Rain with chances of a thunderstorm : on the role of anger in depression

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Chapter 1
General introduction

Depression

In the Netherlands, major depressive disorder (MDD) affects an estimated 15.4% of individuals during their lifetime (Bijl et al., 1998). This number is comparable with the reported lifetime prevalence of MDD in the United States, which is 16.2% (Kessler et al., 2003). The impact of depression on the individual and society is as big as that of common medical illnesses (Merikangas et al., 2007), making it an important target of research over the past decades. This research has resulted in extensive knowledge about the disease and how to treat it. However, this knowledge is still far from complete. For example, 50% of depressed patients react only partially or even not at all to antidepressant treatment (Souery et al., 2006). Moreover, about one third of depressed patients will in time become resistant to treatment (Fava and Davidson, 1996). One explanation for this hiatus may be that depression is a very heterogeneous disease. To be diagnosed with MDD, an individual has to fulfill five of the eleven criteria of a major depressive episode, as stated by the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV; American Psychiatric Association, 2001) (Table 1.) (The studies described in this thesis were all conducted before the introduction of DSM 5 in 2013).

Thus, theoretically, two patients can be diagnosed with MDD based on two entirely different symptom profiles. Identifying certain subtypes of MDD could contribute to differentiation and specification of treatment strategies, improving an individuals' likelihood of treatment-response and as such improving chances of remission (Wong and Licinio, 2001).

Subtypes of depression

At the end of the 19th century, Paul Julius Möbius further developed Morel's (1857; as cited in Mendels and Cochrane, 1968) theory of distinction between exogenous (caused by the environment) and endogenous (caused by heredity) psychiatric disorders (Möbius, 1893 as cited in Beer, 1996). This in turn inspired Kraepelin's dichotomization of endogenous depression (or 'manic-depressive psychosis') and exogenous or reactive depression (Kraepelin, 1913). In a review of seven studies that used factor analysis, Mendels and Cochrane (1968) confirmed the independence of endogenous and reactive factors, but proposed an alternative take on this dichotomy; the endogenous factor may represent a 'classical' depressive syndrome, whereas the reactive factor may reflect a (group of) psychiatric disorders where depression is only one of the symptoms (Mendels and Cochrane, 1968). In the early 70s of the 20th century, Akiskal and McKinney argued for the unification of these two types of depression, stating that depressive illness should be seen as the result of several processes that interact in brain areas associated with e.g. arousal, mood and motivation. These processes can be influenced genetically, developmentally, psychosocially, physiologically or by personality traits, eventually resulting in biochemical alterations, of which depression is one of the possible outcomes (Akiskal and

Table 1

DSM-IV criteria for Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

(1) *Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful).*

(2) *Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).*

(3) *Significant weight loss when not dieting or weight gain (e.g. a change of more than 5% of body weight in a month), or increase or decrease in appetite nearly every day.*

(4) *Insomnia or hypersomnia nearly every day.*

(5) *Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).*

(6) *Fatigue or loss of energy nearly every day.*

(7) *Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).*

(8) *Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).*

(9) *Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.*

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The symptoms are not due to the direct psychological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition.

Mckinney, 1973, 1975). Shortly thereafter, in 1980, the unitarian model of depression was recorded in the newest version of the DSM-III (American Psychiatric Association, 1980). Not only etiologically is the distinction between endogenous and exogenous depression untenable, another difficulty is the notion that depressive disorder is a highly recurrent disorder. The risk of recurrence of depression increases from 50% after one's first episode to 80% after 2 or more episodes (Kupfer et al., 1996, Post, 1992). This suggests that even though a depression may initially be initiated by adverse life events, therefore being classified as exogenous, its occurrence then increases the risk of recurrence without further life events, turning into endogenous depression.

Besides diagnostic criteria, the DSM-IV describes three levels of classification of MDE: first, the clinical status of the current (or in case of (partial) remission most recent) depressive episode is defined. Besides level of remission (current episode, partly remitted, or fully remitted), description of the clinical status includes severity (mild, moderate, or severe). Severe depression can be further classified by absence or presence of psychotic symptoms. A second level of definition used by the DSM-IV-TR is based on the course of the disorder (the 'chronicity specifier') or on specific symptoms (catatonic features, melancholic features, atypical features, and postpartum onset). The third classification of depressive episodes according to the DSM-IV-TR is based on the characteristics of recurring episodes (longitudinal course specifiers and seasonal pattern).

Thus, in the DSM-IV, a subtype of depression is based on behavioral and course characteristics of depressive episodes. Other factors that may influence course and treatment success of the disease like gene polymorphisms or biomarkers are not considered.

