Consumed by a forbidden emotion: anger and aggression in patients with psychiatric disorders

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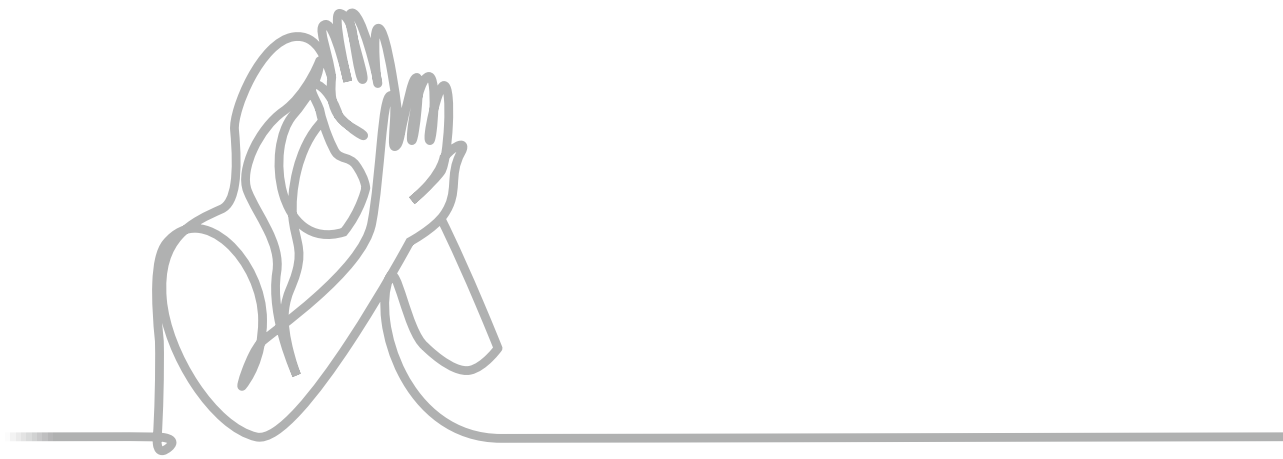
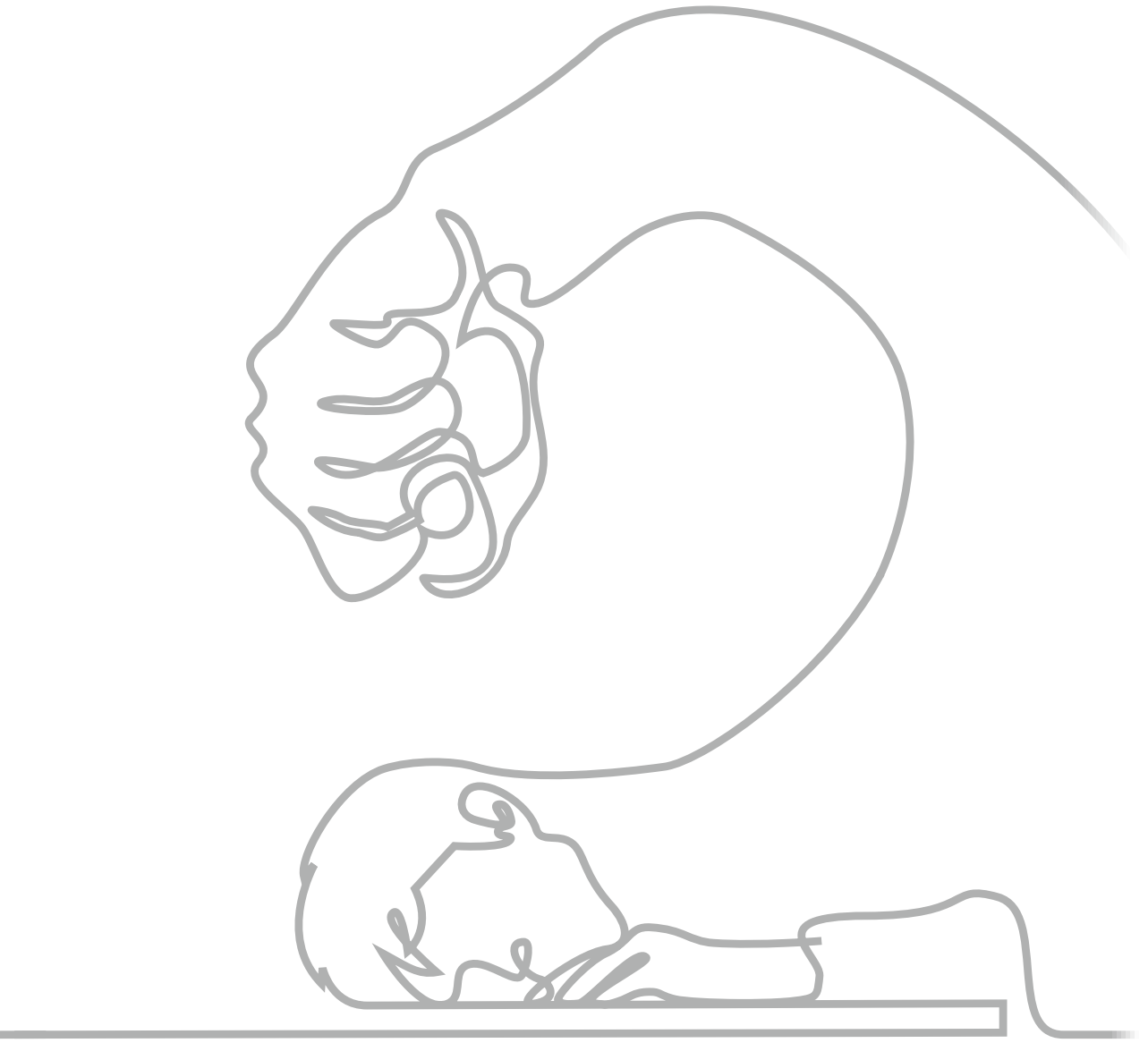


