, on core depressive symptoms (depressed mood, guilt, reduced interest, retardation, psychic anxiety and general somatic symptoms) and melancholic symptoms. While prophylactic treatment using these other antidepressants has not been thoroughly assessed in randomised controlled trials, they may be an acceptable treatment option if there are contraindications for the use of bupropion, or if there are issues with the tolerability of bupropion. Bupropion has however the largest evidence base in the preventive treatment of SAD.

Looking at the outcomes of the three efficacy studies, it is noticed that, while bupropion is significantly better than placebo, 13-19% of the bupropion treatment group had a recurrence of a depressive episode versus 21-31% in the placebo group. This raises the question whether the drug-placebo difference is clinically significant, and whether it is worth treating a patient without symptoms for a possible recurrence, exposing patients to possibly unnecessary side effects. However, a large placebo response rate is seen in many antidepressant trials, which can be attributed to many factors, one of which may be that nonspecific interventions inherent to a clinical trial may have a therapeutic effect (Walsh et al., 2002). This may imply that the number of patients who experience a depressive episode if not treated preventively may be higher in clinical practice. It is thus not unlikely that in clinical practice prophylactic antidepressant treatment may have a larger effect, and as such may be an appropriate treatment option. Given the morbidity of a major depressive episode and the safety of bupropion, preventive treatment may be warranted, particularly for those who experience severe depressive episodes during the winter months.

In conclusion, bupropion is safe and effective for the treatment of SAD. While bupropion is available in three dosage formulations, an immediate, a sustained, and an extended release formulation, the extended release formulation is easier to use due to it's once daily dosing interval, and is the only formulation registered for the prophylactic treatment

of SAD. Due to reduced peak concentrations compared with the IR formulation, there is possibly a reduced incidence of side effects, although no head-to-head trials comparing different dosage formulations of bupropion were done. While there are some concerns about bupropion's ability to induce seizures, the risk with bupropion SR and XR seems to be similar to other antidepressants. Caution should be used when combining bupropion with other drugs which lower the seizure threshold or which may interact with bupropion metabolism, and when bupropion is used in special populations where exposure may be increased (Jefferson et al., 2005).

It is recommended to start the prophylactic treatment with bupropion in the autumn starting with 150mg/day and increasing the dose to 300mg/day after one week. The treatment should be tapered off in the first weeks of spring. Caution should be used in special populations, such as the elderly and patients with seizure disorders. Pharmacokinetic evaluations show that caution should be used in patients with severe liver failure and/or co-medication use that either affects CYP2B6 (e.g. ritonavir, efavirenz) or drugs that rely on the CYP2D6 isoenzyme for their metabolism(e.g. most SSRIs, tricyclic antidepressants, several antipsychotics), which is inhibited by bupropion.

It can be concluded that bupropion is proven to be safe and effective for the prevention of SAD. It is probably also effective in the acute treatment of SAD, but more and larger studies are needed.

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Supplementary table

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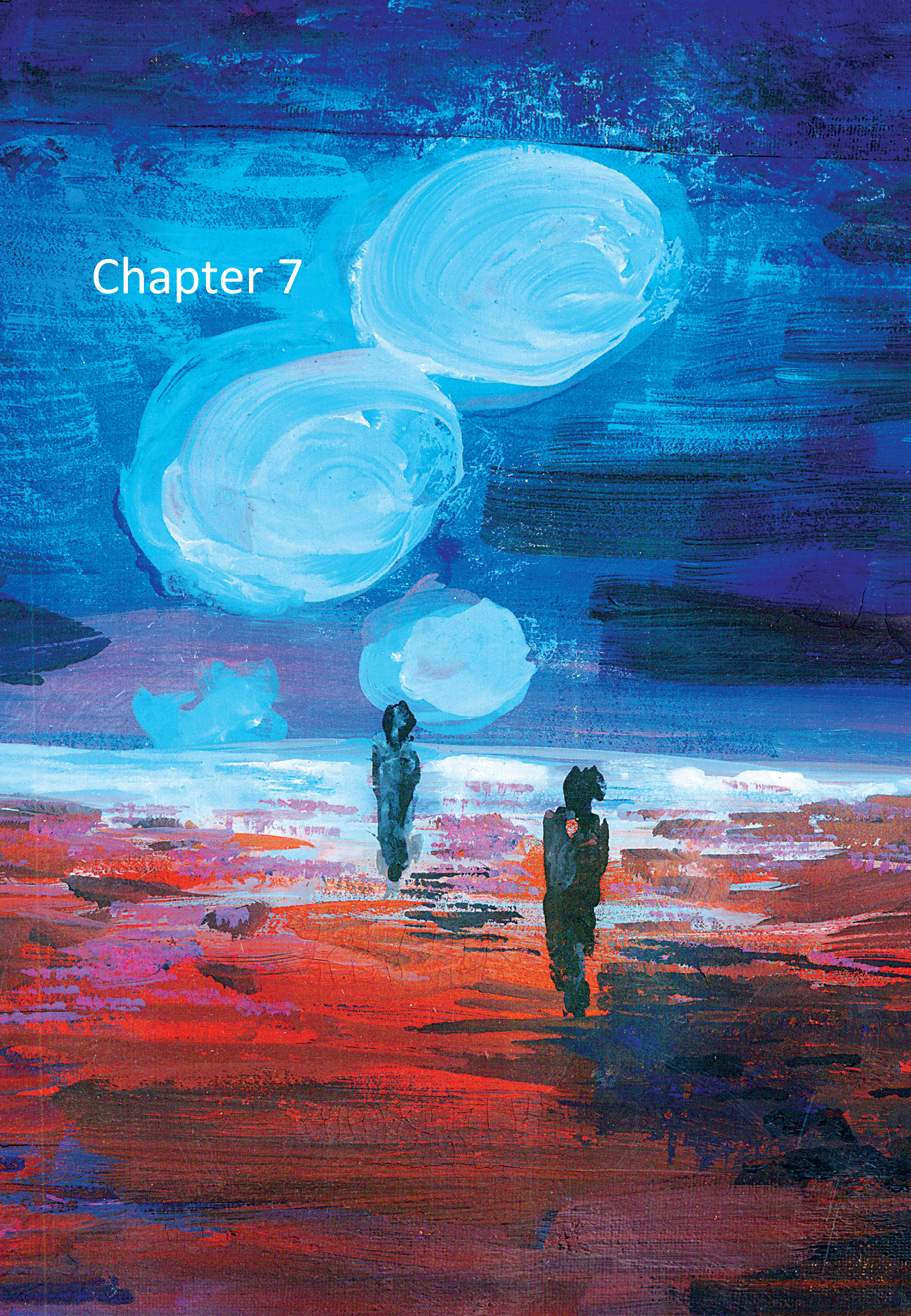
Chapter 7

General Discussion

Major Depressive Disorder (MDD) is a severe and debilitating disorder that is the leading cause of disability worldwide (World Health Organization, 2017). Despite many available treatment options, a significant minority of patients do not attain recovery of symptoms after several treatment steps (Sinyor et al., 2010). A majority of patients relapses after remission (Mueller et al., 1999).

As outlined in **Chapter 1**, MDD is a complex, multifaceted, and heterogeneous disorder, for which several pathophysiological mechanisms have been proposed. After discovering monoaminergic antidepressants, the primary research focus was on the monoamines, finding disturbances in serotonin, norepinephrine, and dopamine (Hasler, 2010). Later, the research focus shifted towards disturbances in the Hypothalamic-Pituitary-Adrenal (HPA) axis, and more recently, to abnormalities of the inflammatory and glutamatergic system (Keller et al., 2017, Miller and Raison, 2016, Sanacora et al., 2012). Besides these findings, altered neurocircuitry and decreased neurogenesis are also observed in MDD patients (Eisch and Petrik, 2012, Price and Drevets, 2010).

The purpose of the thesis is primarily to elucidate further the different pathophysiological mechanisms of MDD and secondly to identify strategies and further research targets for optimizing the treatment of MDD and decreasing the relapse rates. This thesis encompasses different research projects that cover different topics of the pathophysiology and treatment of MDD. They respect various aspects of this multifaceted disorder.

First, the effects of inflammatory and social stress in MDD were studied. In **Chapter 2** we present a study examining the effects of a psychosocial and inflammatory stressor on mood and biomarkers in healthy controls and patients with remitted recurrent MDD. The main finding is that after inflammatory stress, but not after psychosocial stress or the combination of both, there was a lowering in mood in patients with a recurrent MDD in remission. As these effects were observed in patients in remission, this may point to a certain sensitization to these stressors, which persists after remission.

Next, we further examined the cognitive symptoms of depression, as cognitive dysfunction is a major symptom of MDD which often persists during remission (Rock et al., 2014, Lamers et al., 2011). In **Chapter 3** we examined the cognitive effects of the inflammatory and psychosocial stress. The main finding is that in patients with remitted recurrent MDD, but not in healthy controls, there is a decrease in cognitive functions after the inflammatory stressor. Interestingly, there was also a change in emotion-driven cognitions, with an increased negative bias following the inflammatory stressor in patients, but not in controls. In **Chapter 4**, we examined the effect of nicotine on cognition in healthy young and elderly volunteers. While nicotine improved performance on several subdomains in the elderly population, the most striking finding was that in both populations, the effects

of nicotine were dependent on baseline performance, with subjects performing on the lower end having the most positive effects

Finally, we examined the use of novel and existing treatments of MDD. In **Chapter 5**, we discuss a case of ECT-resistant MDD, which reacted to combination therapy of ECT with ketamine anesthesia. In **Chapter 6**, we examined the use of bupropion for the prevention of mood episodes in seasonal affective disorder (SAD).

Given these results, we will first discuss the role of stress, inflammation, and the interaction of both in MDD. Then the role of stress sensitization and its possible role in MDD is further explored. Afterwards, we will further go into the role of cognitive dysfunction in MDD, and the role of inflammation in it, as well as the nicotinergic system as a potential treatment for cognitive dysfunction. Subsequently, emerging treatment strategies for MDD are explored, with the focus on ketamine and bupropion. Eventually, we discuss the clinical implications of these findings and perspectives for further research.

Inflammation and stress in depression

As discussed in **Chapter 1**, both the stress system and the immune system seem to play a pivotal role in the pathophysiology of MDD. The results of the study presented in **Chapter 2** and **3** further confirm their involvement in MDD.

