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

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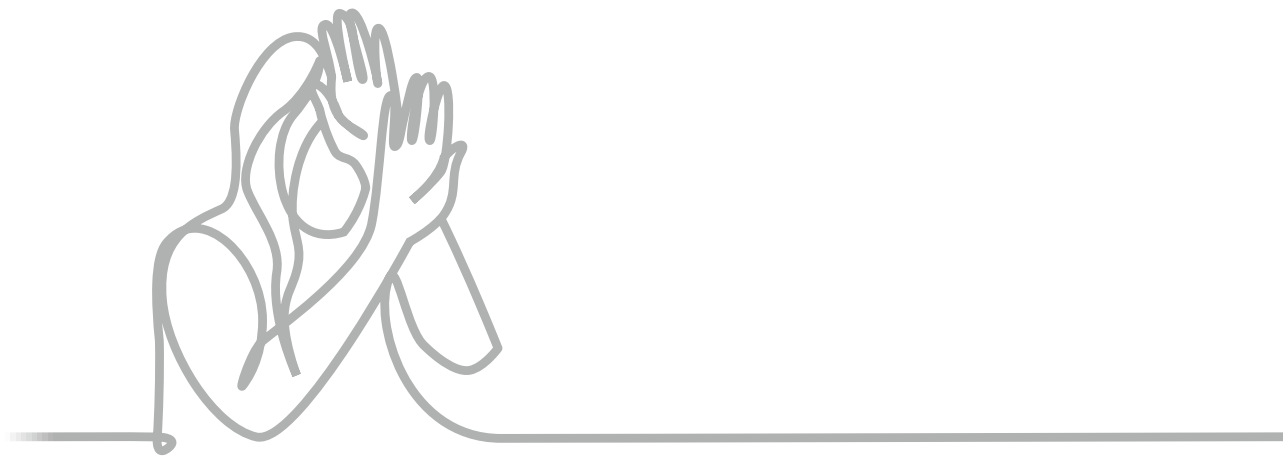
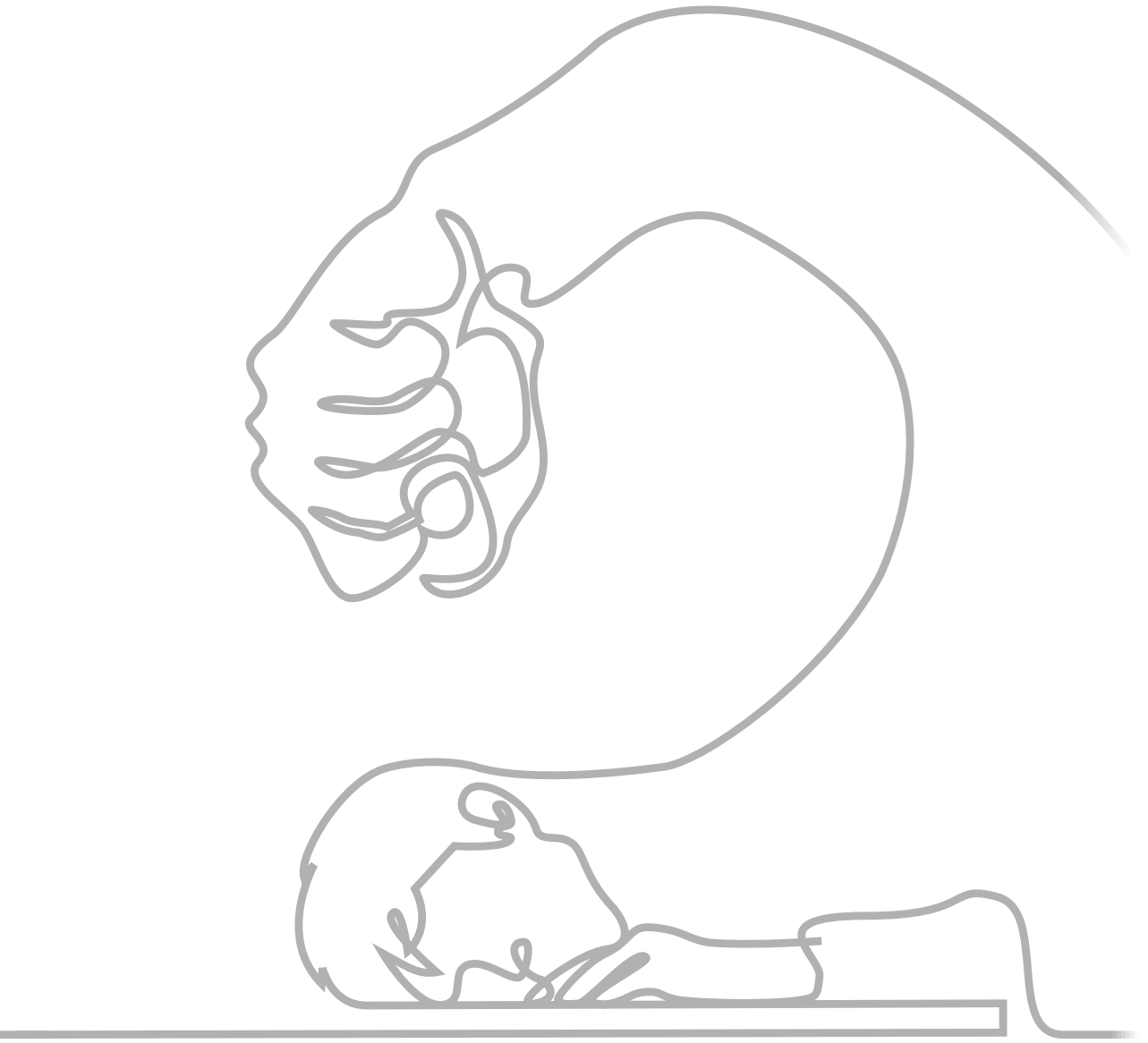