1 General introduction and outline of the thesis



Background

> *Anybody can become angry, that is easy; but to be angry with the right person, and to the right degree, and at the right time, for the right purpose, and in the right way, that is not within everybody's power and is not easy.*
>
> – Aristotle (384 BC – 322 BC)

Emotions are a universal part of the human condition. Like sadness and fear, anger is one of the negative emotions and is experienced regularly across cultures. When someone becomes angry, it is easy to recognize the emotion: frowning eyebrows, protruding nostrils, pursed lips. In appropriate (and usually mild) forms, anger has teleologic (evolutionary) advantages, as it ensures that we can set our boundaries and protect ourselves or loved ones in threatening situations. More accurately stated, in our evolutionary ancestry, this defence mechanism may have generated reproductive advantages for our genes, resulting in more replications of the multiple genes that determine the many facets of anger. However, anger becomes problematic if it occurs regularly or is very intense, especially in our current 'civilized' societies, where it is related to numerous negative (health) outcomes and poorer quality of life [1-4]. Although not always, anger can also trigger aggression and violent behaviour [5], including self-directed violence [6]. Despite these substantial effects of anger on individuals, relatives, and society, anger has long been overlooked in both research and clinical practice.

Anger

Since ancient times philosophers like Aristotle, Marcus Aurelius, and Nietzsche have pondered the definition of anger. One of the first modern definitions of anger was given by Spielberger,[7] and was described as follows:

> 'Anger is an emotional state that comprises feelings that vary in intensity from mild annoyance and aggravation to fury and rage, and that is accompanied by arousal of the autonomic nervous system'.

Although important aspects of anger are covered, the definition also has some limitations. First, it is limited to subjective feelings, and does not include cognitive or

behavioural components. Second, the definition states that annoyance and rage are synonyms of anger, rather than other related concepts. Third, it is a mere descriptive definition that does not encompass the purpose or goals of the emotional state. Consequently, Kennedy [8] described anger as:

> 'An affective state experienced as the motivation to act in ways that warn, intimidate, or attack those who are perceived as challenging or threatening. Anger is coupled to and is inseparable from a sensitivity to the perception of challenges or a heightened awareness of threats (irritability). This affective motivation and sensitivity can be experienced even if no external action occurs'.