Depression and anger regulation problems

Anger regulation problems, ranging from irritability and hostility to verbal and/or physical aggression, e.g. in the form of anger attacks, have long been associated with depression. This recognition dates back as far as Kraepelin, who already recognized the occurrence of anger as a symptom of depression (Kraepelin, 1883). According to Kraepelin, when the inner tension that comes with depression can no longer be restrained, release will be found in an uncontrolled act of aggression. This act can be directed towards oneself, resulting in suicide. When the fear of dying is too great, however, release can be sought in an act of aggression directed at others, even resulting in murder. Freud also recognized the concept of anger in the context of depression. He saw anger as something that could not only be expressed outwards, but can also turn inwards, resulting in depression (Freud, 1917). More recently, Van Praag suggested that aggression is one of the core symptoms of depression caused by 5-HT disturbance, and mood lowering is only a secondary symptom (Van Praag, 1992). Moreover, studies by Fava et al. confirmed that 30 to 40% of depressed patients report anger attacks (Fava and Rosenbaum,

1998, 1999). Moreover, irritable mood is considered a core symptom of depression in children and adolescents (American Psychiatric Association, 2001). However, in adult patients with depression, it is not part of the diagnostic criteria, despite the fact that about 30-40% of adult patients report symptoms of irritability and anger (Fava et al., 2009, Fava and Rosenbaum, 1999, Perlis et al., 2009, Fava and Rosenbaum, 1998). Antidepressant medication has been used successfully to reduce these symptoms (Van Praag, 2001, Katz et al., 1987).

In the early 90s of the 20th century, Van Praag proposed a subtype of depression which he called 'Serotonin-related, anxiety/aggression-driven, stressor-precipitated depression' (Van Praag, 1996). The primary symptoms of this subtype were not sadness and anhedonia, but anxiety and aggression. Evidence for this subtype came mainly from association studies, for example from a study showing higher anxiety scores for depressed patients with lower concentrations of the metabolite 5-Hydroxyindoleacetic acid (5-HIAA) which indicates lowered serotonin (or 5-hydroxytryptamine – 5-HT) turnover (Van Praag, 1998). The theoretical background of this subtype however remained rather unclear. An undefined combination of biological and psychological predisposition or impairment results in susceptibility to stress which in turn can cause increased risk of anxiety and suppressed anger, eventually resulting in depression (Van Praag, 1998, 1996).

Fava et al. investigated the differences between depressed patients with and without anger attacks (Fava et al., 1997, Fava and Rosenbaum, 1999, Fava et al., 1993). Anger attacks were defined as: 'sudden spells of anger accompanied by symptoms of autonomic activation such as tachycardia, sweating, hot flashes, and tightness of the chest which resembles panic attacks but without the predominant affects of fear and anxiety' (Fava and Rosenbaum, 1998). Depressed patients with anger attacks were found to differ from depressed patients without anger attacks, for example in their clinical profiles. Specifically, depressed patients with anger attacks had higher levels of hostility and anxiety (Fava et al., 1993) and more comorbid axis II psychopathology (Tedlow et al., 1999) compared to depressed patients without anger attacks. Physiological differences were also observed between these patient groups, with depressed patients with anger attacks having higher cholesterol levels and an increased risk of cardiac dysfunction (Fraguas et al., 2007) compared to depressed patients without anger attacks.

A milder form of anger regulation problems in depression -irritability- was also found to be present in about 40% of depressed patients (Fava et al., 2009, Perlis et al., 2009). These irritable depressed patients reported an 'irritable, grouchy or […] bad mood almost every day during the worst two weeks of the index [depressive] episode' (Fava et al., 2009). Comparing depressed patients with and without irritability, those with irritability had a higher number of aggression-related axis II disorders (Fava et al., 2009), reported symptoms of dysthymia more often (Perlis et al., 2009), and had a greater prevalence of comorbid anxiety disorders (Fava et al., 2009, Perlis et al., 2009). Irritable depressed patients had also more often attempted suicide

(Perlis et al., 2009) than depressed patients who were not irritable during their depression. Based on the aforementioned studies, anger attacks and irritability might be characteristics to distinguish different types of depression from each other.

Factors contributing to depression & anger/aggression

Maladaptive behavioral patterns such as depression and aggression generally do not have one specific cause. Rather, numerous factors can contribute to the onset and relapse of depression and aggression, and some, if not all of them might interact. Literature on factors associated with depression and aggression is further discussed below.

Serotonin

An important aspect of depression is its association with 5-HT; more specifically, impairments of the 5-HT system have been found relatively consistently in depression (Maes and Meltzer, 1995). Animal models (Sanchez and Meier, 1997), post-mortem studies in suicide victims (Åsberg et al., 1976) as well as the beneficial effect of serotonin reuptake inhibitors (SSRI's) in large numbers of depressed patients (Trivedi et al., 2006, Willner et al., 2013) support this hypothesis.