9 Summary and General Discussion



The overall purpose of this thesis was threefold: (1) To examine whether and to what extent anger and aggression are associated with psychiatric disorders; (2) to deepen our understanding of some aspects of the pathophysiology of anger manifestations; and (3) to investigate the effectiveness of nutritional supplementation to reduce aggressive incidents among psychiatric inpatients. The first and second part of this thesis were based on data from the Netherlands Study of Depression and Anxiety (NESDA), which recruited individuals from community care, primary care, and specialized outpatient mental health care. The third part of this thesis comprised data from the Diet and Aggression trial, which randomized individuals who resided at facilities for long-term psychiatric inpatient care.

In this last chapter, the main findings of this thesis will be summarized and discussed in the context of current research. Subsequently, implications for clinical practice and public health will be outlined. In addition, suggestions for future research to prevent anger and aggression among psychiatric patients are proposed and discussed.

Summary of findings

Part I: Anger measures and psychiatric outpatients

The first part of this thesis, *Chapters 2* and *3*, examined the relationship between different anger measures and depressive-, anxiety- and bipolar disorder among psychiatric outpatients.

Chapter 2: Trait anger and anger attacks in relation to depressive and anxiety disorders

Depressive and anxiety disorders are closely linked to anger. Yet, most previous studies conducted in patients with depressive- and anxiety disorders used insufficiently validated instruments or used only a single item to measure solely an aspect of anger such as irritability. Therefore, we investigated the prevalence of anger using a validated 10-item Spielberger Trait Anger Scale and the 19-item Anger Attacks Questionnaire in 2402 participants from the Netherlands Study of Depression and Anxiety (NESDA). Anger was most prevalent in participants with comorbid depressive and anxiety disorders—followed by anxiety-, depressive-, and remitted disorder—and these participants exhibited a higher prevalence of anger than healthy controls. Our findings showed robust evidence of a relationship between anger and psychopathology, although the strength differed across both anger constructs.

Chapter 3: Anger and cluster B personality traits and the conversion from unipolar depression to bipolar disorder

Patients with bipolar disorder (BD) have often experienced one or more episodes of depression before the onset of (hypo)mania, and consequently are frequently initially diagnosed with a unipolar depression. Identifying risk factors for the conversion to BD may yield anchor points for early recognition and appropriate treatment. We examined whether patients who converted to BD showed more feelings of anger, irritability, and antisocial and borderline personality traits than people with a history of unipolar depression who did not convert using the data from NESDA. Furthermore, we prospectively examined whether higher aggression reactivity could predict conversion from unipolar depression to BD later on. Different constructs of anger and affective instability (i.e., trait anger, aggression reactivity, anger attacks, and cluster B personality traits) showed consistent associations, with the strongest association and highest prevalence in the 77 participants who converted in comparison to the 1159 with a remitted and 349 with a current depression. Furthermore, aggression reactivity was a predictor for the conversion to BD in persons with a history of unipolar depression. These results suggest that assessment of anger might have clinical value in earlier recognition of conversion into (hypo)mania.