Inflammation and depression

Throughout the past two decades, the involvement of pro-inflammatory cytokines in MDD became more and more apparent. Sickness is associated with *sickness behavior*, a set of behavioral changes such as anhedonia, fatigue, weakness, and a reduction of appetite, which overlap remarkably with some of the symptoms of MDD. This sickness behavior is caused by pro-inflammatory cytokines (Dantzer, 2009). Indeed, pro-inflammatory cytokines, such as Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-α), are elevated in patients with MDD, a finding confirmed by several meta-analyses (Osimo et al., 2020, Haapakoski et al., 2015, Dowlati et al., 2010). Moreover, an often-observed side effect of pro-inflammatory cytokine treatment of diseases such as hepatitis C is the development of MDD (Schafer et al., 2007). Finally, administration of pro-inflammatory agents such as *lipopolysaccharide* (LPS) or the typhoid vaccine results in a temporary decrease in mood in healthy volunteers (Brydon et al., 2009, Wright et al., 2005, Strike et al., 2004). This last finding was further studied in patients with remitted recurrent MDD in **Chapter 2**.

A central finding of this study is that inflammatory stress (i.e., the typhoid vaccine) decreased the mood of remitted recurrent MDD patients, contrary to controls. While the adverse effects of inflammatory stress on mood had mainly been investigated in healthy controls (Brydon et al., 2009, Wright et al., 2005, Strike et al., 2004), this was, to our knowledge, the first study to examine this in remitted MDD. These results suggest that MDD patients, even when remitted, stay more susceptible to the adverse effects of inflammation.

Interestingly, the patients' mood score worsening was mainly driven by a significant decrease in the "Vigor and Activity" subscale, which may point to reduced positive affect following the vaccine. Besides increased negative affect, depressive episodes are also associated with a reduction in positive affect and reward processing, resulting in anhedonia (Dooley et al., 2018). Furthermore, previous research showed that the Vigor and Activity subscale correlated mainly with positive affect (Terry et al., 2003). This finding suggests that one of the main drivers of decreased mood due to inflammation is the reduction of positive affect and reward processing.

This finding agrees with previous observations that pro-inflammatory states are associated with anhedonia. Increased levels of pro-inflammatory cytokines are associated with anhedonia across different psychiatric disorders (Felger et al., 2016, Miller, 2020, Mehta et al., 2020, Rengasamy et al., 2021). On the neurobiological level, it is hypothesized that inflammation reduces dopaminergic function in the ventral striatum (Capuron et al., 2012). Indeed, several studies showed that endotoxin administration led to decreased reward sensitivity in the striatum both in healthy volunteers and MDD patients (Eisenberger et al., 2010, Felger et al., 2016).

Although the mood decrease in our study was mainly driven by a reduction in "Vigor and Activity", pro-inflammatory states are also frequently associated with increases in fatigue. Like anhedonia, fatigue is also a prominent characteristic of sickness behavior and is also a symptom of MDD (Miller and Raison, 2016, Karshikoff et al., 2017). In previous research, mood decrease after the typhoid vaccine was mainly driven by increases in "Fatigue and inertia" scores (Brydon et al., 2009). Our study did find a numerical, though not significant, increase in fatigue score after an inflammatory stressor in remitted MDD patients and not in controls.

It should be noted that anhedonia and fatigue, as observed in our study following the inflammatory challenge, are also observed in diseases characterized by a pro-inflammatory state, such as rheumatoid arthritis and inflammatory bowel disease (Korte and Straub, 2019, van Hoogmoed et al., 2010, Carpinelli et al., 2019, Nocerino et al., 2020). As mentioned before, these diseases are also associated with an increased incidence of

MDD (Margaretten et al., 2011, Keefer and Kane, 2017). This, together with the results of our study and previous similar studies, corroborates earlier findings that the effect of inflammation on mood is mainly due to sickness behavior. Indeed, a 14-year longitudinal study showed that hair cortisol and plasma CRP levels were primarily associated with somatic symptoms of depression, namely anergia and sleep disorder, (Iob et al., 2020).

However, the effects of pro-inflammatory states may not be limited to the symptoms of sickness behavior. For example, although treatment with IFN-α for hepatitis C, known to induce depressive symptoms, is mainly associated with the somatic symptoms of depression, the emergence of these somatic symptoms also predicts the onset of cognitive-affective symptoms later in treatment (Lin et al., 2020, Loftis et al., 2013). This may indicate that only initially, pro-inflammatory states are particularly associated with the sickness behavior symptoms of MDD, but in the longer term, may also lead to the cognitive-affective symptoms of MDD.

Stress and depression

MDD is associated with HPA-axis hyperactivity. As discussed in **Chapter 1**, psychosocial stress leads to the release of Corticotropin-Releasing Hormone (CRH), which stimulates the anterior pituitary to release Adrenocorticotropic Hormone (ACTH), which leads to the release of cortisol by the adrenal glands (Smith and Vale, 2006, Mikulska et al., 2021). In addition, prolonged psychosocial stress results in desensitization of the negative feedback loops of the HPA-axis, which leads to continued hyperdrive of the HPA-axis, ultimately leading to the symptoms of MDD (Claes, 2004).

The Trier Social Stress Test (TSST) is an experimental paradigm of psychosocial stress, where the subject has to perform a fictitious job interview and an arithmetic exercise for a critical audience (Kirschbaum et al., 1993). It has been shown to reliably induce the stress response, with increased plasma levels of cortisol and ACTH (Allen et al., 2017). In addition, patients with MDD or at risk for MDD have been shown to have higher cortisol elevations after the TSST (Dienes et al., 2013).

In our study, administration of the TSST activated the HPA-axis, with increases in cortisol and ACTH. This further validates the treatment paradigm. No differences were seen between the controls and the patients. However, the study had a relatively small sample size, and was underpowered to find small differences.

Contrary to our expectations, the TSST didn't affect the total mood score, except for minor changes on some subscales (increased "Confusion and bewilderment" in both groups, decreased "Anger and hostility" in patients, and increased "Fatigue and inertia" in controls),

that didn't follow a clear pattern. It should be noted that while previous research, such as van Winkel et al. (2015), studied mood directly after the TSST, in our study, administration of the mood questionnaires only started 60 minutes post-intervention, which may have been too late to find an effect.

Interactions between stress and inflammation in depression

Converging lines of evidence suggest multiple interactions between the immune system and the HPA-axis. As the body encounters stress, both the sympathetic nervous system (SNS) and the HPA-axis are activated (Smith and Vale, 2006), which are also known to interact. By releasing norepinephrine, which activates Corticotropin-Releasing Hormone (CRH)-producing neurons, the SNS activates the HPA-axis (Levy and Tasker, 2012). In its turn, vice versa, CRH activates the SNS, as injection of CRH in rat brain leads to activation of SNS neurons (Dunn and Swiergiel, 2008). Moreover, increasing plasma levels of norepinephrine due to SNS activation stimulates the bone marrow production of myeloid cells such as monocytes and increases pro-inflammatory cytokines (Miller and Raison, 2016). Pro-inflammatory cytokines, such as IL-6, also activate the HPA-axis, acting as a negative feedback loop (Silverman et al., 2005, Bellavance and Rivest, 2014).

The implication of both the HPA-axis and the inflammatory system in the pathophysiology of depression seems contradictory, as glucocorticoids are known to have an anti-inflammatory effect (Coutinho and Chapman, 2011). However, increasing evidence suggests that glucocorticoids are not completely anti-inflammatory but can also show pro-inflammatory effects (Duque Ede and Munhoz, 2016). Glucocorticoids can have a "priming" effect on the inflammatory response, where prior administration of glucocorticoids increase further inflammatory responses (Sorrells et al., 2009). CRH can also activate microglia, leading to increased pro-inflammatory cytokines (Kritas et al., 2014). Moreover, while there is already glucocorticoid resistance due to HPA-axis hyperactivity, pro-inflammatory transcription factors by themselves can also induce glucocorticoid resistance, which can further reduce the anti-inflammatory effects of glucocorticoids (Silverman and Sternberg, 2012).

As inflammation can activate the HPA-axis, an increase in HPA-axis parameters can be expected following an immune stressor. This was observed following the typhoid vaccine in our study with a trend for a rise in adrenocorticotropic hormone (ACTH), though only in healthy controls. There was also a numerical increase in cortisol, as expected following a rise in ACTH, though this failed to reach significance. As this ACTH-rise was only observed in healthy controls, this may point to a blunted HPA-axis response in the patient population and often replicated finding in MDD, which sometimes continues into remission (Van Den Eede et al., 2006, Vreeburg et al., 2009).

However, the psychosocial stressor, i.e., the Trier Social Stress Test (TSST), alone did not activate the immune system, contrary to the expectations. Even more, there seems to be a reduction in the inflammatory parameters after the psychosocial stressor (though not after the combination of the psychosocial and immune stressor) in both groups. This contrasts with previous research, which showed an increase in inflammatory parameters after psychosocial stress (Carpenter et al., 2010, Izawa et al., 2013, de Brouwer et al., 2014, Boyle et al., 2023). While the reduction in inflammatory parameters could be due to the anti-inflammatory effect of cortisol, which was increased due to the psychosocial stressor, this increase was also seen in the other studies, and as such do not explain the different outcome compared to previous research (Coutinho and Chapman, 2011). A possible explanation may be that there are different responses to acute psychosocial stress. Rodriguez-Medina et al. (2019) identified two different responses to the Trier Social Stress Test (TSST): one group reacted with an increase in IL-6, while the other group saw a reduction in inflammation. It should be noted that a major limitation of this study is the small sample size. A possibility is that the majority in the group receiving only the psychosocial stressor reacted with the latter response. The finding of reduced inflammation due to the cortisol rise also suggests the absence of HPA-axis desensitization, which was hypothesized to continue into remission. However, as shown by Van Den Eede et al. (2006), this does not apply to all remitted MDD patients. As such, due to the small sample size, the sample that received only TSST may not have demonstrated the HPA-axis desensitization.