The first studies to investigate 5-HT neurotransmission in depression experimentally included so-called 5-HT neuroendocrine challenge tests. An example of such a neuro-endocrine challenge test that was commonly used up to the late 1990s, included the administration of thyrotropin releasing hormone (TRH) or DL-fenfluramine hydrochloride (Jans et al., 2006). 5-HT inhibits the release of thyrotropin releasing hormone (TRH), a hormone that normally stimulates the release of prolactin. Fenfluramine is a 5-HT releasing agent and re-uptake inhibitor (Mcbride et al., 1990) which increases plasma prolactin in healthy volunteers (Cowen, 1993) through the activation of 5-HT2a/2c receptors. Compared to depressed patients without anger attacks, depressed patients with anger attacks showed blunted prolactin response to both TRH and fenfluramine (Fava et al., 2000, Rosenbaum et al., 1993), as well as an increased response to the selective serotonergic reuptake inhibitor (SSRI) fluoxetine (Rosenbaum et al., 1993). Another study with fluoxetine reports no significant differences in the improvement of depressive symptoms after fluoxetine intake between depressed patients with anger attacks and depressed patients without anger attacks (Fava et al., 1993).The only study to investigate the use of antidepressant medication as a treatment of anger attacks found that sertraline (an SSRI) and imipramine (a tricyclic antidepressant or TCA) were more effective than placebo in reducing the anger attacks in depressed patients (Fava et al., 1997).

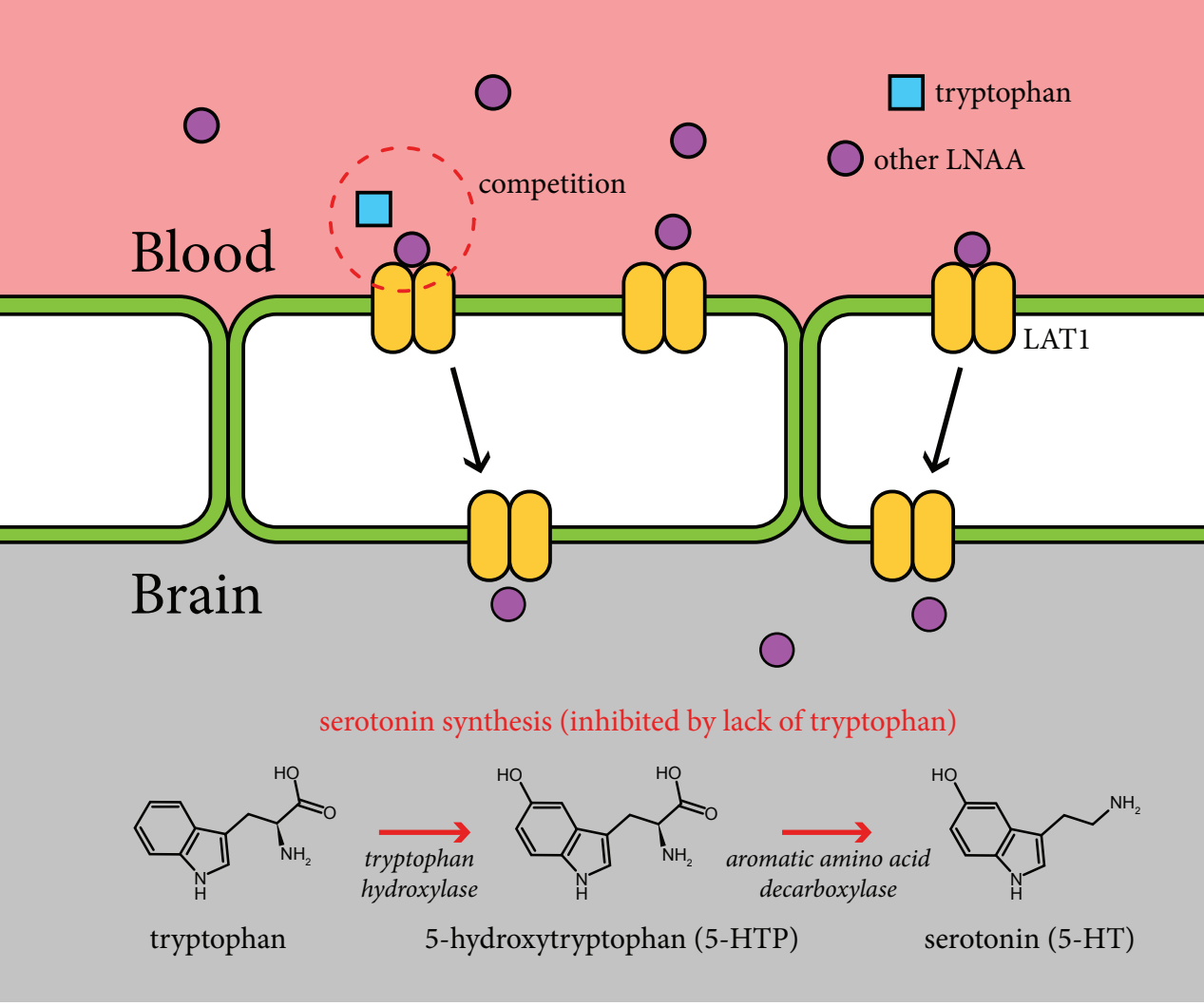

Figure 1. Acute Tryptophan Depletion (ATD)