Part II: Pathophysiology of anger manifestations

The second part of this thesis addressed the pathophysiology of anger among psychiatric outpatients. The aim was to unravel the associations between childhood trauma, *Chapter 4*, and *T. gondii* infection, *Chapter 5*, with anger manifestations.

Chapter 4: Childhood trauma and anger in adults with and without depressive and anxiety disorders

Stress in early life could induce long-lasting alterations of the HPA axis, which is associated with severe sequelae that can perpetuate long into adulthood. We investigated (1) whether childhood trauma is associated with anger in adulthood and, if so, (2) to explore which types of childhood trauma predominate in the prediction of anger in a cohort that included participants with and without lifetime affective disorders. Therefore, the associations between childhood trauma and anger in adulthood, including trait anger, anger attacks, and borderline- and antisocial personality traits as constructs of anger, were examined in 2276 participants from NESDA. The results showed that all types of childhood trauma were significantly associated with borderline personality traits, independently of depression and anxiety. Additionally, all types

of childhood trauma except for sexual abuse were associated with higher levels of trait anger, and a higher prevalence of anger attacks and antisocial personality traits in adulthood, which may suggest that multiple anger manifestations are potentially the result of childhood trauma.

Chapter 5: Toxoplasma gondii seropositivity in patients with depressive and anxiety disorders

We also need to better understand the neurobiology of aggression. Latent Toxoplasma gondii (T. gondii) infection has been linked to several neuropsychiatric mood disorders and behaviours, yet studies provided no clear consensus on these associations. We hypothesized (1) that *T. gondii* seropositivity would be associated with the presence and severity of depressive and anxiety disorders, and (2) that *T. gondii* seropositivity would be associated with aggression reactivity and suicidal thoughts. In our study, a total of 1731 titers were obtained from participants from NESDA, of which 673 participants (38.9%) were seropositive for T. gondii antibodies, with a higher age associated with a higher risk. However, no significant associations were found between T. gondii seropositivity and disorder status, aggression reactivity and suicidal thoughts. Considering previous studies and our new findings, it seems unlikely that T. gondii seropositivity plays a major role in the risk of affective disorders, suicidality, and aggressive thoughts.

Part III: Aggression and psychiatric inpatients

The last part of this thesis focused on aggression among long-stay psychiatric inpatients. In *Chapter 6* and *7*, we examined the incidence and economic impact of aggressive incidents and determined the effectiveness of nutritional supplementation to reduce these incidents. Finally, in *Chapter 8*, we described the challenges and practical lessons learned from setting up and conducting a randomized controlled trial involving long-stay psychiatric inpatients.

Chapter 6: The incidence and economic impact of aggression in closed long-stay psychiatric wards

Aggressive behaviour is highly prevalent in psychiatric inpatient care, with substantial physical, mental, and economic consequences. However, estimates have often been based on data collected from (acute) admission wards and (forensic) hospitals, while data from long-stay facilities for psychiatric care are much scarcer. We hypothesized that the incidence rates of aggression, the workload for staff members, and the associated direct costs in closed long-stay psychiatric wards would be high. We found an

incidence rate of 90 incidents per patient year in closed psychiatric long-stay wards belonging to three regional mental healthcare centres. The incidence amounted to five incidents per day in an average ward with 20 inpatients. The average time spent was 125 min per incident, which indicates that each individual nurse spent more than half an hour per shift dealing with aggression. The direct costs related to incidents amounted to approximately €78 per incident. Based on our incidence rate, this would result in an estimate of €7000 per patient per year. These costs are likely to be an underestimation, as we did not include costs that were indirectly caused by aggression (e.g., staff absence, re-admissions, and assistance of police or ambulance). Aside from the financial perspective, reduction of aggression is highly valuable for both patients and staff. A positive change in aggression level need not affect the budget directly but would be compensated by the time that is available for therapeutic and social activities, as a result of which quality of care will likely improve.