We also hypothesized that, because of the expected interactions between the stress and the immune system, the combination would have a synergistic effect both on mood and biomarkers, in line with previous research (Frank et al., 2010, Brydon et al., 2009). This was not observed on the behavioral measures, contrary to the expectations. However, after the combination intervention, there was a significant increase in Interferon (IFN)-γ in the patient population, which was not observed after the single interventions. This may suggest a synergistic effect, although this did not reflect in the behavioral measures.

It should be noted that the effects of both stressors were only measured for a limited time after their administration (6 h). It is possible that some of the impacts of the interventions were more pronounced after a longer time (e.g., after several days). As mentioned before, the small sample is also a significant limitation. To make more definitive conclusions, these findings should be replicated in larger samples.

The role of stress sensitization in depression

An often-replicated finding is that severe psychosocial stress is associated with the onset of a first major depressive episode, with up to 85% relapsing after a first episode (Charney and Manji, 2004, Mueller et al., 1999). A striking finding is that while the onset of MDD is often associated with psychosocial stress, with an increase in the number of episodes, it seems to be progressively less associated with episode onset (Kendler et al., 2000). This can either be explained by the *stress autonomy* model, in which the episodes occur without trigger, or by the *stress sensitization* model, in which previous episodes lead to sensitization to stress, with minor stressors being associated with depressive symptoms (Monroe and Harkness, 2005, You and Conner, 2009). Several studies indeed point to stress sensitization in MDD development and progression (Moylan et al., 2013). For example, Morris et al. (2010) found in a study in 240 adolescents that the relationship between stress and depressive symptoms strengthened with increasing depressive episodes.

In the study in **Chapters 2** and **3**, it was hypothesized that patients who experienced multiple depressive episodes would be more sensitive to stress than healthy controls. As such, they would develop more depressive symptoms following the administered stressors. As stress sensitization seems to increase with a higher number of episodes, patients who experienced at least 2 MDE's were included in the study. As expected, the patient group experienced a mood lowering and changes in cognition, while the healthy controls did not. These results corroborate the hypothesis that after several depressive episodes, there is sensitization to stress.

It should also be noted that several known risk factors for depression are also associated with increased sensitization to stress. For example, childhood maltreatment is a known risk factor for the development of MDD (Negele et al., 2015, Baldwin et al., 2023). In addition, previous evidence showed that it is associated with increased HPA-axis activation after psychosocial stress and increased levels of pro-inflammatory cytokines in healthy subjects (Carpenter et al., 2010). In our sample, patients in the MDD group also had a significantly higher score on a childhood maltreatment questionnaire than controls. However, as the statistical analysis controlled for childhood maltreatment scores, we can assume that our findings are mainly due to the history of depressive episodes and not to childhood maltreatment.

Interestingly, other risk factors of MDD are also associated with changes in HPA-axis function and pro-inflammatory states. For example, lower socioeconomic status is a risk factor for MDD and was associated with increased production of IL-6 after stress (Wilson et al., 2014, Brydon et al., 2004). Another study showed that male adolescents growing up in a disadvantaged neighborhood demonstrated increased cortisol reactivity, suggesting a sensitization to stress (Nurius et al., 2013).

Such observations suggest that there is already a sensitization to stress before the development of MDD. Interestingly, the risk for the development of MDD with IFN-α treatment increases in patients with pre-existing mild depressive symptoms, which may suggest a pre-existing sensitization to stress (Lotrich et al., 2007, Udina et al., 2012). Furthermore, while depression with IFN-α can be interpreted as a temporary side effect of treatment, the development of IFN-α induced depression significantly increases the risk of a recurrent episode even when treatment is finished, compared to controls who did not develop MDD under IFN-α (56.8 and 4.1 per 100 000 person-years, respectively) (Chiu et al., 2017). This can also be explained by the increased sensitization after an IFN-α-induced depressive episode.

In conclusion, when in remission, patients with a history of MDD seem to be more sensitive to stress, as shown in our study. This sensitization has probably already been partly occurring before the onset of the first depressive episode, as people with known risk factors for the later development of MDD, show already sensitized responses on inflammatory and HPA-axis parameters. However, with an increased number of depressive episodes, there seems to be further stress sensitization and increased risk for additional episodes. This sensitization also seems to happen with depressive episodes induced by IFN. As such, this stress sensitization seems to play a role in both the development and progression of MDD.

Cognition in depression

Cognitive dysfunction is an often replicated finding in MDD (Pan et al., 2017, Kriesche et al., 2022). It is a significant mediator of psychosocial impairment, particularly of workplace performance (McIntyre et al., 2013). However, the effect of antidepressants on cognition is modest (Prado et al., 2018). Cognitive dysfunction also seems to be particularly relevant in late-life depression (Butters et al., 2008, Gandelman et al., 2018).

Inflammation, stress, and cognition in recurrent depression

In **Chapter 3**, the effects of psychosocial and inflammatory stress on cognition were discussed. Patients with remitted depression, although there were no differences with healthy controls on baseline, showed reduced processing speed and verbal memory after an inflammatory stressor. This is in line with earlier research showing a negative effect of chronic inflammation or treatment with IFN-α on cognition (Scheibel et al., 2004). These cognitive domains can be described as “cold” cognitions, as they are not emotionally

laden and dependent on mood. Previous research showed that these “cold” cognitions are impaired in MDD (Stange et al., 2018).

An intriguing finding in our study is that inflammatory stress also mediates the “hot” cognitions, by increasing the negative bias in patients with remitted MDD. “Hot” cognitions are emotionally-laden cognitions, which are also impaired in MDD patients, resulting in a negative bias or increased emotional reactivity (Roiser and Sahakian, 2013). Increased negative bias is indeed an often replicated finding in MDD (Lu et al., 2017). It was shown to be reversed by antidepressant therapy (Wells et al., 2014). This study shows that, even in remission, inflammatory stress increases this negative bias, further corroborating the hypothesis that inflammation plays a role in the pathogenesis of depression. This is in line with previous research that showed that inflammatory stress increased reactivity to negative information (Brydon et al., 2009, Dooley et al., 2018).

Nicotine for cognitive dysfunction

In **Chapter 4**, the effects of various dosages of nicotine on cognition were examined in young and elderly volunteers. The nicotinic acetylcholine receptor (nAchR) is often implicated in human cognition (Sacco et al., 2004). While the pro-cognitive effects of nicotine were mainly researched in healthy populations and populations with schizophrenia or neurodegenerative disorders, it can also be relevant in the treatment of depression (Valentine and Sofuoglu, 2018, Lopez-Arrieta et al., 2001, Gandelman et al., 2018).

In our study, an effect was only found in the elderly population on attention, working memory, and visual memory. However, secondary analysis revealed that the results of nicotine were dependent on baseline cognitive functioning. Both in the young and the elderly group, people with lower baseline functioning had larger cognitive benefits of nicotine administration compared to the people with higher baseline functioning.
This suggests that there may be a subgroup that can benefit cognitively from a treatment that targets the nAchR. Our study suggests that this could be the subgroup that exhibits lower cognitive functioning, though this should be researched in a population with MDD.

Former studies examined the effect of acetylcholinesterase inhibitors (AchEI) on cognition in late-life depression. While there were positive effects on cognition in some studies in patients with mild cognitive impairment (Reynolds et al., 2011), results were conflicting, and AchEI treatment was associated with high drop-out (Holtzheimer et al., 2008). In patients without mild cognitive impairment or dementia, no positive effect was observed on cognition (Reynolds et al., 2011).

Emerging treatment strategies for depression

While a multitude of treatment options is available for MDD, the current monoaminergic antidepressants are not effective in a significant minority of patients. For example, in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, in which four different treatment steps were done in a real-world sample of 2876 MDD patients, there was only a cumulative response rate of 67% after these treatment steps (Sinyor et al., 2010). As such, new pharmacotherapeutic treatment options are needed for MDD treatment.

Treatment-resistant depression

In **Chapter 5**, we presented a case report of depression resistant to ECT, which improved after ECT combined with ketamine augmentation. Electroconvulsive therapy (ECT) is a highly effective treatment for treatment-resistant depression (TRD). It is particularly effective in melancholic depression and psychotic depression, showing remission rates of up to 80% (Husain et al., 2004). There is very little evidence for augmentation strategies in patients who do not respond to ECT. Most studies describe procedures to optimize the convulsion, such as refraining from using anesthetics that increase the seizure threshold or use interventions that decrease the seizure threshold, such as administration of xanthines (e.g., theophylline or caffeine) or sleep deprivation, although these strategies have not proven to lead to improved outcomes (Loo et al., 2010, Gilabert et al., 2004).

Ketamine is a promising new agent for TRD. It is an antagonist of the NMDA receptor. In the past years, its active S-enantiomer esketamine was thoroughly investigated in the treatment of TRD (Zheng et al., 2020, Jha et al., 2023). In December 2019, nasal esketamine was approved for the treatment of TRD in the European Union (European Medicines Agency, 2019).

Several RCTs have evaluated ketamine anesthesia in ECT, hypothesizing it leads to a quicker and more pronounced effect. The results are, however, conflicting. Several studies failed to find an additional antidepressant effect (Ray-Griffith et al., 2017, Zavorotnyy et al., 2017, Zhang et al., 2018, McGirr et al., 2017). Other studies did find either a larger or a quicker antidepressant effect, though at the cost of an increased side effect burden (Li et al., 2017, Rybakowski et al., 2016, Chen et al., 2017, Ghasemi et al., 2014). A meta-analysis showed that ketamine increased seizure duration and made it possible to decrease electrical dose, though without increased antidepressant effect (Ainsworth et al., 2020).

As such, the added value of routine use of ketamine for anesthesia in ECT is unclear at best. However, our case is different because the patient was resistant to ECT, and ketamine was used as augmentation. We found one publication of a similar case, neither responsive

to ketamine nor ECT, which responded to alternating ECT and ketamine administration (Bartova et al., 2017). As such, in the rare cases that don't respond to ECT, augmentation with ketamine anesthesia may be a valid strategy.

Prophylactic treatment of depression

The use of bupropion as a treatment for SAD was reviewed in **Chapter 6**. SAD differs from other subtypes of MDD because the onset and course of depressive episodes are very predictable, with onset in autumn and remission in spring. In that sense, antidepressants can be administered only in autumn and winter, as this is the period that patients experience depressive episodes. For that indication, bupropion proved to be an effective intervention, preventing the onset of depression in the winter months significantly more than placebo.