Normally free tryptophan (Trp) is transported through the blood brain barrier (BBB), as are other large neutral amino acids (LNAAs), after which it is converted via 5-hydrxytryptophan (5-HTP) into serotonin (5-HT). ATD consists of LNAAs without the addition of Trp, resulting in increased competition at the BBB, resulting in less available free Trp in the brain and subsequently lower levels of 5-HT.

Acute tryptophan depletion

While the 5-HT hypothesis of depression in its original formulation postulated 5-HT impairments as the cause of depression, this hypothesis has been refined over the years (Booij et al., 2013). One specific procedure that has been used extensively to investigate the role of 5-HT in depression, and in fact contributed to the refinement of the 5-HT hypothesis of depression, is acute tryptophan depletion (ATD). This method temporarily lowers the precursor of 5-HT, the amino acid L-tryptophan (Trp) in the brain (Young et al., 1985, Van der Does, 2001) (Figure 1). Normally, Trp is taken up from the blood. Most of the Trp in the blood is protein-bound, but the 5% that is not is called free Trp which is transported across the blood-brain barrier, where it competes with five other large neutral amino acids (LNAA's: valine, leucine, isoleucine, phenylalanine and tyrosine) (Young et al., 1985). In the brain, Trp is converted into 5-HT. ATD in humans consists of the intake of a mixture of LNAA's. These LNAA's promote protein synthesis and compete with Trp at the blood-brain barrier, eventually causing decreased Trp levels in the brain, which in turn causes lowering of 5-HT synthesis. ATD therefore allows the investigation of the causal effects of lowered serotonin neurotransmission on human behavior in a controlled experimental design (Young et al., 1985).

Numerous studies have investigated the effects of this transient lowering of 5-HT on depressed mood. The first ATD studies in depression showed that remitted depressed patients using SSRIs have a greater increase in depressive symptoms in response to ATD than those using monoamine oxidase inhibitors or TCAs (Delgado et al., 1990, Delgado et al., 1999). Participants who were recovered and symptom-free (Smith et al., 1997) showed an increase in depressive symptoms in reaction to ATD relative to placebo, as did healthy individuals with an extensive family history of depression (Benkelfat et al., 1994). In currently depressed patients, no immediate effect of ATD on depressive symptoms was found (Delgado et al., 1994, Booij et al., 2005,). Moreover, in remitted/recovered depressed patients, a greater response to ATD has been associated with recurrent past episodes, female gender, history of suicidal ideation (Booij et al., 2002), certain genotypes of specific 5-HT genes (Neumeister et al., 2006) and impaired 5-HT2A receptor function (Yatham et al., 2012). These studies, in combination with other challenge studies in vulnerable populations (e.g. Bhagwagar et al., 2002) suggest that impaired 5-HT function in depression might be an indication of someone's vulnerability to depression rather than a direct cause of depression (Booij et al., 2003, Willner et al., 2013, Booij et al., 2013).

5-HT and aggression

In addition to vulnerability to depression, impaired 5-HTergic function has also been associated with a range of vulnerability to aggression-related behaviors, such as impulsive

and violent criminal behavior (Marsh et al., 2002), suicide attempts (Åsberg et al., 1976), physical aggression (Booij et al., 2010), and completed suicides (Träskman-Bendz and Mann, 2001). Cleare and Bond (1995) found increased anger, aggression, annoyance and hostility after ATD in healthy males with high trait aggression compared to healthy males with low trait aggression.

Antidepressant treatment and aggression

The Multidisciplinary Guideline for Depression (MDRL; Spijker et al., 2013) provides recommendations and instructions of operation for use in daily practice of mental health care for depression in adults. When the use of antidepressant medication is indicated, e.g. for moderate to severe depression and depression with melancholic or psychotic symptoms, the MDRL recommends the use of SSRIs for all outpatients. Anderson et al. (1998, 2000) showed that TCAs were only more effective compared to SSRIs in inpatients, which is however not necessarily related to depression severity (Anderson, 2000).

The SSRI fluoxetine has also been shown to reduce irritability and aggression scores in patients with personality disorder (Coccaro and Kavoussi, 1997). Together with recommendations from previous studies on anger regulation problems in depression (Van Praag, 2001, Katz et al., 1987, Fava et al., 1993, Rosenbaum et al., 1993) it seems for depression with anger regulation problems SSRIs may be preferable.