Chapter 7: Multivitamin, mineral, and n-3 PUFA supplementation to reduce aggression among long-stay psychiatric inpatients: a randomized clinical trial

Previous studies found nutritional supplementation to be effective in reducing aggressive incidents and rule violations among forensic populations and children with behavioural problems. Yet, this had never been confirmed in a sample of long-stay psychiatric inpatients. We hypothesized that nutritional supplementation would reduce aggressive incidents, feelings of aggression, and affective symptoms and would increase the patients' quality of life. We therefore assessed the effectiveness of multivitamin, mineral, and n-3 PUFA supplementation in reducing aggressive incidents among 176 long-stay psychiatric inpatients. Our findings provided no support for the effectiveness of the current intervention in reducing the number of incidents during a 6-month intervention. Zooming in on the severity or type of aggressive incidents corroborated this conclusion. Our results suggest that the promising effects of nutritional supplementation on aggressive incidents found in previous studies cannot be replicated in these psychiatric inpatients. Although healthy diets should be stimulated for reasons of well-being and general health issues, there is yet no role for supplements in order to reduce aggression.

Chapter 8: Lessons learned from two clinical trials on nutritional supplements to reduce aggressive behaviour

Randomized controlled trials (RCTs) are considered to provide evidence for the effectiveness of a particular treatment. Setting up and conducting an RCT required

continuous decision making and has many challenges—particularly trials that include vulnerable individuals with behavioural problems or who reside in facilities that focus on care and not on research. As a consequence, vulnerable individuals with behavioural problems are underrepresented in RCTs, resulting in a lack of evidence-based care for these groups. We described the challenges and practical lessons learned from two RCTs in two care settings involving long-stay psychiatric inpatients and people with intellectual disabilities. We described five main difficulties and how these were overcome: (1) multisite setting, (2) inclusion of vulnerable participants, (3) nutritional supplements and placebos, (4) assessment of behavioural outcomes, and (5) collecting bio samples.

Clinical perspectives

Assessment of anger and aggression

Anger and aggression are both multifaceted constructs that are difficult to differentiate in clinical practice. Therefore, it is relevant to distinguish the subjective experience and the (physical) expression of anger and aggression [1]. Another distinction is that between state versus trait anger and aggression, which is of importance to determine whether a construct is rather constant or fluctuates over time within a person (4). For example, The Anger Attacks Questionnaire [2] aims to assess a certain mental state, whereas the Aggression Questionnaire [3] aims to assess trait aspects of aggression. The State-Trait Anger Expression Inventory-II (STAXI-2) is a self-report questionnaire that distinguishes trait and state anger, but also distinguishes between the expression and regulation of anger [4, 5]. To identify individuals most prone to anger, aggression, and related constructs, it is important to be aware of the aspect that someone aims to measure.

Another important consideration involves the choice of method for data collection. Although the instruments mentioned before are all self-report questionnaires, a more fundamental disadvantage of these constructs is that many people tend to give socially desirable answers [6]. In addition, psychiatric inpatients might suffer from limited intellectual and self-reflective capacities and consequently be less capable of completing self-report scales accurately. Hence, observer-rated scales are also a preferred method to investigate state aggression [7]. These scales include the Social Dysfunction and Aggression Scale [8], the Staff Observation Aggression Scale – Revised [9], and the Modified Overt Aggression Scale [10], amongst others. A downside of these scales is that observers, often care professionals, are regularly exposed to aggressive

behaviour, and may be desensitized to the more subtle forms of aggression, leading to underreporting and a lack of interobserver reliability. The latter could be compensated by training observers to calibrate assessments [11].

Additional issues that could influence the validity of an instrument are the characteristics of the study population and the instrument itself. Various study populations including the general population and psychiatric patients have been studied in the development of self-report questionnaires like the Aggression Questionnaire and the STAXI-2. More specifically, the SOAS-R has been validated among psychiatric populations and has been used in psychiatric settings worldwide [12]. Anger and aggression are often assessed through the measurement of a subscale as part of a larger questionnaire. Examples are the aggression subscales of the revised Leiden Index of Depression Sensitivity (LEIDS-R) [13, 14] and the SQ-48 [15]. Hence, the validity of these subscales for actual measured anger or aggression is unknown and may rather reflect irritability than aggression.