An important aspect of Kennedy's definition is that it includes the motivational aspect of anger. More recently, these and other existing definitions have been integrated in the following broader definition:

> 'Anger is a subjectively experienced emotional state with high sympathetic autonomic arousal. It is initially elicited by a perception of a threat (to one's physical well-being, property, present or future resources, self-image, social status or projected image to one's group, maintenance of social rules that regulate daily life, or comfort), although it may persist even after the threat has passed. Anger is associated with attributional, informational, and evaluative cognitions that emphasize the misdeeds of others and motivate a response of antagonism to thwart, drive off, retaliate against, or attack the source of the perceived threat. Anger is communicated through facial or postural gestures or vocal inflections, aversive verbalizations, and aggressive behaviour. One's choice of strategies to communicate anger varies with social roles, learning history, and environmental contingencies' [9].

Yet, these given definitions are all characterized by their focus on anger as a state. However, Spielberger [7] stresses the importance of the distinction between states and traits of emotions. State anger is defined as an emotional–physiological condition that occurs in response to an immediate stressor or threat. If severe, such a state can develop into an anger attack: sudden spells of anger accompanied by symptoms of autonomic activation such as tachycardia, sweating, hot flashes, or tightness of the chest [10]. Trait anger, on the other hand, refers to individual differences in anger proneness as a personality trait. Trait anger is related to state anger as it is assumed

that high trait anger individuals experience more frequent state anger [7, 11]. Another important distinction that is often made, is between the experience and the expression of anger. Making a distinction between individuals who are often feeling angry but never express these feelings, and individuals who are expressing anger every time they are feeling angry is of clinical importance. The same is true for individuals with an angry disposition as a constant factor embedded in personality, and individuals who respond angrily to an immediate situation. In conclusion, the definition of anger and related concepts remains subject to semantic discussion; definitions differ. To identify individuals most prone to anger, it is important to be aware of what is and what is not considered anger.

Aggression

Aggression is a behaviour that ranges from mild acts, such as swearing, to more severe acts, such as physical assaults [12, 13]. Although aggression shows a robust relationship with anger, they serve as distinct outcomes of interest, as anger does not always lead to aggression, nor is aggression necessarily motivated by anger [14]. Due to the variety of forms and contexts, it is not always clear to define what is, and what is not aggression. Aggression has been defined as:

> 'Any behaviour directed toward another individual that is carried out with the proximate (immediate) intent to cause harm. In addition, the perpetrator must believe that the behaviour will harm the target, and that the target is motivated to avoid the behaviour' [15].

This operational definition comprises four characteristics of aggression that need nuancing. First, aggression relates to behaviour, and does not include an emotion or cognition. Second, aggression is intentional, though sometimes unconscious. Third, aggressive behaviour comprises another individual, meaning that aggression towards objects does not fall under the definition unless it is intended to harm another individual. And last, the target is motivated to avoid the behaviour. The latter characteristic excludes suicide-related behaviour from the realm of aggression, which could be relevant in the context of monitoring aggression amongst psychiatric patients. The necessity of intention to commit aggressive behaviour is still subject to debate [16]. Unintentional aggression is especially common among psychiatric patients, as aggressive acts could be a consequence of a psychotic state. Therefore, several measures of

aggression, such as the Staff Observation Aggression Scale – Revised (SOAS-R) monitor a broader range of aggressive behaviours, including self-mutilation and aggressive acts in the context of a psychosis. The underlying definition for the SOAS-R described aggression as 'any verbal, non-verbal or physical behaviour that was threatening or physical behaviour that actually did harm (to self, others or property)' [17].