Figure 2 is based on the MDRL and shows the potential use of anger regulation problems in diagnostic decisions for treatment of depression. In line with the 'profiling' concept to identify characteristics that influence the course of depression and/or treatment outcome, anger regulation problems may have a place in diagnostic and treatment related decisions.

Cognition

In addition to depressed mood, and symptoms of irritability, anger and/or aggression in some subgroups of depressed patients, cognitive impairments often occur in depression. Concentration and memory problems are part of the diagnostic criteria of MDD (DSM-IV; American Psychiatric Association, 2001). Moreover, it has been shown that depressed patients show a bias towards negative information in various emotion processing tasks (Gur et al., 1992, Burt et al., 1995, Bouhuys et al., 1999, Elliott et al., 2011, Gotlib and Mccann, 1984, Gollan et al., 2008, Mikhailova et al., 1996, Segal et al., 1995, Surguladze et al., 2004). This bias might persist after remission from depression (Bhagwagar et al., 2004, de Raedt and Koster, 2010, Hayward et al., 2005, Joormann and Gotlib, 2007). Merens et al. (2008b) found some persisting bias for emotional stimuli such as fearful faces in a sample of remitted depressed

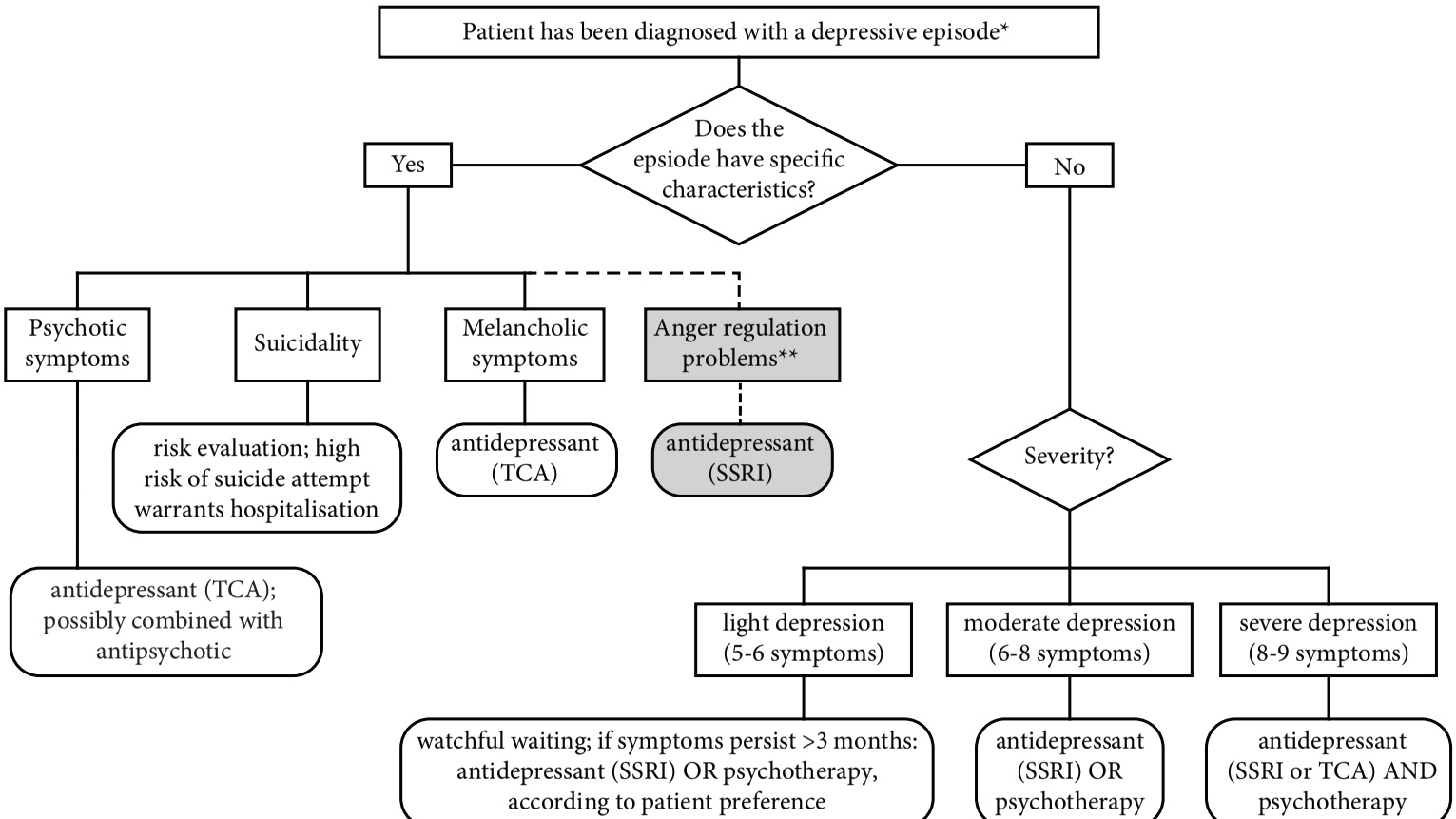

Figure 2. The potential place of anger regulation problems in diagnostic decision making in depression.
(based on the Multidisciplinary Guideline for Depression; Spijker et al., 2013)
TCA: Tricyclic antidepressant; SSRI: selective serotonin reuptake inhibitor