Currently, the only routine use of prophylactic antidepressant treatment is as continued treatment for relapse prevention after the acute treatment of depression, for which they are effective (Glue et al., 2010). The use of bupropion described in **Chapter 6** is different in the sense that the antidepressant is started preventively before the onset of symptoms. This can be done because of the predictiveness of mood episodes in SAD. This is an interesting treatment paradigm and can be a strategy in other situations where the onset of depression can be expected.

There are indeed several situations where there is a clear risk of the development of MDD. IFN treatment for diseases such as hepatitis C is, as mentioned above, associated with an increased risk for the development of depression (Schafer et al., 2007). Therefore, a possible treatment intervention is to start SSRI treatment with the start of IFN treatment preventively. This was researched in several studies with conflicting findings (Morasco et al., 2007, Morasco et al., 2010, Schaefer et al., 2012, Al-Omari et al., 2013, Udina et al., 2014). Other studies showed that preventive SSRI treatment was effective in patients with a history of psychiatric disorder or elevated depressive symptoms (Schaefer et al., 2005, Raison et al., 2007). Evidence of routine preventive antidepressant treatment in patients treated with IFN is up to now insufficient. However, as depressive episodes can lead to stress sensitization and increase the risk of further episodes, it can be considered in patients at risk.

Besides using the preventive antidepressant treatment for IFN-induced depression, there are also studies to prevent post-partum depression, with inconclusive evidence (Molyneaux et al., 2018). As depressive episodes can lead to stress sensitization and increase the risk for further episodes, the preventive use of antidepressants in high-risk situations

should be further researched. On the other hand, antidepressants are not without side effects. For example, in the case of IFN treatment, still, a majority of patients do not develop a depressive episode during treatment (Lotrich, 2009). As such, routine use of antidepressants may do more harm than good. Further research should elucidate the place of preventive antidepressant treatment in these conditions.

Implications for clinical practice

Anti-inflammatory treatment for depression

In **Chapters 2** and **3**, it was shown that patients with recurrent MDD in remission were more sensitive to inflammatory stress, resulting in a lowering of mood, increased negative cognitive bias, and changes in cognition. This suggests that the inflammatory pathway can also be a potential target for the treatment of MDD and TRD. Up to now, no anti-inflammatory treatments are approved or routinely used in the treatment of MDD. Still, there are some encouraging findings on their efficacy in MDD. It should be noted that none of these therapies are, as of now, well enough researched for routine use in MDD treatment.

Non-steroidal anti-inflammatory drugs (NSAID), cytokine inhibitors, and minocycline were already studied for MDD treatment in past years (Kohler-Forsberg et al., 2019, Cai et al., 2020). Adjunctive therapy to an antidepressant with the COX-2-selective inhibitor celecoxib leads to improved response and remission rates in MDD (Na et al., 2014, Kohler-Forsberg et al., 2019, Wang et al., 2022, Esalatmanesh et al., 2023). While no studies were done in treatment-resistant unipolar depression, efficacy was shown in treatment-resistant bipolar depression (Castillo et al., 2019).

Minocycline is a tetracyclic antibiotic and has neuroprotective and anti-inflammatory properties (Soczynska et al., 2012). A meta-analysis showed a statistically significant antidepressant effect compared to placebo (Rosenblat and McIntyre, 2018). However, the number of published RCTs is small, with heterogeneous and small samples. Efficacy was also shown in TRD (Husain et al., 2017), though this finding was not replicated in a larger sample (Hellmann-Regen et al., 2022).

When used for autoimmune conditions such as psoriasis or rheumatoid arthritis, several cytokine inhibitors reduce comorbid depressive symptoms (Kohler-Forsberg et al., 2019, Wittenberg et al., 2020). The TNF-α infliximab was evaluated in TRD, showing only a significant effect in those with a higher baseline concentration high-sensitive CRP, a marker of systemic inflammation (Raison et al., 2013). A recent meta-analysis corroborated these

results, showing only an effect of infliximab in patients with increased TNF-α and CRP (Bavaresco et al., 2020).

There is also evidence that anti-inflammatory treatment is mainly effective on specific symptom domains of MDD (Lee et al., 2018). For example, recent evidence shows that anti-cytokine treatments particularly reduced anhedonia (Cully, 2020, Lee et al., 2018, Wittenberg et al., 2020). This is in line with our results, where the inflammation-induced mood decrease was primarily driven by a decrease in positive affect. Another symptom of depression that seems to be associated with inflammation is fatigue. Up to now, there seem to be no studies examining the effect of anti-inflammatory treatments on fatigue in MDD. However, several trials of anti-TNF-α agents in autoimmune disease showed that they could reduce the fatigue associated with autoimmune disease (Lee and Giuliani, 2019, Harrold et al., 2017, Fukuoka et al., 2017).

While the effect of anti-inflammatory treatment on cognition was not systematically studied in patients with MDD, several studies show encouraging results in other conditions. Treatment with anti-TNF-α therapy resulted in increased cognition in patients with rheumatoid arthritis and Alzheimer's disease (Raftery et al., 2012, Tobinick and Gross, 2008, Decourt et al., 2017). The COX-2-selective inhibitor celecoxib also increased cognition in patients with schizophrenia (Muller et al., 2005).

Targeting the nicotinic system in MDD treatment

In **Chapter 4,** we presented a study about the effect of different doses of nicotine on several domains of cognition. The main observation was that nicotine mostly positively affected the subjects with relatively low baseline scores on the cognitive tests. This proves that in the subjects with lower cognitive functioning, it had a positive effect.

Nicotine has not yet been studied as a pro-cognitive agent in MDD. Other agents that increase cholinergic tone were researched for cognitive dysfunction in MDD or the treatment of MDD, but results were conflicting (Reynolds et al., 2011, Holtzheimer et al., 2008). As such, the nicotinic system is, for the time being, not yet a target in current MDD treatment practice.

Ketamine for treatment-resistant depression and bupropion for seasonal affective disorder

In **Chapter 5**, we discussed a case report of a patient with TRD that also didn't react to ECT, who reacted to ECT in combination with ketamine anesthesia. Ketamine as a treatment for TRD is now approved by the European Medicines Agency. It is in the process of being brought on the market in the different European Union countries (European Medicines Agency, 2019). As such, it is ready for routine use in TRD. In patients not responding to ECT or ketamine alone, based on our case report, the use of ketamine anesthesia as an augmentation strategy is, in our opinion, a possible treatment option.

The use of bupropion for SAD was reviewed in **Chapter 6**. Bupropion was studied in SAD specifically to prevent depressive episodes, starting administration in autumn and stopping it in spring. This strategy was researched in three studies and, as such, gained approval by the Food and Drug Administration for this indication in the USA, though not in the European Union (GlaxoSmithKline, 2011). In the treatment of SAD, this is an adequate strategy and can be routinely used. While only bupropion was studied to prevent SAD, and as such, the preferred antidepressant for this use, there is no a priori reason to assume that this strategy would not work with other antidepressants. If SAD patients do not respond to or do not tolerate bupropion, SAD prevention with other antidepressants can be tried. Up to now, there is not enough evidence for routine preventive antidepressant treatment in other patients with a high risk of developing a depressive episode. However, it may be considered in at-risk patients who have to be treated with IFN.

Conclusion and future perspectives

Millions of people have to deal daily with the symptoms of MDD, the number one cause of disability worldwide (World Health Organization, 2017). While many pharmacological treatments are available, most of them target only the monoaminergic system (Dupuy et al., 2011). Although they are effective agents, only around two-thirds of patients achieve complete remission after several treatment steps (Sinyor et al., 2010). Many patients continue to suffer from residual symptoms, such as cognitive dysfunction (Pan et al., 2017). Even after recovery, a majority of patients experience recurrence (Monroe and Harkness, 2005).

Our study further confirmed the involvement of the inflammatory system in the pathophysiology of MDD, showing that patients with remitted MDD were more vulnerable to the effects of inflammatory stress. It was hypothesized that there would be a synergistic effect with psychosocial stress, but this was not observed in the behavioral measures.

Inflammatory stress was also shown to lead to decreased performance in cognitive tests and an increased negative bias in patients with remitted MDD. As such, the inflammatory system is a novel treatment target for MDD treatment. Indeed, anti-inflammatory therapies such as celecoxib, minocycline, and cytokine inhibitors are currently studied with promising results (Na et al., 2014, Cai et al., 2020, Bavaresco et al., 2020).

In our study, the inflammatory stressor had particularly a negative effect on the subdomains of mood associated with positive affect. This is in line with previous research, showing that pro-inflammatory states are associated with increased anhedonia and fatigue, and the use of anti-inflammatory agents in MDD have mainly an effect on anhedonia (Lee et al., 2018, Mehta et al., 2020). Furthermore, cytokine inhibitors seemed to be only effective in MDD patients who have an elevated CRP at baseline, providing a possible biomarker that can predict the efficacy of anti-inflammatory treatment of MDD (Bavaresco et al., 2020).

Such observations open the door to more personalized treatment of MDD, where treatment response can be predicted based on specific patient characteristics, or specific symptom domains can be targeted by specific treatments (Simon and Perlis, 2010). Identifying symptom domains that respond to particular treatments or finding biomarkers that predict treatment response can make the treatment of MDD more targeted and effective (Nierenberg, 2012). In this line of thinking, our study of the effects of nicotine on cognition showed that mainly the subgroup with lower cognitive performance at baseline benefited from the pro-cognitive effects of nicotine, suggesting it might be beneficial in specific subgroups of patients.

Another difficulty in MDD treatment is that most patients will eventually experience recurrence, even after successful treatment (Burcusa and Iacono, 2007). A possible explanation is that depressive episodes induce stress sensitization, increasing the risk of new depressive episodes (Morris et al., 2010). Our study provided further evidence for this stress sensitization, as patients, though remitted, have an increased sensitivity to inflammatory stress. While currently, the continuation of antidepressant treatment is the primary strategy in relapse prevention, further research into this process of stress sensitization may provide insights that can lead to new approaches in relapse prevention.

Existing therapies can be repurposed or applied more targeted in MDD treatment. In this thesis, a case of depression resistant to ECT was presented, where add-on ketamine brought solace. This strategy can already be applied in the rare MDD cases that are resistant to ECT. We also reviewed the use of the existing antidepressant bupropion for the preventive treatment of SAD, where depressive episodes occur predictively in the winter months. As such, antidepressant therapy could be initiated before the expected onset of de episode, thus preventing it.