Anger and aggression among psychiatric patients

Currently, there is only one disorder described in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) with a primary focus on anger and aggression among adults, which is the Intermittent Explosive Disorder (IED) [18]. However, anger and related concepts such as irritability are mentioned as a diagnostic criterion for some other disorders, including Post-Traumatic Stress Disorder (PTSD) and Borderline Personality Disorder (BPD). Nevertheless, even without anger or aggression being mentioned as a diagnostic criterion, it is suggested that pathological anger is common across different psychiatric disorders [19]. Research has shown that half of psychiatric outpatients reported moderate to severe anger [20]. Furthermore, aggression is highly prevalent among psychiatric inpatients, as aggressive behaviour regularly was the triggering event that led to a referral to inpatient care. Thus, anger and aggression play a prominent role beyond anger-related disorders as mentioned by the DSM-5, and could have a substantial influence on the development and treatment of psychiatric disorders [19]. However, despite its presumed meaningfulness, anger is often described as "forgotten emotion", as it is much less studied in the literature compared to emotions such as sadness (depression), fear (anxiety), and even happiness (mania). The term "psychiatry" in combination with "depression" (141,661 results), "anxiety" (68,366 results), or "mania" (7,179 results) revealed much more results compared to "psychiatry AND anger" (4,251 results) on PubMed. These findings might reflect the forbidden aspect of anger, as there is a strong social disapproval of being angry. The expression of anger might lead to harmful events, including events which are prohibited by law, leading to a tendency to suppress the feeling of being angry in a social context. Given the dearth of knowledge with respect to anger in research literature, which has led to a scarcity of anger instruments, and psychological and pharmacological treatment options, there is a serious need to identify individuals most prone to anger and to establish the mechanisms by which anger presents itself, to better initiate effective treatment.

Affective disorders

Strong relationships were found between anger on the one hand, and a range of mood and anxiety disorders on the other hand - even after adjusting for demographics and comorbidity [21-23]. Originally, psychoanalysts like Abraham [24] and Freud (1917) presumed depression to be a result of anger turned inward. In their view, excess anger towards the self may cause feelings of guilt, worthlessness and self-criticism [25]. More recently, another theory assumed that failure to handle anger potentially leads to helplessness, with a depressive disorder as a potential consequence [9]. As both hypotheses assume a prominent role of anger in the onset and course of depression, it is of importance to identify individuals most prone to high levels of anger. Previous studies have shown high levels of irritability among almost half of patients with major depressive disorder (MDD) [26, 27]. Also, elevated levels of hostility, anger, and difficulties with anger expression are often reported in depressed patients [28-31]. The prevalence of anger attacks ranged from 26% to 49% in individuals with MDD [32-38], and from 28% to 53% in patients with dysthymia [2, 38]. Furthermore, two longitudinal studies reported a three times increased risk of violent offending in individuals with depression compared to the general population [39].

Likewise, anger is common across anxiety disorders, with anger attacks being reported by one-third of the patients [40]. However, different patterns of anger experience and anger expression have been suggested for each of the different anxiety disorders [22]. Generalized Anxiety Disorder (GAD) is the only anxiety disorder for which an anger related concept, namely irritability, is mentioned as a diagnostic criterion in the DSM-5 [41]. Indeed, multiple dimensions of anger, including aggressive behaviour, were shown to be related to GAD [20, 22, 42, 43]. Similarly, patients suffering from panic disorder (PD) reported significantly elevated levels of anger compared to controls [22, 44]. Also, patients with obsessive compulsive disorder (OCD) have shown difficulties with the expression of anger, among which anger attacks and anger toward the self [45, 46]. In contrast, although the experience of anger was also elevated among patients with social phobia (SP), these patients were more likely to suppress their anger, resulting in a low prevalence of verbal aggression and anger attacks [22, 40, 43, 44]. Thus, anger and aggression among patients with anxiety disorders seems disorder dependent, which makes it important to study the strength of the relationship with anger separately according to the specific diagnosis.