patients. However, their study suggests that most biases found during the depression may have become latent after remission, and will only be activated after being triggered, for example by ATD. Studies using this technique found evidence for a causal role of 5-HT in these emotional biases in both healthy volunteers (Munafò et al., 2006, Elliott et al., 2011) and remitted/recovered depressed patients (Hayward et al., 2005, Booij et al., 2005, Merens et al., 2008a).

Depressed patients often have dysfunctional cognitive schemas (Beck, 1967), with thoughts such as 'People will probably think less of me if I make a mistake' (Weissman, 1980, Weissman and Beck, 1978). These so-called dysfunctional attitudes merely become inactive instead of actually disappearing during remission (Teasdale, 1988). The ease, with which these latent dysfunctional schemas are reactivated in response to sad mood, is called cognitive reactivity (Segal et al., 1999). Several studies have shown that remitted depressed patients have significantly higher cognitive reactivity levels than never-depressed healthy individuals (Miranda and Persons, 1988, Van Der Does, 2002, de Raedt and Koster, 2010). High levels of cognitive reactivity predicted relapse to depression within four years after treatment (Segal et al., 1999). Moreover, in remitted depressed patients, a greater mood response to ATD was associated with greater cognitive reactivity (Booij and Van Der Does, 2007), thereby showing a possible link between cognitive and 5-HT vulnerability.

Psychophysiology

Several changes in neuroendocrine measures have been associated with depression and aggression/anger. For example, increases in testosterone and cortisol have been associated with aggression (Harris, 1999, Van Bokhoven et al., 2005). Anger problems in MDD have also been associated with increased cortisol levels (Van Praag, 2002, Van Praag, 1996a). Moreover, increased testosterone has frequently been linked to anger and aggression regulation (Persky et al., 1971, Van Honk et al., 1999, Archer, 2006, Mehta and Beer, 2009).

Both cortisol and testosterone have been shown to interact intensively with the 5-HT system (Cowen, 2002, Strickland et al., 2002, Way and Taylor, 2010, Kuepper et al., 2010, Montoya et al., 2012). On the other hand, diminished testosterone levels have been found in female depressed patients (Giltay et al., 2012). Moreover, patients using SSRIs had higher levels of testosterone than those not using SSRIs (Giltay et al., 2012). Administration of testosterone has been suggested to have antidepressant effects in some patients such as older depressed males (Zarrouf et al., 2009). However, randomized controlled trials are lacking.

Depressed patients are more vulnerable to cardiovascular disease (CVD) than non-depressed individuals (Joynt et al., 2003). Lowered heart rate variability (HRV) has been identified as a

possible risk factor for CVD and several studies did find lowered HRV in depressed patients (Agelink et al., 2002, Rechlin et al., 1994). Moreover, in a study which compared remitted depressed patients who reported suicidal ideation during their depression with remitted depressed patients without previous suicidal ideation, Booij et al. (2006) found that ATD significantly lowered HRV in remitted depressed with previous suicidality but not in those without. This suggests that depressed patients with previous suicidal ideation may have an increased risk of CVD which is possibly associated with increased 5-HTergic vulnerability (Booij et al., 2006).

Another CVD risk factor associated with depression, suicide and aggression is cholesterol levels. Lowered serum cholesterol was found for MDD patients compared to healthy controls (Olusi and Fido, 1996, Lehto et al., 2008, Steegmans et al., 2000, Shin et al., 2008) as well as in suicide attempters compared to nonsuicidal psychiatric patients (Kunugi et al., 1997, Troisi, 2009). A study by Buydens-Branchey et al. (2000) suggested that the link they found between lowered cholesterol and poor impulse-control and aggression may be associated with alterations in 5-HT function.

In sum, several neuroendocrine and psychophysiological indices are associated with depression and aggression, and all of those measures have to some extent been associated with 5-HTergic functioning.

Heritability

Depression is known to occur more frequently in individuals with a family history of depression (Kendler et al., 1997, Sullivan et al., 1996, Sullivan et al., 2000) compared to those without a family history of depression. Comparing monozygotic and dizygotic twins and adoption studies have enabled us to disentangle the role of genetic and environmental influences on the development of psychopathology. Several longitudinal twin studies have found moderate heritability rates of depression of 42% in women and 29% in men (Kendler et al., 2006, Kendler et al., 2001, Bierut et al., 1999, Jansson et al., 2004).