In conclusion, MDD is a prevalent though complex and still insufficiently understood mental disorder, which poses a significant burden on global health. This research further corroborates the involvement of the inflammatory system and the possible interaction with psychosocial stress, and further research about it will hopefully lead to new and effective treatments. Progress in understanding the pathophysiology of depression and its recurrence can provide the knowledge to tailor therapies to the individual patient and prevent recurrence. Currently available treatments, such as ketamine and bupropion, can be used tailored for specific subtypes to optimize treatment.

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List of Abbreviations

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5-HIAA	5-Hydroxyindoleacetic acid
5-HT	5-Hydroxytryptamine or Serotonin
5-HTP	5-Hydroxytryptophan
α7nAchR	α-7 Nicotinic Acetylcholine Receptor
AchE	Acetylcholinesterase
AchEI	Acetylcholinesterase Inhibitor
ACTH	Adrenocorticotropic Hormone
ADI	Acceptable Daily Intake
AUC	Area Under the Curve
AVP	Arginine Vasopressin
BBB	Blood-Brain Barrier
BDNF	Brain-Derived Neurotrophic Factor
BH4	Tetrahydrobiopterin
BMI	Body mass index
BVRT	Benton Visual Retention Test
CGI-I	Clinical Global Impression of Severity
CGI-S	Clinical Global Impression of Improvement
Cmax	Maximum Plasma Conentration
CNS	Central Nervous System
COMT	Catechol-O-Methyltransferase
COWAT	Controlled Oral Word Association Test
CPT / CPT-IP	Continuous Performance Test - Identical Pairs
CREB	cAMP Response Element-Binding Protein
CRH	Corticotropin-Releasing Hormone
CRP	C-Reactive Protein
CSF	Cerebrospinal Fluid
CTQ	Childhood Trauma Questionnaire
CYP	Cytochrome P450
DA	Dopamine
DEX/CRH	Dexamethasone/Corticotropin-Releasing Hormone
DOPA	Dihydroxyphenylalanine
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision
DST	Dexamethasone Suppression Test
ECT	Electroconvulsive Therapy
ERM	Emotion Recognition/Matching
GABA	γ-Aminobutyric Acid
GR	Glucocorticoid Receptor
HAM-A	Hamilton Rating Scale for Anxiety
HDRS	Hamilton Depression Rating Scale
HPA-axis	Hypothalamic–Pituitary–Adrenal axis
HVLT	Hopkins Verbal Learning Test

IDO	Indoleamine 2,3-Dioxygenase
IFN	Interferon
IL	Inteleukin
IR	Immediate Release
KYN	Kynurenine
KYNA	Kynurenic Acid
LC	Locus Coeruleus
LCT	*Line Copying Test*
LNS	Letter-Number Sequencing
LPS	*Lipopolysaccharide*
MADRS	Montgomery-Åsberg Depression Rating Scale
MAO	Monoamine-Oxidase
MAPK	p28 Mitogen-Activated Protein Kinase
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MMSE	Mini Mental State Examination
MR	Mineralocorticoid Receptor
nAchR	Nicotinic Acetylcholine Receptor
NE	Norepinephrine
NET	Norepinephrine Transporter
NMDA	N-methyl-D-aspartate
NOEL	No-Effect Level
NSAID	Non-Steroidal Anti-Inflammatory Drug
POMS	Profile of Mood States
QUIN	Quinolinic Acid
RCT	Randomized Controlled Trial
RTME	Reading the Mind in the Eyes test
SAD	Seasonal Affective Disorder
SASS	Social Adaptation Self Evaluation Scale
SDST	Symbol Digit Substitution Test
SERT	Serotonin Transporter
SIGH-SAD	Structured Interview Guide of the Hamilton Depression Rating Scale, Seasonal Affective Disorder version
SNS	Sympathetic Nervous System
SPC	Summary of Product Characteristics
SR	Sustained Release
STA	Stereotypy Test Apparatus
STAR*D trial	Sequenced Treatment Alternatives to Relieve Depression Trial
TNF	Tumor Necrosis Factor
TRD	Treatment-resistant Depression
TrkB	Tropomyosin Receptor Kinase B
TSST	Trier Social Stress Test
XR	Extended Release

English Summary

English Summary

Major depressive disorder (MDD) is a serious, common, and recurrent psychiatric condition affecting more than 300 million people worldwide.

There are several theories about the pathophysiology of depression. The observation that antidepressants increase the synaptic concentration of monoamine neurotransmitters led to the monoamine hypothesis of MDD, which suggested disruptions in the levels of the neurotransmitters serotonin, norepinephrine, or dopamine. The hypothalamic-pituitary-adrenal (HPA) axis is also involved in the pathophysiology of MDD. The HPA axis is activated by stress in a broad sense (e.g., psychological stress, infection, and others). Continued activation of the HPA axis by chronic stress can lead to desensitization of the negative feedback loop, leading to prolonged and uncontrolled activation of the HPA axis, which then leads to depressive symptoms. It appears more and more that the inflammatory system is also involved in MDD. It has been repeatedly shown that proinflammatory cytokines, such as Interleukin-6 and Tumor Necrosis Factor-α, are increased in patients with MDD. Elevated acute phase proteins, such as C-reactive protein (CRP), were also observed in MDD patients.

The treatment of MDD consists mainly of pharmacotherapy and psychotherapy. However, current treatment modalities are inadequate. Although remission and recovery are the goals of treating depression, this is often not achieved with current treatments. In a 2011 study by Sheehan et al., 38% of treated patients achieved remission, 32% functional remission, and only 23% combined functional and symptomatic remission. Many patients also experience residual complaints such as fatigue and cognitive dysfunction.

Relapse is also frequent in MDD: at least 60% of patients will relapse after a first episode, with some studies reporting higher rates (up to 85%). A striking finding is that although the onset of MDD is often associated with psychosocial stress, with an increasing number of episodes, psychosocial stress appears to be less and less associated with the onset of an episode. An explanation for this is that following several episodes, there is a sensitization to stress, causing relapses even after minor stressors. The aim of the thesis is to investigate new strategies to improve the treatment of depression.

Chapters 2 and **3** discuss a study in which the effects of inflammatory stress, psychosocial stress, and the combination of both on mood and biomarkers (**Chapter 2**) and cognition (**Chapter 3**) were examined.

In this single-blind, placebo-controlled study, the effects of inflammatory stress (i.e., typhoid vaccination), psychosocial stress (i.e., the Trier Social Stress Test [TSST]) or a combination of both were examined in women (25–45 years old) with recurrent depression in (partial) remission (n = 21) and healthy female controls (n = 18). After administration of the stressor, the effect on mood, markers of hypothalamic-pituitary-adrenal (HPA) activity and activation of the inflammatory system, and on cognition was measured over a period of 6 hours. The study was conducted over two days of testing, separated by a 7–14-day washout. In a crossover design, the subjects received one of the interventions one day and placebo the other day.

A decrease in mood was seen in patients after vaccination, but not after TSST or the combination; this effect was not observed in controls. Controls showed a significantly different response to adrenocorticotropic hormone (ACTH) after vaccination, with an non-significant overall increase in ACTH observed in controls but not patients. The TSST activated the HPA axis in both groups and suppressed inflammatory parameters.

Interestingly, the deterioration of mood score in the patient group was mainly caused by a significant decrease in the subscale of “vigor/activity”, which may indicate a reduced positive affect after the vaccine. This finding is consistent with previous observations that pro-inflammatory states are associated with anhedonia. Contrary to our expectations, the TSST had no influence on the total mood score. We also hypothesized that, due to the expected interactions between psychosocial stress and the immune system, the combination would have a synergistic effect on both mood and biomarkers. However, this was not observed. However, after the combined stressor, there was a significant increase in Interferon-γ in the patient population, which was not observed after the other interventions.

After the administration of one of the stressors, several cognitive measures were also measured, namely short-term and verbal memory, working memory, attention, word fluency, information processing speed, psychomotor skills, and the attentional bias for positive, negative, or neutral emotions. In patients, inflammatory stress reduced information processing speed and verbal memory and increased working memory; after psychosocial stress, there was an increase in attention. There was also an increased negative attentional bias in patients after inflammatory stress. Neither stressor had any effect on controls. This is in line with previous research showing a negative effect of chronic inflammation or treatment with IFN-α on cognition. An intriguing finding in our study is that inflammatory stress influences emotionally charged cognitions. This study shows that, even in remission, inflammatory stress amplifies this negative emotional bias, supporting the hypothesis that inflammation plays a role in the pathogenesis of depression.

Because stress sensitization appears to increase with a higher number of episodes, patients with recurrent depression were included. As expected, the patient group experienced a mood reduction and changes in cognition, while the healthy controls did not. This means that sensitivity to stress remains present even when remission occurs. These results corroborate the hypothesis that there is a sensitization to stress after one or more depressive episodes. However, the study was not designed to prove a causality.

Chapter 4 discusses a study that investigated the pro-cognitive effects of nicotine in healthy volunteers as a proof-of-concept for potential research in clinical populations. We conducted a double-blind, randomized, placebo-controlled crossover study investigating the effects of placebo, 1 and 2 mg nicotine on cognition in young (n=16, age 18-30 years) and healthy elderly (n=16, age 60-75 years) subjects. Nicotine had no effect on the young volunteers and reduced performance on working memory and visual memory in the elderly. Contrary to our hypothesis, the effect of nicotine in both groups was dependent on baseline performance, with subjects with lower baseline performance benefiting from nicotine administration, while those with higher baseline performance performing worse after nicotine administration. This suggests that although nicotine generally had no or negative effects in our study, subjects with lower cognitive performance, regardless of age, may benefit from nicotine.

Chapters 5 and **6** discuss the use of existing treatments for subtypes of depression. In **Chapter 5**, a case is presented with treatment-resistant depression that does not respond to ECT. Remission was achieved when ketamine anesthesia was started for ECT, suggesting that ketamine augmentation is a possible treatment strategy for ECT-resistant depression.