Thus, there are various instruments to assess the many different facets of aggression, and the choice of which to use depends on the aims of clinicians and researchers. These aims comprise identifying individuals prone to anger and aggressive behaviour, measuring change after an intervention, or predicting the potential of aggression in the future. Considerations that are of importance in selecting an instrument include the conceptualization of anger, aggression, and related concepts like irritability, as well as the method of data collection, study population, and instrument characteristics.

Outpatient settings

The current thesis demonstrated a high occurrence of anger and aggression among psychiatric patients. These results were in line with those from large population-based cohort studies as well as a patient-based study of psychiatric outpatients [1, 16, 17]. Chapter 2 showed that 30% of the patients with a depressive or anxiety disorder reported high trait anger scores. Anger attacks were reported by 4.9% and 11.5% of the patients with a depressive or anxiety disorder, respectively. Patients with comorbid depressive and anxiety disorders had the highest prevalence for both trait anger (43.7%) and anger attacks (22.1%). These patients showed the same level of trait anger and prevalence of anger attacks as patients with a bipolar disorder, which we found and reported in Chapter 3. Due to the observational and cross-sectional nature of our study design, it remains unknown whether anger and aggression are the result of (residual) affective symptoms or that the presence of anger and aggression may increase the vulnerability to psychopathology. Yet, in the prospective study of

Chapter 3, we found that anger predicted for the conversion of a (history of) unipolar into a bipolar disorder (BD) independent of depression severity and comorbid anxiety disorders. Thus, we demonstrated that anger could be a potential risk factor for the conversion to BD.

Our findings have several clinical implications. It means that anger symptoms are important to inquire about for the diagnosis, treatment, and prognosis of each patient with an affective disorder. Although common, anger may be easily overlooked or ignored by clinicians and patients themselves because they are not part of the core DSM-5 symptoms, and insight and self-consciousness of feelings of anger may be hampered. Moreover, this emotional state is also prone to conscious or unconscious denial as a taboo subject, and therefore needs a balanced approach to address. Yet, addressing anger in therapy may help clinicians to reduce conflicts or resistance to therapy [18].

As a first step, interventions aimed at better self-recognition and self-control may be helpful. Frequently, anger will be externalized or attributed to the psychiatric condition. It is therefore important to support patients in taking control over their harmful behaviour. These interventions comprise cognitive behavioural therapies, which are the most studied type for anger treatment, but also relaxation, social skills and cognitive therapies, or a combination of these approaches [19]. Meta-analyses comparing these interventions show that effects are comparable and moderately effective [20-22].

In the light of effective therapy, it is urgent to understand mechanisms underlying anger in adulthood. Prior cross-sectional and longitudinal studies found associations between childhood trauma and anger outcomes in adulthood. However, most studies focused on trait anger, while different forms of childhood trauma may affect the development of different aspects of anger and aggression [23]. This is line with findings described in Chapter 4, stating that childhood trauma is most strongly linked with trait anger and borderline personality traits, but physical abuse was the strongest predictor for anger attacks and antisocial personality traits. A complicating layer to these relationships is that experienced trauma and neglect by parents and hereditary factors interact in complex ways. In clinical practice, it is important to explain and validate the relationship between childhood trauma and anger in adulthood. Unfortunately, symptom complexity such as emotion regulation difficulties and impulsive behaviour is often viewed upon as a limiting factor in trauma-focused therapy, thinking it may worsen these symptoms. As a result, it could be that patients are prevented from receiving a beneficial additive treatment. A meta-analysis that included those that

had experienced childhood trauma did not find symptom complexity to be a contraindication for trauma-focused psychological interventions [24]. So, in addition to anger control, trauma-focused treatments might lead to reductions in anger. To inform future treatments, it remains important to further personalize treatments, and to identify which components work for which individuals.