Candidate gene studies have been done in an attempt to identify specific genes involved in depression. Many of these are linked to the 5-HT system, although many other genes of other biological systems have been identified, and all of them might interact (Lesch, 2004). Below is a description of the most commonly studied candidate genes in the context of depression, aggression and suicidality.

5-HT transporter gene (SLC6A4)

Probably the most widely investigated polymorphism in psychiatry is the 5-HT transporter (5-HTT) linked polymorphic region (5-HTTLPR) of the SLC6A4 gene (Risch et al., 2009, Lesch, 2004) and its association with depression. Function of SLC6A4, involved in 5-HT uptake in the brain, is known to be altered in several disorders e.g. depression, as well as bipolar disorder and schizophrenia (Heils et al., 1996). SLC6A4 is also a prime target for antidepressant action (Heils et al., 1996). The most commonly investigated polymorphism of the 5-HT transporter, 5-HTTLPR, has two variants. The short allele (s) variant results in reduced transcriptional efficiency compared to the long allele (l). More recently, another polymorphism (rs25531) has been described (Wendland et al., 2006). This G allele in the l variant of the polymorphism is functionally similar to the s allele, with lower 5-HTT mRNA expression (Hu et al., 2006). Carriers of at least one s allele have a higher risk of depression and increased anxiety-related traits (Lesch et al., 1996a) compared to homozygote long allele carriers (ll). Comparing depressed and non-depressed women, Gonda et al. (2011) found an association between the s allele and aggression/hostility, which was even more marked in the presence of depression. One psychological concept extensively studied in relation to depression is neuroticism: the tendency to more easily experience negative emotions, including feelings of depression, anxiety and anger (Matthews et al., 2003). Lesch et al. found increased levels of anxiety associated with the s allele (Lesch et al., 1996b). In another study in healthy women, the s allele was associated with traits and characteristics related to the concept of neuroticism, e.g. anxiety, depression, hopelessness and hostility (Gonda et al., 2009).

However, the findings are not consistent. As Levinson (2006) already pointed out, the positive associations between depression and 5-HTTLPR found by previous studies are mostly small and indirect. The meta-analysis by Karg et al. (2011) found evidence of increased stress sensitivity in association with the s allele of the 5-HTTLPR polymorphism, whereas two meta-analyses by Munafò et al. (2009) and Risch et al. (2009) found no such association. The inconsistency between these studies may partly be explained by methodological differences between studies used in these meta-analyses (Uher et al., 2010).

5-HT1A receptor gene

The 5-HT1A receptor is a 5-HTergic autoreceptor in the raphe; it is also expressed post-synaptically in other brain-regions. It is involved in the regulation of 5-HT transmission by reduction of firing rate through negative feedback; one relatively common variant (Wu and Comings, 1999) of this receptor (C-1019G) has been shown to lead to a decrease in 5-HT transmission (Lemonde et al., 2003, Neumeister et al., 2004) and has been linked to major depression and suicide to (Lemonde et al., 2003, Kishi et al., 2013). Although the observation of the relationship between the G-allele of the 5- HT1A C(-1019G) gene and MDD has been

replicated (e.g. Albert et al., 2011), findings have not been entirely consistent (e.g. Arias et al., 2002), as is the case for all other candidate gene studies in MDD.

Tryptophan hydroxylase

Tryptophan hydroxylase (TPH) is a rate-limiting enzyme which is critical for the biosynthesis of 5-HT – converting the amino acid Trp to 5-hydroxytryptophan (5-HT) which in turn is decarboxylated into 5-HT (Bondy et al., 2006). Two forms of TPH exist; TPH1 is found mainly peripherally, whereas another variant (now called TPH2) is found only in the brain (Zhang et al., 2004). One study showed that genotypic variation in several TPH2 polymorphisms in humans predicted individual variation in brain serotonin synthesis in frontal limbic regions vivo, using Positron Emission Tomography (Booij et al., 2012), supporting the relevance of this gene for controlling brain 5-HT synthesis in humans in brain regions involved in emotion regulation.

The TPH1 gene has two common polymorphisms in intron 7 consisting of an A to C substitution at nucleotides 779 (A779C) and at 218 (A218C) which are in tight, but not complete, linkage disequilibrium. Literature on the association between variation in the TPH1 gene and depression or aggression/suicidality is inconsistent (Lalovic and Turecki, 2002, Bellivier et al., 2004).

Since TPH2 is expressed only in the brain, the TPH2 gene (located on chromosome 12q15) is arguably a more promising candidate gene to investigate the association between TPH and suicidality, aggression and depression (Bondy et al., 2006). Variations in TPH2 polymorphisms have previously been associated with MDD, suicide, anxiety and hyperactivity (Booij et al., 2012). Moreover, TPH2 haplotype linkage to anxiety/depression phenotypes and suicide attempts bas been identified in 2 different populations (Zhou et al., 2005, Zill et al., 2004). However, many inconsistencies in the literature still occur.