Bipolar Disorder (BD), which is characterized by both manic and depressive episodes, was found to be most robustly correlated with symptoms of anger compared to depressive- and anxiety disorders [43]. Evidence suggests that the relationship

between anger and BD was largely independent from the mood (i.e., manic or depressive) episodes, and anger was also found to be common during prodromal phases [47]. Furthermore, anger attacks were reported twice as often (62%) among depressed bipolar patients compared to unipolar depressed counterparts (26%) [33]. Prevalence rates of anger attacks did not differ between bipolar I versus bipolar II subtypes [48], which was in line with a longitudinal study that reported higher scores on self-reported anger and aggression among individuals with either bipolar I or bipolar II disorder compared to nonbipolar psychiatric controls and healthy controls across 4-year follow-up [49]. Aggression among patients with BD comprises mainly impulsive aggression and occurs during the manic phase [50, 51].

Personality disorders

Personality disorders are characterized as enduring, cognitive, behavioural, or emotional disturbances in more than one domain of function. The development of personality disorders is a complex interaction between genes and environmental factors, including childhood trauma [52]. Core dimensions in – especially cluster B – personality include affective instability and impulsive aggression amongst others. Personality disorders were found to be associated with elevated levels of subjective anger and a threefold increase in the odds of aggressive behaviour compared with the general population, with cluster B personality disorders (i.e., antisocial, borderline, histrionic, and narcissistic personality disorder) making a unique contribution to these outcomes [20, 23, 53]. This is particularly the case for Borderline Personality Disorder (BPD), being one of the few disorders for which intense anger or difficulty controlling anger, and emotional instability including irritability is listed as a diagnostic DSM-5 criterion [41]. In addition, being easily provoked or aggressive is a diagnostic criterion for Antisocial Personality Disorder (ASPD) [41]. Therefore, existing literature regarding anger and aggression among personality disorders most often refers to BPD and ASPD. These studies found higher scores on trait anger, state anger, and lifetime aggression, including against themselves, among patients with BPD compared to controls [54-56]. Among inpatients diagnosed with BPD anger was reported by almost 90% [57], and 73% engaged in violence over the course of one year [58]. These high percentages could be explained by comorbid ASPD amongst others [58, 59]. Consistently, individuals diagnosed with ASPD had an almost thirteenfold increase in violent outcomes compared to the general population [53]. Despite the high prevalence of anger and aggression, evidence for the efficacy of psychotherapy [60, 61] and psychopharmacology [62, 63] among personality disorders is limited.

Schizophrenia spectrum disorders

Schizophrenia and related psychoses have also been associated with aggression, although the mechanisms through which people with a psychotic illness progress to actual acts of violence has been understudied [64, 65]. It is suggested that the direct relationship between the experience of anger and aggressive behaviour which is often seen in the general population is different in the context of psychotic illness. Among the latter, the experience and expression of anger and aggression could be a product of paranoid delusions and perceptual distortions [65, 66]. This was in line with studies that found heightened levels of trait anger to be associated with delusional pathology, paranoia, and impulsivity among individuals with schizophrenia [67, 68]. Among inpatients with psychotic illness, angry feelings were particularly problematic, as they were related to self-harming behaviours and attentional demands towards the staff [69]. Furthermore, aggressive behaviours were found among approximately one third of the people with schizophrenia worldwide [70], with the risk of aggression being 51.5% among inpatients versus 15.2% among schizophrenic outpatients [71]. These aggressive behaviours are related to numerous negative outcomes for patients themselves, including coercion and involuntary hospitalization [72]. In addition, involuntary patients have been found to be more aggressive during hospitalization, which may lead to distress and may be traumatic for other patients and staff [13, 73]. Aggression reduction already has a high priority in psychiatric inpatient care (e.g., de-escalating programs, adequate pharmacotherapy), but more effective and innovative methods to prevent aggression are needed [74].

Substance use disorders

Individuals with psychiatric disorders often have cooccurring substance use disorders (SUDs) and vice versa [75]. SUDs have been shows to be associated with elevated anger [43], including state and trait anger and difficulties controlling anger [76-78], leading to aggressive behaviour. Aggressive behaviour was observed either as a direct result of the substance consumed, or during substance withdrawal. Aggression might be a result of disinhibitory effects of alcohol intoxication [79], while on the contrary, cannabis intoxication might reduce aggression in the first place, but increases during withdrawal [80, 81]. A meta-analysis showed that the risk of aggressive behaviour among patients with schizophrenia spectrum disorders with substance abuse is similar to that for patients with substance abuse without psychosis [64]. In sum, it could be hypothesized that elevated anger and aggression among psychiatric patients could be explained by

(comorbid) SUDs rather than the mental illness itself, which might be of interest for aggression reduction strategies.