Inpatient settings

Aggression and violent incidents are highly prevalent in psychiatric inpatient care, as aggressive behaviour is often the triggering event that leads to a referral to these settings [25]. In addition, patients have been found to be more aggressive during hospitalization [26]. So, a substantial number of individuals admitted to inpatient settings express aggressive behaviours not only as the reason for admission but also as a consequence thereof. However, exact estimates of the prevalence and incidence are mixed, which may be explained by large variations in types of patients, settings, the types of aggression that is measured (e.g., including or excluding verbal aggression and self-harm), and the fact that incidents are less often reported officially, compared to what is actually experienced by staff members [27, 28]. In addition, incidence estimates have often been based on data collected from (acute) admission wards [29, 30] and (forensic) hospitals [31, 32]. As a consequence, a wide range of incidence rates have been reported varying from less than 1 to 60 incidents per patient year, mostly in acute and forensic settings [12, 33], and up to 90 incidents in closed long-stay wards as described in Chapter 6 of the current thesis.

The main treatment approaches to reduce aggression comprise psychotherapy, including behavioural interventions, and psychopharmacological therapy [34, 35]. However, evidence for the efficacy of these interventions is not conclusive [36-39]. RCTs are often underpowered and long-term outcomes are lacking [34]. In addition, only 30% of the patients displaying aggression would be eligible to participate in RCTs investigating pharmacological interventions targeting aggression, which may decrease the generalizability to clinical practice [40]. Consequently, clinical guidelines emphasise the need for additional and innovative treatment options [41]. Despite some promising effects of multivitamin, mineral and n-3 polyunsaturated fatty acid (PUFA) supplementation on aggressive incidents found in previous studies [42-51], we found no evidence of a beneficial effect in chronically ill psychiatric in-patients.

Aggressive behaviour and the management thereof do not only focus on patient factors, but also concentrate on other variables including the physical environment and staff factors. Thus, interventions include aggression management courses for

staff, such as the Safewards model, providing ten interrelated interventions [52, 53]. Despite the increased awareness and efforts to reduce aggression in clinical care, it remains important to establish robust evidence to improve the experience of safety in inpatient settings for both patients and staff [54, 55].

Public health impact

Anger and aggression have substantial public health implications, both for individuals, mental healthcare organizations, and society. Implications may comprise primarily anger reactions in a social context, especially the people described as loved ones by these individuals [56]. Additionally, high levels of anger might trigger self-directed aggression [57] and aggression towards others. In case aggressive behaviour is a risk to patients or their environment, it could result in the use of coercive measures, such as involuntary admissions to psychiatric wards, which patients often describe as traumatic [58, 59]. Among the different disciplines of these wards, nursing staff is particularly at risk, with psychiatric nurses having a three times increased risk of physical aggression from patients compared to nonpsychiatric nurses [60]. These incidents sometimes lead to serious injuries (e.g., fractures, eye injuries and permanent disability), which was reported by 26% of psychiatric nurses [61]. The exposure to aggression may also lead to acute stress disorder, and post-traumatic stress disorder (PTSD) in severe cases (14–17% of exposed staff members), but more frequently, it leads to subclinical burnout-related symptoms [62, 63]. A review on workplace violence towards healthcare staff employed in psychiatric wards reported that 7.5 to 33% of the victims developed symptoms including anxiety, depression, and avoidance behaviour after the occurrence of an incident [64].

Mental health sequalae among healthcare staff have substantial consequences on an organizational level as well; the exposure to aggression seems to be related to job dissatisfaction [65], burnout [66], and absenteeism [67]. These symptoms are concerning, as it may result in lower standards of care [68] and increased intent to leave the organization [69]. In addition, lost staff work-days due to the physical and psychological consequences that might follow critical incidents are accounted by high costs, even long after the initial incident happened. Other costs include the time spent on aggression by staff, damaged property, higher use of psychotropic medication, and longer hospital admissions [70]. As a result, the few studies that provided information on the costs of aggression showed an enormous economic burden on the organizations budget yet are thought to be conservative estimates as indirect costs are often not or not completely taken into account.

In the long-term, aggression towards professionals might also have an impact on society, not only limited to the psychiatric population as the aggressor, but also other individuals from the general population. As a consequence, aggression is not only experienced by mental healthcare professionals, but also by other healthcare professionals, police officers, firefighters and traffic controllers [71]. It is disputed whether there is a stagnation in the scope of aggression, due to increased reporting and broader aggression definitions. Nevertheless, the exposure to aggression is experienced as high, which became even more evident in recent years during the COVID-19 pandemic and the accompanying restrictions [72, 73]. A recent report among 11,092 respondents found that three quarters of healthcare professionals in the Netherlands have been exposed to aggression or unwarranted behaviour from patients or clients at least once during the past year. These incidents ranged from verbal or physical aggression to sexual or other harassment or threat, causing 4% of the respondents thinking about leaving the sector [72]. Interventions to reduce these behaviours include adequate registration, the development of specific protocols, and training. However, these approaches do not focus on the role of aggressive individuals within the general population, for example through campaigns or education. In addition, most interventions have not been evaluated for their effectiveness. As these professions, including healthcare professionals, police officers, firefighters, and traffic controllers, are essential to ensure the continuity and resilience of our society, it is of utmost importance that aggression receives high priority among public health interventions.