Chapter 6 discusses the effectiveness of bupropion, a norepinephrine and dopamine reuptake inhibitor, for the treatment of seasonal affective disorder. Bupropion was primarily studied as a preventive treatment, initiated in the fall and discontinued in the spring. The efficacy of bupropion for this indication was investigated in three randomized controlled trials. Due to the predictable nature of seasonal affective disorder, preventive treatment is a relevant treatment option.

In this thesis, first, the pathophysiology of depression was explored, examining the effects of inflammatory and psychosocial stress on mood and biomarkers. The study examined the impacts of both inflammatory and psychosocial stressors on cognition in greater detail. A study on the pro-cognitive effects of nicotine was also discussed. The effects of existing treatments, in particular ketamine and bupropion, in specific patient populations were finally discussed.

Anti-inflammatory treatments, namely COX-2 inhibitors, cytokine inhibitors, and minocycline have been investigated in recent years for the treatment of MDD, with some studies showing positive effects. Despite this, none of these therapies have yet been well enough researched for routine use in the treatment of depression. Nicotine has not yet been studied for the treatment of cognitive problems in depression. Ketamine as a treatment for treatment-resistant depression has been approved and can be used for this indication. In patients who do not respond to ECT, ketamine anesthesia can be chosen as augmentation based on the case study discussed. The use of bupropion for the prevention of seasonal affective disorder is well-researched, and it is licensed for this indication in the United States.

In conclusion, MDD is a common but complex and still insufficiently understood mental disorder. Further research into the pathophysiological mechanisms of depression and relapse can hopefully provide insights that could lead to new treatments for these patients.

Nederlandse Samenvatting

Nederlandse Samenvatting

Majeur depressieve stoornis is een ernstige, veel voorkomende en recurrente psychiatrische aandoening, die wereldwijd meer dan 300 miljoen mensen treft.

Over de pathofysiologie van depressie zijn er verschillende theorieën. De observatie dat antidepressiva de synaptische concentratie van monoamine-neurotransmitters verhogen leidde tot de monoamine-hypothese, die suggereerde dat er bij depressie veranderingen zijn in de niveaus van de neurotransmitters serotonine, noradrenaline of dopamine. De hypothalamus-hypofyse-bijnier (HPA)-as is ook betrokken bij de pathofysiologie van depressie. De HPA-as wordt geactiveerd bij stress in de brede zin (bijvoorbeeld psychologische stress, infectie, etc.). Voortdurende activering van de HPA-as door chronische stress kan leiden tot desensitisatie van de negatieve feedback, wat leidt tot een langdurige en ongecontroleerde activering van de HPA-as, wat dan tot depressieve klachten zou leiden. Steeds meer blijkt ook het inflammatoir systeem te zijn betrokken bij depressie. Er is herhaaldelijk aangetoond dat pro-inflammatoire cytokines, zoals Interleukine-6 en Tumor Necrosis Factor-α, verhoogd zijn bij patiënten met depressie. Er werden eveneens verhoogde acute fase proteïnen, zoals C-reactief proteïne (CRP), gemeten.

De behandeling van depressie bestaat voornamelijk uit farmacotherapie en psychotherapie. De huidige behandelingsmodaliteiten zijn echter ontoereikend. Hoewel remissie en herstel de doelen zijn van de behandeling, wordt dit vaak niet bereikt met de huidige behandelingen. In een studie van Sheehan e.a. uit 2011 bereikte 38% van de behandelde patiënten remissie, 32% functionele remissie en slechts 23% gecombineerde functionele en symptomatische remissie. Ook ervaren veel patiënten residuele klachten zoals vermoeidheid en cognitieve dysfunctie.

Er is eveneens frequent herval: ten minste 60% zal hervallen na de eerste episode, waarbij sommige onderzoeken een hoger percentage (tot 85%) rapporteren. Hoewel het begin van een depressieve episode aanvankelijk vaak geassocieerd is met psychosociale stress, lijkt stress naarmate het aantal depressieve periodes toeneemt minder gelinkt te zijn aan het ontstaan van een episode. Een verklaring hiervoor is dat er na verschillende episodes een sensitisatie is voor stress, waardoor er na kleine (onmeetbare) stressoren reeds herval is. Het doel van het proefschrift is om nieuwe strategieën te onderzoeken om de behandeling van depressie te verbeteren.

In **hoofdstuk 2** en **3** wordt een studie besproken waarin de effecten van inflammatoire stress, psychosociale stress en de combinatie van beiden op stemming en biomarkers (**hoofdstuk 2**), alsook cognitie (**hoofdstuk 3**) werden onderzocht.

In dit enkelblind, placebogecontroleerd onderzoek werden de effecten onderzocht van inflammatoire stress (nl. tyfusvaccinatie), psychosociale stress (nl. de Trier Social Stress Test [TSST]) of een combinatie van beide bij vrouwen (25– 45 jaar oud) met recidiverende depressie in (gedeeltelijke) remissie (n = 21) en gezonde vrouwelijke controles (n = 18). Na toediening van de stressor werd gedurende een periode van 6u het effect op stemming, markers van de activiteit van de HPA-as en activering van het ontstekingssysteem, en op cognitie gemeten. De studie werd uitgevoerd tijdens twee testdagen, gescheiden door een wash-out van 7-14 dagen. In een cross-over design kregen de proefpersonen de ene dag een van de interventies en de andere dag placebo.

Een verlaging van de stemming werd bij patiënten gezien na vaccinatie, maar niet na TSST of de combinatie; dit effect werd niet waargenomen bij controles. Er was een significant verschillend effect van het vaccin op adrenocorticotroop hormoon (ACTH), waarbij er een niet-significante algemene stijging van ACTH werd waargenomen bij controles maar niet bij patiënten. In beide groepen activeerde de TSST de HPA-as en onderdrukte het de inflammatoire parameters.

Interessant is dat de verslechtering van de stemmingsscore van de patiënten voornamelijk werd veroorzaakt door een significante afname van de subschaal van “kracht en activiteitsniveau”, wat kan wijzen op een verminderd positief affect na het vaccin. Deze bevinding komt overeen met eerdere waarnemingen dat pro-inflammatoire toestanden geassocieerd zijn met anhedonie. In tegenstelling tot onze verwachtingen had de TSST geen invloed op de totale stemmingsscore. We veronderstelden ook dat, vanwege de verwachte interacties tussen de stress en het immuunsysteem, de combinatie een synergetisch effect zou hebben op zowel stemming als biomarkers. Dit werd echter niet geobserveerd. Na de gecombineerde stressor was er echter een significante toename van Interferon-γ in de patiëntenpopulatie, wat niet werd waargenomen na de andere interventies.

Na de toediening van de stressor werden ook verschillende cognitieve maten gemeten, met name kortetermijn- en verbaal geheugen, werkgeheugen, aandacht, woordvlotheid, informatieverwerkingssnelheid, psychomotoriek en de aandachtsbias voor positieve, negatieve en neutrale emoties. Bij patiënten verminderde inflammatoire stress de informatieverwerkingssnelheid en het verbale geheugen, en het verbeterde het het werkgeheugen; na psychosociale stress was er een toename van de aandacht. Er was ook een verhoogde negatieve aandachtsbias bij patiënten na inflammatoire stress. Geen van beide stressoren had enig effect bij controles. Dit is in lijn met eerder onderzoek dat een negatief effect van chronische inflammatie of behandeling met IFN-α op cognitie aantoont. Een intrigerende bevinding in onze studie is dat inflammatoire stress ook een effect heeft op de emotioneel geladen cognities. Deze studie toont aan dat, zelfs bij remissie,

inflammatoire stress deze negatieve emotionele bias versterkt, wat de hypothese bevestigt dat inflammatie een rol speelt in de pathogenese van depressie.

Omdat stresssensitisatie lijkt toe te nemen met een hoger aantal episodes, werden patiënten met recidiverende depressie geïncludeerd. Zoals verwacht ervoer de patiëntengroep een stemmingsverlaging en veranderingen in cognitie, terwijl de gezonde controles dat niet deden. Dit wil zeggen dat de gevoeligheid voor stress aanwezig blijft, zelfs wanneer er remissie optreedt. Deze resultaten suggereren dat er inderdaad een sensitisatie is voor stress. De studie is echter niet opgezet om causale verbanden aan te tonen.

In **hoofdstuk 4** wordt een studie besproken waarin de pro-cognitieve effecten van nicotine bij gezonde vrijwilligers werd onderzocht, als een proof-of-concept voor mogelijk onderzoek in klinische populaties. We hebben een dubbelblinde, gerandomiseerde, placebo-gecontroleerde cross-over studie uitgevoerd, waarbij de effecten van placebo, 1 en 2 mg nicotine op cognitie werden onderzocht bij jonge (n=16, leeftijd 18-30 jaar) en gezonde ouderen (n=16, leeftijd 60-75 jaar) proefpersonen. Nicotine had geen effect bij de jonge vrijwilligers en verminderde prestaties op het werkgeheugen en het visuele geheugen bij ouderen. Uit een secundaire analyse bleek echter dat het effect van nicotine in beide groepen afhankelijk was van de baselineprestaties, waarbij proefpersonen met lagere baselineprestaties op de cognitieve maten meer baat hadden bij nicotinetoediening dan degenen met hogere baselineprestaties. Dit suggereert dat, hoewel nicotine over het algemeen geen of negatieve effecten had in ons onderzoek, proefpersonen met lagere cognitieve prestaties, ongeacht hun leeftijd, baat kunnen hebben bij nicotine.

Hoofdstukken 5 en **6** bespreken het gebruik van bestaande behandelingen bij bepaalde subtypes van depressie. In **hoofdstuk 5** wordt een casus gepresenteerd met therapieresistente depressie die niet reageert op ECT. Bij de start van gebruik van ketamineanesthesie voor ECT werd er wel remissie bereikt, wat suggereert dat ketamine-augmentatie bij ECT-resistente depressie een mogelijke behandelstrategie is.

In **hoofdstuk 6** wordt de effectiviteit geëvalueerd van bupropion, een noradrenaline- en dopamineheropnameremmer, voor de behandeling van seizoensgebonden depressie. Bupropion werd voornamelijk onderzocht als preventieve behandeling, waarbij het werd opgestart in de herfst en werd gestopt in de lente. De werkzaamheid van preventief gebruik van bupropion voor deze indicatie werd onderzocht in drie gerandomiseerde gecontroleerde onderzoeken. Vanwege het voorspelbare karakter van seizoensgebonden depressie is preventieve behandeling een relevante behandeloptie.