Neurobiological correlates of anger and aggression

From the reviewed literature, anger and aggression seem prevalent among diverse psychiatric patients. Yet, it does not apply to all psychiatric patients. Therefore, to develop effective interventions for those who are at risk, it is also important to better understand the underlying neurobiological processes, besides the social, psychological, and psychiatric causes, underlying both anger and aggression. One of these suggested approaches that could be of transdiagnostic relevance comprises the identification of biological markers. However, one must notice that mental disorders might not be explained by monocausal frameworks, but rather by a network approach point of view, where symptoms may cohere as syndromes because of mutually reinforcing symptoms [82].

Serotonin

One of the best-studied neurotransmitters related to aggression is 5-hydroxytryptamine (5-HT), commonly known as serotonin. Extensive research showed that serotonin seems to be inversely related to aggression [83]. Selective serotonin reuptake inhibitors (SSRI) including fluoxetine have shown anti-aggressive effects in randomised trials among psychiatric patients [84-86]. There are also indications that the deprivation of the amino acid tryptophan, the dietary precursor of serotonin, can induce aggressiveness, although effects are small [83]. In addition, the serotonergic system seems to be involved in brain regions including the amygdala and prefrontal regions, specifically when processing angry faces [87-89]. In sum, evidence leads to the hypothesis that serotonin does not act as a unitary system but rather is involved in complex parallel circuits.

Hypothalamic–pituitary–adrenal (HPA)-axis

The contributing role of the hypothalamic-pituitary-adrenal (HPA)-axis is another focus of research in unravelling aggressive behaviour. The HPA-axis is central in stress-regulating mechanisms and is often assessed using measures of its most important end-product cortisol. Cortisol only has an effect after binding to one of two related transcription factors: the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR). Whereas MR is important in maintaining basal conditions, GR plays an

important role in the stress response via a negative feedback loop regulating HPA-axis activity. Severe stress in early life could induce long-lasting alterations of the HPA axis [90]. For example, a decrease of GR activation was seen after lower maternal care, leading to hypoactivity of the HPA-axis due to an impaired feedback loop [91]. It has been hypothesized that a heightened HPA axis response to stress might be linked to reactive aggression [92]. As a result of the latter, individuals with decreased basal levels of cortisol may be more sensitive to provocation and react more aggressively compared to others [93].

Immune system

In the past few decades, an important link has been found between the immune system, cytokines, and aggression [16, 94]. The immune system is composed of innate and adaptive immune responses, with the intracellular parasite *Toxoplasma gondii (T. gondii)* provoking one of the most potent pro-inflammatory responses [95]. Inflammatory cytokine levels might contribute to sickness behaviour and other psychological effects, including irritability and aggression [94, 96, 97]. Elevated inflammatory cytokine levels including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) have been found to be linked to high aggression traits among healthy individuals [98]. Studies among psychiatric patients confirmed these findings. A chronic inflammatory state was linked to aggressive BD patients both towards themselves as well as towards others [99]. In addition, a positive relationship was found between cerebrospinal fluid soluble interleukin-1 Receptor II (sIL-1RII) and aggression in individuals with a personality disorder [100]. Increased levels of pro-inflammatory markers including IL-6, TNF-α, IL-1β, and IL-RA have also been found among schizophrenic patients [101]. However, meta-analyses found inconsistent results which could be explained by differences in antipsychotic treatment amongst others [101].