Future directions

This thesis adds and broadens robust evidence confirming the relationship between anger and aggression, and psychopathology, as well as expanding upon some aspects of the pathophysiology of these relationships. However, this thesis also raises some key issues for future studies.

Dynamic interplay between the context,
anger, and other symptoms psychiatric disorders

Our research implies that participants with a remitted psychiatric disorder still exhibited higher levels of trait anger and recent anger attacks compared to controls, which may be the result of residual symptoms or psychiatric disorders that were not assessed in our study. A common residual symptom that is often mentioned is irritability [74]. Furthermore, symptomatically remitted patients with schizophrenia or

bipolar disorder remain impaired in the recognition of facial expressions depicting anger [75]. Interestingly, while studies show irritability and the identification of anger as residual symptoms, the experience and expression of anger among remitted patients often remains neglected in the literature. The question whether anger is a residual symptom could be of importance as residual symptoms are relevant clinical predictors for the recurrence of depression. Recurrence of depression is especially high in specialized mental health care with a percentage of up to 85% after 15 years [76]. Thus, the identification of residual symptoms might lead to an improvement of therapy and the course of mental illness to prevent relapse.

Higher levels of anger, however, may also indicate vulnerability to psychopathology. Despite the connection between anger and psychopathology, anger is often overlooked as it may come and go during the course of psychopathology. According to the DSM-5, only Intermittent Explosive Disorder (IED) has a primary focus on anger and aggression among adults [77]. Nevertheless, the research in the current thesis seems to confirm that pathological anger is common across different psychiatric disorders, as described in Chapter 2 and 3, and it could have a substantial influence on the development and treatment of these disorders [78]. Underlying this relationship, it is suggested that an angry disposition embedded in personality leads to expressed anger, resulting in conflicts and difficulties in interpersonal relationships, which may in turn lead to psychopathology [79-81]. Additionally, there is increasing evidence that childhood trauma is linked to psychopathology in adulthood [82], with trait anger as possible mediating pathway [83]. Among individuals who experienced childhood trauma it is seen that the amygdala becomes overactive, in order to facilitate the rapid detection of potential threats [84]. This results in heightened emotional reactivity and emotional dysregulation [84-88] across the life course, including heightened anger symptoms in adulthood as described in Chapter 4. Elevated emotional reactivity, emotional dysregulation, and alterations in amygdala have all been shown to mediate the link between childhood trauma exposure and transdiagnostic psychopathology later in life [89-93].

A longitudinal cohort study may help to disentangle the temporal and causal relationships between anger and transdiagnostic psychopathology, using both self- and observer-rated anger measures and incorporating the exposure to childhood trauma. More idiographic study approaches, in which time series of symptoms including anger as assessed sequentially may help to increase the insight of precursors of aggression for the individual patient [94]. Such designs may have beneficial consequences for (psychotherapeutic) interventions targeting anger and the development of psychopathology.

Include long-term inpatients to provide evidence for the effectiveness of a particular treatment.

A large share of healthcare costs is spent on long-term care, with aggression being a relevant component of these costs [70, 95, 96]. As described in Chapter 7, the promising effects of nutritional supplementation on aggressive incidents found in previous studies were not replicated in psychiatric inpatients, indicating that we should be careful to generalize previous results to (long-term) psychiatric inpatients or others with severe mental illness (SMI).