In deze thesis werd eerst dieper ingegaan op de pathofysiologie van depressie, waarbij de effecten van inflammatoire en psychosociale stress op stemming en biomarkers werd onderzocht. Vervolgens werd er dieper ingegaan op de effecten van inflammatoire en psychosociale stress op cognitie. Er werd eveneens een studie besproken naar de procognitieve effecten van nicotine. Vervolgens werden de effecten van bestaande behandelingen, met name ketamine en bupropion, in specifieke patiëntenpopulaties besproken.

Anti-inflammatoire behandelingen zoals COX 2-inhibitoren, cytokineremmers en minocycline werden de afgelopen jaren al onderzocht voor de behandeling van depressie, waarbij enkele studies positieve effecten aantoonden. Ondanks dit zijn geen van deze therapieën tot nu toe goed genoeg onderzocht voor routinematig gebruik bij de behandeling van depressie. Nicotine is nog niet onderzocht voor de behandeling van cognitieve problemen bij depressie. Ketamine als behandeling voor therapieresistente depressie is goedgekeurd en kan gebruikt worden voor deze indicatie. Bij patiënten die niet reageren op ECT kan op basis van de besproken gevalsstudie hiervoor geopteerd worden. Het gebruik van bupropion voor de preventie van seizoensgebonden depressie is goed onderzocht en het is voor deze indicatie geregistreerd in de Verenigde Staten.

Concluderend, depressie is een veel voorkomende maar complexe en nog onvoldoende begrepen psychiatrische aandoening. Verder onderzoek naar de pathofysiologische mechanismen van depressie en herval kan hopelijk inzichten geven die kunnen leiden tot nieuwe behandelingen.

Curriculum Vitae

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Personalia

Peter Niemegeers
Geboren op 30 maart 1986 te Bonheiden
Wonende te Solvynsstraat 43/002, 2018 Antwerpen
E-mail: peter.niemegeers@outlook.com

Opleiding

Postgraduaat in de gedragstherapie (volwassenen)
KU Leuven, 2015-2019
Master na master in de specialistische geneeskunde: volwassenenpsychiatrie
Universiteit Antwerpen, 2011-2018
Bachelor en master in de geneeskunde
KU Leuven, 2004-2011
Secundair onderwijs Latijn-Wiskunde
Sint-Ursula Instituut, Onze-Lieve-Vrouw Waver, 1998-2004

Extra opleidingen

EMDR-basisopleiding
Vereniging EMDR Nederland, 12-13 juni, 5 september en 6 november 2015
Acceptance and Commitment Therapy basisopleiding (6 dagen)
ACT Academie, Ranst, België, 2018
Mentalisation Based Treatment, deel I en II (4 dagen)
MBT Nederland, Breda, Nederland, 2019
Management voor de Zorgprofessional
Vlerick Business School, 2020-2021

Klinische Ervaring

Psychiater
Ziekenhuisnetwerk Antwerpen (ZNA), 2018 – nu

- Verslavingszorg: residentiële behandeling van verslavingsproblematiek (augustus 2019 – nu)
- Liaisonpsychiatrie op verschillende ZNA-campussen (april 2018 – september 2023)
- Mobiel Psychiatrisch Team 't Stad: mobiel team voor outreachende behandeling van patiënten met een ernstige psychiatrische aandoening (EPA) (oktober 2019 – september 2022)
- Psychogeriatrie te ZNA Jan Palfijn (april 2018 – september 2021)
- PAAZ-afdeling van het acuut traject psychiatrie van ZNA Sint-Erasmus (augustus 2018 – juli 2019)

Psychiater
ADIC vzw, 2023 – nu

Arts-specialist in opleiding, volwassenenpsychiatrie
Universiteit Antwerpen, 2014 – 2018

- Universitair Ziekenhuis Antwerpen (6 maanden; 2014-2015):
  Liaisonpsychiatrie en ambulante consultaties
- Psychiatrisch Ziekenhuis Duffel (6 maanden; 2015):
  Afdeling "De Spinnaker": dialectische gedragstherapie voor persoonlijkheidsstoornissen
  Dagcentrum "Arkel": dialectische gedragstherapie voor persoonlijkheidsstoornissen en ik-versterkende therapie
- Federale overheidsdienst justitie, gevangenis van Antwerpen en Merksplas (6 maanden; 2015-2016):
  Psychosociale dienst (PSD) van de gevangenis van Antwerpen en Merksplas: ondersteuning van gedetineerden doorheen hun detentie en reclassering en psychiatrische evaluatie en formulering van psychiatrisch advies voor de reclassering van geïnterneerden
  Psychiatrische zorg voor gedetineerden en geïnterneerden in de gevangenis van Merksplas
- ZNA Psychiatrisch Ziekenhuis Stuivenberg (1,5 jaren; 2016-2017):
  Afdeling intensieve psychiatrische zorg (IPZO): gesloten opnameafdeling voor de acute intensieve psychiatrische zorg (6 maanden; 2016)
  Verslavingszorg: behandeling van alcohol-, cannabis- en medicatieafhankelijkheid, alsook secundaire drugsverslaving en gokproblematiek (6 maanden fulltime en 6 maanden halftime; 2016-2017)
- CGG VAGGA (6 maanden; 2017)
  Ambulante verslavingszorg (6 maanden halftime; 2017)
- ZNA Sint-Erasmus (6 maanden; 2017-2018)
  PAAZ-afdeling van het acuut traject psychiatrie

Doctoraatsonderzoeker
Universiteit Antwerpen / PZ Duffel, 2011-2014

Overige activiteiten

Wetenschappelijk secretaris
Vlaamse Vereniging voor Psychiatrie (VVP), januari 2022 – nu

Publicaties & Presentaties

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Niemegeers P, de Boer P, Schuermans J, Dumont GJH, Coppens V, Spittaels K, Claes S, Sabbe BCG, Morrens M. *Digging deeper in the differential effects of inflammatory and psychosocial stressors in remitted depression: effects on cognitive functioning.* J Affect Disord. 2019;245:356-63. doi: 10.1016/j.jad.2018.11.020

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Niemegeers P, Schrijvers D, Sabbe BGC. Remission of ECT-resistant depression with ketamine anaesthesia. Poster session presented at: 22nd European Congress of Psychiatry (EPA 2014); 1-4 maart 2014; München, Duitsland

Lezingen en presentaties

21 juni 2022: CAPRI research club, Universiteit Antwerpen. *Differentiële effecten van inflammatoire en psychosociale stress.*

28 april 2022: Congres Verslavingsbeleid Kempen. *Transitieleeftijd en verslaving.*

25 mei 2018: Interoriëntale studiedag van opleidingen psychotherapie van de KU Leuven. *Exposuretherapie bij posttraumatische-stressstoornis.*

3 oktober 2017: Postgraduaat Psychiatrie, Universitair Ziekenhuis Antwerpen. *Differentiële effecten van inflammatoire en psychosociale stress.*

17 september 2016: Geneeskundige Dagen van Antwerpen. *Differentiële effecten van inflammatoire en psychosociale stress.*

13 september 2016: CAPRI research club, Universiteit Antwerpen. *Differentiële effecten van inflammatoire en psychosociale stress.*

19 november 2015: Symposium “Slaap-in-zicht” door NVKVV, Herentals, Belgium. *Overzicht van de farmacologische behandeling van insomnia.*

2 oktober 2015: BCNBP Research in Psychiatry Day, Leuven, Belgium. *Differential effects of inflammatory and psychosocial stress in remitted major depressive disorder.*

26 september 2014: BCNBP Research in Psychiatry Day, Duffel. *An inflammatory stressor increases the negative attentional bias in remitted major depression.*

17 juni 2014: CAPRI research club, Universiteit Antwerpen. *Inflammatie, psychosociale stress en depressive.*

16 april 2013: CAPRI research club, Universiteit Antwerpen. *Ketamine en minocycline voor therapieresistente Depressie.*

21 februari 2012: CAPRI research club, Universiteit Antwerpen. *Het effect van een inflammatoire of psychosociale stressor bij jongere en oudere vrouwen en vrouwen met een voorgeschiedenis majeure depressie.*

Onderwijservaring

Cursus: "Psychopathologie"
Thomas More Hogeschool, Mechelen. Bachelor in de Verpleegkunde, 2018 – 2021

Cursus: "Psychopathologie 1"
Thomas More Hogeschool, Mechelen. Bachelor in de Verpleegkunde, 2012 – 2017

Cursus: "Psychopathologie 2"
Thomas More Hogeschool, Mechelen. Bachelor in de Verpleegkunde, 2015 – 2018

Cursus: "Etiologie en pathogenese van psychiatrische stoornissen in volwassen en oudere patiënten"
Artesis Plantijn Hogeschool, Antwerpen. Bachelor in de Verpleegkunde, 2012 – 2014

Dankwoord

Dankwoord

Eindelijk! Het proefschrift is er!

Het was een lange en soms hobbelige weg maar het is dan toch gelukt! Als ik terugkijk op de jaren waarin ik aan dit doctoraat heb gewerkt, kan ik de mensen aan wie ik dank verschuldigd ben niet op één hand (en misschien zelfs niet op 10 of 20 handen) tellen. Zonder jullie was dit nooit mogelijk geweest! Ik heb geprobeerd om het onderstaand dankwoord zo volledig mogelijk te maken, maar ongetwijfeld zal ik toch enkele mensen over het hoofd hebben gezien, waarvoor ik mij alvast excuseer: het was niet mijn bedoeling en ik ben jullie daarom niet minder dankbaar.

Eerst en vooral wil ik mijn promotoren en begeleider bedanken.

Prof. dr. Bernard Sabbe, u wakkerde mijn interesse voor het wetenschappelijk onderzoek aan en begeleidde me doorheen dit hele traject. Uw goede raad, deskundige adviezen en aanmoediging maakten dit proefschrift mogelijk. In de eerste plaats was dit doctoraat natuurlijk een verdieping in de wetenschap en het onderzoek, maar ik neem er ook lessen uit mee die ik voor de rest van mijn carrière en leven zal koesteren. Ik mag me gelukkig prijzen dat dit mogelijk was onder uw begeleiding. Bedankt voor alles!