Nutritional psychiatry

An important role in biological processes including the synthesis of neurotransmitters and inflammation, is the supply of essential nutrients, such as lipids, amino acids, vitamins, and minerals, with the gut-brain axis as a potential mediating pathway [102-106]. Deficiencies of these essential nutrients are consequently thought to deteriorate the brain's structure and functioning. For example, vitamin B6, vitamin B12 and folate are crucial in the formation of neurotransmitters such as epinephrine, norepinephrine, γ-amino butyric acid, and serotonin [102]. In particular, a deficiency in serotonin seems

to play a key role in depressed mood, considering that selective serotonin reuptake inhibitors (SSRIs) are generally accepted in the recovery from mental illness [107], and the deprivation of the amino acid tryptophan, the dietary precursor of serotonin, can induce a lowered mood [108]. As a consequence, diet is suggested to be a modifiable factor affecting mood and behaviour [105, 109-111], giving rise to the field that is often called 'nutritional psychiatry' [112].

Nutritional supplementation and mental illness

Mounting evidence suggests that micronutrient supplementation may have a beneficial effect among people with mental illnesses. Strongest evidence was found for polyunsaturated fatty acids (PUFA), with several meta-analyses that reported the efficacy of PUFA on depressive symptoms in major depressive disorder (MDD) [113]. However, the quality of these studies was being questioned, and small-to-modest positive effects of n-3PUFAs were not clinically beneficial on depressive symptomology [114]. Mixed results were also found among people with schizophrenia. Meta-analyses reported a lack of significant benefits [115, 116], although a recent review found n-3PUFAs to be effective in reducing psychotic symptom severity in the prodromal phase of schizophrenia on [117]. The relationship between other vitamins (such as vitamin E, C or D) and mental illness have scarcely been studied [118], especially among long-stay psychiatric inpatients [111]. Such inpatients are likely to have a poorer nutritional status than the general population, due to the consumption of more energy-dense and nutrient-poor diets, insufficient outdoor activities (lowering vitamin D status), as well as potential detrimental effect of psychotropics (e.g., antipsychotics) on appetite, gastrointestinal function, the microbiome, and (energy and micronutrient) metabolism [119-121]. Studies have found that participants with the lowest nutrient concentrations seemed to have benefited the most from nutritional supplementation [117, 122]. It can therefore be hypothesized that psychiatric inpatients are liable to deficiencies and may benefit from supplementation with essential nutrients.

Nutritional supplementation and aggressive behaviour

Previous literature has explored the effectiveness of nutritional supplementation in the reduction of aggressive behaviour. These studies focused on young male prisoners [122-125] and children with behavioural problems [126-128], some of whom were diagnosed with autism spectrum disorder (ASD) [129], attention deficit hyperactivity disorder (ADHD) [130], conduct disorder (CD), and oppositional defiant disorder (ODD) [131]. These randomized controlled trials showed reductions in aggression, with 26% to 47% less

aggression-related incidents in the group receiving nutritional supplements compared to those receiving a placebo [122-126]. In addition, trials that assessed subjective feelings of aggression as an outcome showed findings that were in line with these studies that assessed actual aggressive behaviour [127-131]. However, in these previous trials, patients with psychosis were often excluded [127, 128, 130, 131] or no information on the use of psychotropic medication was given [123, 126]. Therefore, the effectiveness of nutritional supplements in reducing aggressive incidents needs to be confirmed in a sample of long-stay psychiatric inpatients among whom aggressive incidents are common.

Data

The Netherlands Study of Depression and Anxiety (NESDA)

The first part of this thesis is based on data from the Netherlands Study of Depression and Anxiety (NESDA). NESDA is an ongoing longitudinal, multisite, naturalistic cohort study and was designed to examine the long-term course and consequences of depressive and anxiety disorders. At baseline, a total of 2981 participants (18–65 years) were recruited from community care (19%), primary care (54%), and specialized mental health care (27%) in the Netherlands. This population was composed of participants with current or remitted depressive and anxiety disorders, and comorbid depressive and anxiety disorders. The control group consisted of participants without lifetime psychiatric disorders. Exclusion criteria were (1) the presence of other psychiatric disorders (e.g., psychotic, obsessive–compulsive, bipolar, or severe addiction disorder) and (2) not being fluent in Dutch. Assessments included a face-to-face interview, written questionnaires, and biological measurements. These assessments started in 2004 and since then have been repeated six times over a period of 9 years. Data on anger, including trait anger and anger attacks, were gathered at the 4th wave at 4-year follow up between August 2008 and May 2011. Participants who completed this wave totalled 2402 (80.6% of the original cohort). A more detailed description of NESDA is given elsewhere [132].