The gap that is present between eligible patients and real-world patients became recently evident in a review that found that almost 80% of patients with schizophrenia spectrum disorders were ineligible for RCTs on the efficacy of antipsychotics, due to strict exclusion criteria [97]. The most frequent reasons for ineligibility were concomitant use of mood stabilizers or antidepressants and serious somatic comorbidities, while precisely these patients have moderately higher risks of admission. Moreover, individuals with SMI including schizophrenia and related psychotic disorders have a higher prevalence of comorbid chronic somatic disorders, predominantly cardiovascular and metabolic diseases [98-100]. This translates to shortened life expectancy of over 10 years as compared to the general population [101-103]. Consequently, clinical trials that do include individuals with SMI in an inpatient setting, most often focus on both mental and physical health, for example by using motivation techniques to reduce cardiometabolic risk factors [104, 105].

In sum, it is important for both individual and public health in general that future researchers conduct pragmatic trials and well-designed observational studies to investigate treatment strategies among underrepresented subgroups such as long-stay psychiatric inpatients who could still gain much from improved clinical care.

Investigate nonpharmacological interventions to improve mental and physical health.

A vast majority of the participants recruited for the Diet and Aggression trial were using antipsychotics during the intervention (91.2%). A novel hypothesis is that antipsychotics may cause undesirable mental and physical effects that could be mediated by their deleterious effects on the microbiome; the genes and genomes found in the microbiota inducing dysbiosis [106, 107].

Intestinal microbiota and diet are suggested to play a role in the gut-brain axis, with diet as an important factor to influence the gut microbiome rapidly [108]. The gut-brain axis connects the enteric nervous system to the central nervous system [109].

This way, the intestine and the brain are thought to communicate bidirectionally. The disruption of bacterial species of the gut microbiota, dysbiosis, seems to be related to several mental disorders as well as obesity and type 2 diabetes [110]. For example, research in germ-free mice has shown that gut microbiota is required for normal brain development and consequential healthy social and exploratory behaviours [111-114]. Preclinical rodent studies revealed that probiotics (i.e., supplements with beneficial viable gut microbes) had an antidepressant effect, indicating that probiotics may intervene serotonin metabolism [115].

Knowledge is increasing on the relation between the gut microbiota and brain function, but less is known about the effects of modification of the gut microbiota on affective and anger symptoms in humans. Adverse effects of antipsychotics may be highest in case of chronic antipsychotic use [107, 116, 117] and long periods of hospitalization, which is associated with more physical inactivity. Therefore, it is important to investigate interventions that target the gut microbiota to improve both mental and physical health among long-stay psychiatric inpatients to provide effective care, treatment, and prevention for this population.

Concluding remarks

This thesis leads to empirical insights in the relationship between anger and aggression, on the one hand, and psychopathology, on the other hand, using robust study designs and a broad spectrum of anger manifestations. In the previous Chapters, it became clear that the occurrence of anger and aggression are common among both psychiatric outpatients, including individuals with depressive-, anxiety-, and bipolar disorders, and psychiatric inpatients, including individuals with psychotic- and personality disorders. Therefore, we emphasize on the importance to address anger in patient interviews and (psycho)therapy. This way, it might be possible to break the taboo of feeling angry. Addressing this might help clinicians to reduce conflicts or resistance to therapy. Even so, management of anger is a major public health and safety concern due to the strong link between anger and aggression.

Aggressive behaviour regularly leads to a referral to long-stay inpatient care. As supported by this thesis, the costs of aggression within long-stay wards are high, although these estimates are most likely underestimated. The societal relevance to reduce aggression was also recognized by policymakers, resulting in a grant from ZonMw (The Netherlands Organisation for Health Research and Development) under grant number 836031016. However, despite the increased awareness and efforts to

reduce violence in clinical care among healthcare workers and policymakers, aggression incidents remain highly prevalent in psychiatric inpatient facilities. Research suggests diet to be a modifiable factor affecting mood and behaviour. However, the promising effects of nutritional supplementation on aggressive incidents found in previous studies were not replicated in psychiatric inpatients. These results strengthen the need for study of additional preventative and treatment options. Furthermore, our results underline the importance of including vulnerable populations, who are often underrepresented in RCTs, to provide evidence-based care for these groups. An important characteristic of psychiatric inpatients is the extensive use of antipsychotic medication amongst others.

In conclusion, early recognition and appropriate treatment of anger and aggression could enormously influence the ultimate functioning of care professionals, society, and, most important, patients themselves. It is in the interest of all of us that patients are able to verbalise their feelings of anger, but to no longer being consumed by anger.

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