MAOA gene

The MAOA gene was associated with aggression in the early 2000s in the Dunedin study (Silva and Stanton, 1996, Arseneault et al., 2000, Caspi et al., 2003) and has since been identified as the 'warrior gene' in popular media. The monoamine oxidase A (MAOA) gene has been studied mainly in association with aggression. MAOA is an enzyme essential for the degradation of monoamines in the central nervous system (Oreland, 1991). The MAOA gene is located on the X chromosome (Xp11.23-11.4) and one of the most investigated variations is that of a variable number of tandem repeats (VNTR). Alleles with 3.5 or 4 copies lead to

2-10 times more efficient transcriptional activity (indicating high expression; MAOA-H) than alleles with 3 copies (low expression; MAOA-L) (Sabol et al., 1998).

The MAOA enzyme has both been linked to aggression and to the development and pharmacological treatment of depression (Aklillu et al., 2009, Pare, 1985). Recently, variations in other polymorphisms than the VNTR were also found to be related to levels of anger expressed outwards by male and female suicidal patients (Antypa et al., 2012) (63.7% of which were patients with affective disorder).

Gene by environment interaction

Although the examples given indicate that variants of certain polymorphisms may predispose to depression and aggression, the putative vulnerability of carrying a certain variant may especially be expressed in the presence of adverse events, e.g. childhood maltreatment or stressful life events.

For example, the association between stressful life events and depression was stronger in carriers of at least one s allele of the 5-HTTLPR compared to ll homozygotes (Caspi et al., 2003). Null findings have also been reported, although a meta-analysis confirmed this association (Karg et al., 2011), and some of the non-significant studies appear to be attributed to less rigorous methodology.

Childhood maltreatment can result in symptoms of depression as well as antisocial behavior later in life; however, MAOA-H carriers seem less likely to develop antisocial behavior after childhood maltreatment than MAOA-L carriers (Caspi et al., 2002). Little is known about gene by environment interactions of other commonly studied 5-HT genes associated with depression.

Research aims & outline of this thesis

This thesis investigates the significance of anger regulation problems in the context of depression. Both depression and aggression have been studied extensively, but although 30-40% of depressed patients may have aggression problems, reports on the significance and implications of their co-occurrence are limited. Aggression as well as depression have been associated with some similar biological mechanisms (5-HT, genetic, neuroendocrine, and psychophysiological). This thesis may shed some light on the extent to which the presence of anger regulation problems represents a putative subtype of depression, possibly guiding treatment preferences as well.

In Chapter 2, we compare currently depressed patients reporting irritability to those not reporting irritability in terms of clinical and demographic characteristics. For this comparison, we use data from the Netherlands Study of Depression and Anxiety (NESDA), from which we selected the 913 participants who met the criteria for major depression, minor depression, or dysthymia during the month prior to study admission. We compare those with and without irritability on clinical features, psychological characteristics and physiological measures.

Heritability appears to contribute to the development of psychopathology, and heritability of both depression and aggression has been studied extensively. However, little is known on the heritability of aggression regulation problems in the context of depression. The aim of Chapter 3 is to investigate a possible genetic mechanism for the occurrence of aggression in the context of depression. To investigate this, we specifically focus on the association between monoamine oxidase A (MAOA) genotypic variation and aggression, especially in well-documented interaction with childhood trauma (Caspi et al., 2002, Kim-Cohen et al., 2006, Haberstick et al., 2005). To investigate the role of the MAOA gene in aggression in the context of depression, we test whether the low expression variant is associated with trait and state measures of anger and measures of aggression including cognitive reactivity to sad mood.

Since both depression and aggression have repeatedly been associated with lower 5-HT neurotransmission, our next step is to investigate 5-HTergic vulnerability in aggression in the context of depression. Specifically, given the association with lower 5-HT neurotransmission, we investigat whether patients with depression and aggression problems have more impairment in the 5-HT system compared to patients without aggression during depression using ATD. Chapters 4 and 5 discusses the results of this experimental study we conducted, where remitted depressed patients with (MDD+A) and without (MDD-A) anger problems during their depression participated in an acute tryptophan depletion (ATD) study. In Chapter 4, we examine differences in depressive symptom reactivity in response to ATD between remitted depressed patients with (MDD+A) and without (MDD-A) anger regulation problems during their depression. We also investigate testosterone and cortisol responses, two hormones implicated in both in depression as well as aggression. In Chapter 5, we investigate differences in cognition between the MDD+A and MDD-A group; more specifically, we investigate whether depression with anger regulation problems is associated with increased impulsivity compared to depression without anger regulation problems. Moreover, we investigate differences in recognition of and reaction to emotional faces.

A summary of chapters 2-5 and a General Discussion of the studies in this thesis are given in Chapter 6.

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