Diet and Aggression

The second part of this thesis comprises data from the Diet and Aggression trial, which was registered in the Clinical Trials Register (NCT02498106). This pragmatic, multicentre, randomized, double-blind, placebo-controlled, intervention trial aimed to assess whether multivitamin, mineral, and n-3 PUFA supplementation would reduce aggressive incidents among long-stay psychiatric inpatients. The trial was coordinated

in the department of psychiatry at the Leiden University Medical Centre (LUMC). Participants were recruited between 25 July 2016 through 29 October 2019 from 8 local sites for mental healthcare in the Netherlands and Belgium. Data collection took place at the ward where the participants resided. Inclusion criteria were (1) being 18 years or older and (2) expected to reside at a facility for long-term psychiatric inpatient care for at least 6 months, irrespective of their specific psychiatric disorder. Exclusion criteria were (1) pregnancy, (2) breastfeeding, (3) contra-indication for nutritional supplements, (4) expected discharge or transfer within eight weeks, (5) restrictions against the consumption of pork gelatine, and (6) continuous use of other nutritional supplements (within the preceding eight weeks), exceptions included vitamin B1 and D, which are mostly prescribed to prevent complications of alcoholism or to treat low vitamin D plasma levels in Northern countries, respectively, and which entailed no health risks in combination with this study's supplements. We assessed 1,121 patients for eligibility and excluded 945. In total, 176 participants were randomised into the trial (supplements, *n* = 87; placebo, *n* = 89). Most included patients suffered from a psychotic disorder (60.8%).

Aims and outline of this thesis

Aims

This thesis aims to unravel the occurrence, potential determinants, and treatment of anger and aggression among both psychiatric outpatients and psychiatric inpatients. The main objectives of this thesis are:

1. To examine whether and to what extent anger and aggression are associated with psychiatric disorders (Chapter 2, 3 and 6).
2. To deepen our understanding of some aspects of the pathophysiology of anger manifestations (Chapter 4 and 5).
3. To investigate the effectiveness of nutritional supplementation to reduce aggressive incidents among psychiatric inpatients (Chapter 7 and 8).

Outline

In this thesis, we discuss several studies that were undertaken to describe the prevalence and potential pathways of anger and aggression. Chapters 2 and 3 comprise research on the relationship between different anger measures and depressive-, anxiety- and bipolar disorder. In **Chapter 2**, we examined to what extent depressive and anxiety disorders, relevant clinical correlates, and sociodemographics determined the

level of trait anger and the prevalence of recent anger attacks. Thereafter, in **Chapter 3**, we investigated whether patients who converted to BD showed more feelings of anger, including borderline and antisocial personality traits, than people with unipolar depression. Additionally, the predictive role of aggression reactivity in conversion to BD was determined. Chapters 4 and 5 address the pathophysiology of anger among psychiatric outpatients. **Chapter 4** describes the associations of childhood trauma and anger constructs in adulthood. We also address which types of childhood trauma predominate in the prediction of anger. In **Chapter 5**, the associations between *T. gondii* infection and affective disorders, as well as with aggression reactivity and suicidal thoughts were examined. Chapters 6, 7 and 8 focus on aggression among long-stay psychiatric inpatients. In **Chapter 6,** an estimation is given on the overall incidence of aggression and the weighted average financial costs thereof in long-term psychiatric inpatient care. In **Chapter 7**, we describe the results from an RCT which assessed whether multivitamin, mineral and n-3 PUFA supplementation was effective in reducing the number of aggressive incidents among long-term psychiatric inpatients. Lessons learned from the RCT described in Chapter 7, in combination with a comparable RCT, are presented in **Chapter 8.** Finally, in **Chapter 9**, our main findings are summarized and considered within the current perspective. Suggestions are made for future research.

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