Prof. dr. Wouter Hulstijn, bedankt voor alle wijze raad en constructieve feedback op mijn werk. Tot op het einde van dit traject kwam u met suggesties en oplossingen die dit proefschrift gemaakt hebben tot wat het nu is. Bedankt voor alles!

Prof. dr. Manuel Morrens, bedankt om doorheen de jaren alles zo nauwgezet op te volgen. Jij was er altijd om goede raad en feedback te geven over dit proefschrift. Je moedigde mij ook steeds aan om door te zetten. Zonder jou was dit proefschrift er nooit gekomen. Bedankt voor alles!

Ik zou ook graag de leden van de interne jury, prof. dr. Patrick Cras en prof. dr. Guido De Meyer, willen bedanken voor hun feedback en om dit doctoraat al die tijd te blijven opvolgen. Ook de leden van de externe jury zou ik graag willen bedanken. Prof. dr. Chris Baeken, bedankt om de tijd te nemen om dit proefschrift te beoordelen en voor de nuttige feedback. Prof. dr. de Timary, merci d'avoir pris le temps d'évaluer cette thèse et pour vos précieux commentaires.

Bedankt ook aan het Universitair Psychiatrisch Centrum Duffel, om dit onderzoek mogelijk te maken en aan de Universiteit Antwerpen, om mij de kans te geven om dit doctoraatstraject te doen.

Ik wil ook iedereen die aan mijn onderzoek heeft deelgenomen bedanken. Zonder deelnemers geen studie, dus zonder jullie engagement voor deelname zou er van deze studies nooit iets gekomen zijn. Bedankt!

Die deelnemers hebben natuurlijk niet uit zichzelf de weg naar mijn studie gevonden. Daarvoor heb ik kunnen tellen op een uitgebreid netwerk van collega's, vrienden en kennissen die mijn onderzoek onder de aandacht hebben gebracht van potentiële gezonde deelnemers en soms ook zelf hebben deelgenomen. Voor het rekruteren van patiënten heb ik kunnen rekenen op collega's die in hun patiëntenbestand hebben gezocht naar geschikte en geïnteresseerde deelnemers. Ik dank dan onder andere: prof. dr. Filip Van Den Eede, Magdaleen De Breuckere, dr. Carmen De Grave, dr. Iris De Mulder, dr. Esther Maris, dr. Charel Quisenaerts en dr. Jos Verbelen. Bedankt hiervoor, zonder jullie had het nooit mogelijk geweest!

In het UPC Duffel werd ik omringd door fijne en ondersteunende collega's. Ik denk aan prof. dr. Livia De Picker en dr. Claudia Cornelis, die steeds klaar waren voor overleg en een luisterend oor, en met wie ik tot op het laatste moment kon overleggen over dit proefschrift en de verdediging. Glenn Dumont, jij stond me in de periode dat het onderzoek werd gevoerd met raad en daad bij en kwam steeds met oplossingen als ik het niet meer zag. Bedankt aan Sara Vermeylen, Mona Laureys en Joke Lauwers om alles in goede banen te leiden.

In het bijzonder wil ik Silke Apers bedanken. Op de momenten dat mijn executief functioneren het liet afweten wist jij steeds de nodige orde en structuur te brengen. Jij stond altijd klaar om mij mee te ondersteunen bij het uitvoeren van de studie. Daarnaast zijn er natuurlijk ook al de fijne momenten tijdens het werk maar ook later buiten het werk. Bedankt voor alles!

Ik wil ook graag Peter de Boer, Maarten Timmers en Kurt Spittaels van Janssen Research en Development bedanken voor het mogelijk maken van dit project. Ik dank ook de mensen van de Clinical Pharmacological Unit te Merksem voor de deskundige technische en praktische ondersteuning bij het voeren van dit onderzoek.

Ik bedank ook de mensen van het UPC KU Leuven – prof. dr. Stephan Claes, dr. Tim Moons, prof. dr. Titia Hompes en Els Huyghe – die hebben meegeholpen aan het uitvoeren van dit onderzoek. Bedankt!

In dit onderzoek werd er ook een sociale stresstest uitgevoerd. Ik zou graag dr. Iris De Mulder, Kaen Enzlin, dr. Jasper Truyens en dr. Seline Van Den Ameele willen bedanken om telkens de tijd te maken om het kritisch publiek te spelen.

Ik wil ook graag mijn collega's van het CAPRI bedanken voor de fijne samenwerking. Ik dank dan onder andere aan Lise Docx, Javier de la Asunción, prof. dr. Marianne Destoop, prof. dr. Linda Van Diermen, dr. Seline Van Den Ameele, dr. Charel Quisenaerts, prof. dr. Cleo Crunelle, dr. Laura Cassiers, Nele De Witte, Ellen Sleuwaegen en Lieve Beheydt. Anke Temmerman, ik herinner me nog hoe ik een van de eerste dagen op het CAPRI aankwam en jou als eerste tegen het lijf liep. Jij gaf me onmiddellijk een welkom gevoel. Doorheen de jaren stond je steeds paraat om mee te denken over mijn onderzoek, of gewoon liefde, leven en werk te bespreken. Bedankt!

Ik zou graag Katrien Steurs, Kaen Enzlin en Famke Silis bedanken voor de uitstekende coördinatie van het onderzoek in het UPC Duffel. Bedankt ook aan Kristin Deby, om vanuit de Universiteit Antwerpen de praktische kant van dit doctoraat in goede banen te leiden. In het bijzonder wil ik ook Karo Vrints bedanken: jij stond altijd klaar voor praktische ondersteuning en coördinatie, maar vooral ook bedankt voor de prachtige cover die je voor dit boekje gemaakt hebt!

Ik heb ook het geluk om te mogen werken in een fijne psychiatergroep, die in mij gelooft en mij alle ruimte bood om dit project af te werken. Vicky Matthysen, Laura Santos Pina, Mirella Stuivenga, Annemie Vermassen, Sandra Geys, Isabelle Libbrecht, Oskar De Wachter en Robin Baeten: bedankt! Isabel Van Poeck, bedankt voor de fijne samenwerking en om mij alle ruimte te geven om dit af te werken. Ik kan me geen betere collega bedenken om mee samen te werken! Kirsten Catthoor, sinds ik in 2016 mijn eerste voet in Stuivenberg zette als assistent bij jou, heb jij gemiddeld minstens één keer per maand achter mijn doctoraat gevraagd, wat je bleef volhouden toen weinig andere mensen er nog achter vroegen. Bedankt voor alle aanmoediging, goede raad en geloof in mij!

Ik mag me eveneens gelukkig prijzen om te mogen samenwerken met zo'n leuk team als het team verslavingszorg in PZ Stuivenberg. Het is geweldig om te kunnen werken in een warm, zorgend en ondersteunend team dat een bron van steun is en dat me ook steeds de ruimte heeft geboden om dit project mogelijk te maken. Ik dank ook de andere teams waar ik in het verleden mee heb samengewerkt of deeltijds mee samenwerk voor de fijne ervaringen en ondersteuning (ik denk aan het psychologenteam van Jan Palfijn, het mobiel crisisteam, het team van ADIC, het team van EPSI en PAAZ van het vroegere ZNA Sint-Erasmus en mijn collega's bij de VVP). Bedankt voor alles!

Ik word ook omringd door een netwerk van familie en vrienden, waarop ik steeds kan tellen. Ik denk dan aan mijn nonkels, mijn nichten en neef, waarmee ik steeds over het werk, de geneeskunde en dit proefschrift kon praten. Ik heb ook een warme vriendenkring op wie ik steeds kan rekenen en die mij ondersteund hebben tijdens dit traject, ik denk onder andere maar niet alleen aan Ans, Dirk, Ann-Laure en Philip, die doorheen de afgelopen jaren

vaak hebben geluisterd naar mijn gedachten over dit proefschrift. Ook bedankt aan prof. Stephane Steurbaut om mij in de eindfase nog raad te geven over de verdediging. Katleen, van kindsbeen af was jij er ook altijd bij en heb jij ook altijd volledig in mij geloofd. Bedankt!

Jasper, ik weet dat als ik in de problemen zit, jij er altijd zal zijn met conventionele en minder conventionele oplossingen. Daarnaast heb je ook doorheen de jaren dat ik aan dit proefschrift werkte vele uren naar mijn twijfels en zorgen hierover geluisterd. Bedankt!

Kristin, doorheen onze studies geneeskunde en nadien ben jij altijd een vaste waarde geweest die steeds voor mij klaar stond en staat, en net zoals vele andere vrienden ook al vele uren empathisch hebt geluisterd naar mijn gedachten rond dit doctoraat, maar ook over het werk en het leven in het algemeen. Bedankt!

Mo, with you, I can always confide my doubts and worries, knowing you'll be there with unwavering support and belief in me. Our lengthy and often intellectual conversations have expanded my mind and shaped me into a better person over the years. I'm grateful to have someone like you in my life who will always belief in me. Thank you for everything!

Ik wil ook mijn zus Karolien bedanken, voor alle ondersteuning en vriendschap die ik niet alleen kreeg doorheen de periode dat ik dit proefschrift schreef, maar ook in ons hele leven. Ik wil ook mijn schoonbroer Andres bedanken voor alle ondersteuning en vriendschap. Tenslotte wil ik nog hun kinderen William en Samuel bedanken; zij konden dan nog niet inhoudelijk bijdragen tot deze thesis, maar hun liefde en warmte is onbetaalbaar. Bedankt voor alles!

Ten slotte wil ik nog mijn ouders bedanken. Dag na dag zie ik in mijn klinische praktijk wat het betekent om niet in een kansrijke omgeving op te groeien. Dag na dag groeit daarom ook het besef hoeveel geluk ik heb gehad geboren te zijn in een warm, liefdevol nest met liefhebbende en zorgende ouders die mij altijd hebben gestimuleerd en ondersteund, tot op de dag van vandaag en in de toekomst. Jullie boden me doorheen de jaren alle kansen om mezelf te ontplooien en moedigden me ook aan om deze kansen te grijpen. Ik kon mijn hele leven altijd bij jullie terecht voor hulp of raad met de nodige liefde en begrip. Dankzij jullie sta ik waar ik nu sta. Bedankt voor alles!