Attending to Anger

Psychological and neurobiological correlates of anger and aggression after military deployment

Lieke Heesink

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Psychological and neurobiological correlates of anger
and aggression after military deployment

Aandacht voor Agressie

Psychologische en neurobiologische correlaten van boosheid
en agressie na militaire uitzending

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op vrijdag 7 juli 2017 des ochtends te 10.30 uur.

door

Lieke Heesink

geboren op 15 september 1987
te Tubbergen

Promotoren:	Prof.dr. R. Kleber
	Prof.dr. J. van Honk
Copromotor:	Dr. S.G. Geuze

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General introduction

Introduction

The military profession is associated with a strong physical and mental load, and during deployment there is an increased exposure to stress and to traumatizing events, such as enemy fire or witnessing colleagues or other people getting injured or killed. After deployment, military veterans often struggle with the adaptation to daily life, in the sense that they have to get used again to a regular family life and to working in a society not afflicted by war. Altogether, these factors can have far-reaching consequences, among which the development of mental disorders. It has been reported that between 8.9% and 19.7% of deployed military personnel develop a mental disorder (Fear et al., 2010; Reijnen, Rademaker, Vermetten, & Geuze, 2015). It also has been reported that about 6.6% of the Dutch military personnel deployed to Afghanistan developed problems with hostility and anger (Reijnen et al., 2015). These veterans reported that they are easily irritated or frequently have angry outbursts.

Anger and aggression are important phenomena in the description of trauma-related disorders (Elbogen et al., 2010; Orth & Wieland, 2006). Posttraumatic stress disorder (PTSD) is a mental disorder that can develop after the experience of a traumatic event and is characterized by intrusion symptoms, avoidance, negative alteration in cognition and mood and alterations in arousal and reactivity (American Psychiatric Association, 2013). It has been found that anger enlarges the vulnerability for the development of PTSD (van Zuiden et al., 2011) and that exposure to events like violence, war and terror can lead to anger and aggression problems. Furthermore, anger and aggression are important predictors for the development and the course of psychological disorders and for the prognosis of psychotherapy (Forbes et al., 2008; McHugh, Forbes, Bates, Hopwood, & Creamer, 2012; Painuly, Sharan, & Mattoo, 2005).

Research into the nature and background of anger and aggression is therefore of great importance for the military. It offers the possibility to gain insight into the causes and development of problems as reported by deployed military personnel. In case of a specific disorder, as described in DSM-5 (American Psychiatric Association, 2013), treatment methods are evident. In case of more diffuse complaints, a suitable method to assist and support the individual is harder to find. Insight into similarities and differences with other disorders can thus be very useful in guiding treatment choice.

The Research Domain Criteria (RDoC) initiative focuses on a new framework for research into the neurobiological mechanisms underlying mental disorders based on dimensions of observable behaviour and neurobiological measures (Cuthbert & Insel, 2013; Insel et al., 2010). It has also been suggested as a framework to help explain aggression (Blair, 2015; Verona & Bresin, 2015).

Hostility, anger and aggression

The definitions of hostility, anger and aggression have been developed over the years and they show great overlap. In short, hostility refers to the negative evaluation or attitude towards people or things (Buss, 1961). Anger is about feelings and emotions; it also represents the affective component of aggressive behavior. The definition of aggression is every form of behavior with the intention to harm (Ramirez & Andreu, 2006). In this paragraph, the specific differences and similarities between these definitions are described.

Hostility has been defined as a negative evaluation of persons and things (Buss, 1961). The feelings that accompany hostility are feelings of resentment, disgust and disrespect (Ramirez & Andreu, 2006). The term hostility has been used to describe a broad construct including affect and behavior, since the attitude of negative evaluation can lead to verbal and motor responses, among which aggressive behavior (Buss & Perry, 1992). The cognitive description of hostility, which consists of negative beliefs and attitudes (Teten et al., 2010) might give the best distinction between the other constructs: anger and aggression. Hostility refers to the negative feelings towards others, or a hostile attribution (Buss, 1961). Others are perceived as likely to be irritating and untrustworthy. Hostility is often accompanied by feelings of anger (Ramirez & Andreu, 2006).

Anger is defined as an emotional state consisting of feelings varying from mild irritation or annoyance to fury and rage (Spielberger, 1991). Frijda described emotions, among which anger, as action readiness, thus a state for achieving an aim (Frijda, 1986). Spielberger (1991) divides anger into a state and a trait variant. State anger refers to the current feelings of anger, whereas trait anger refers to a predisposition to react with anger in certain situations (Spielberger, 1991). Furthermore, anger is typically accompanied by arousal of the autonomic nervous system, such as increases in heart rate and perspiration (Ramirez & Andreu, 2006).

Aggression has been defined as harming behavior towards other objects or persons (Spielberger, 1991). This definition does not include an intention to harm, which was added to later definitions (Anderson & Bushman, 2002; Ramirez & Andreu, 2006). Aggressive behavior has been divided into two distinct subtypes, based on motives (Ramirez & Andreu, 2006). The premeditated subtype is associated with purposeful and goal-oriented behavior, with profit or reward as a goal. It does not require provocation or anger and the objective is profit-based, for example the gain of money or power (Barratt, Stanford, Dowdy, Liebman, & Kent, 1999; Berkowitz, 1993). An example of this type of aggression is a robbery. The other subtype is reactive aggression, which has typically been associated with impulsive and emotionally charged behavior. It often occurs as a reaction to a perceived provocation (Barratt et al., 1999; Ramirez & Andreu, 2006). This type of aggression is associated with hostility and anger, and is characterized by hyperarousal (Ramirez & Andreu, 2006).

Neurobiology of anger and aggression

Anger and aggression are associated with a disturbed balance between on the one hand the signaling role of the limbic system (amygdala, insula) and on the other hand the regulating role of the orbitofrontal cortex (OFC) and the anterior cingulate cortex (ACC) (Davidson, Putnam, & Larson, 2000; Siever, 2008). When the limbic system is hyperactive in case of an emotional or provocative stimulus, and the inhibiting role of the OFC is decreased, one might perceive less control over aggressive behavior (Davidson et al., 2000; Siever, 2008).

Often, a lowered threshold for threat or provocation is described in anger and aggression (Berkowitz, 1993; Blair, 2012). From a neurobiological perspective, brain regions implicated in the basic threat system play a role in the origin of aggressive behavior (Blair, 2012). This system has been studied extensively in animals. These studies indicate that the threat system runs from the amygdala downward, via the stria terminalis to the medial hypothalamus and to the periaqueductal gray (Blanchard, Hynd, Minke, Minemoto, & Blanchard, 2001; Blanchard, Blanchard, & Griebel, 2005). In humans, this system is thought to mediate defensive behavior and reactive aggression as well (Blanchard, Hynd, Minke, Minemoto, & Blanchard, 2001). In humans, it was found that periaqueductal gray activity increases when threat moves from distal to proximate, unavoidable threat (Mobbs et al., 2007).

Brain regions that regulate the basic threat system are also implicated in aggressive responding (Wilkowski & Robinson, 2008). Processes related to automatic hostile interpretations and attention to threatening or negative stimuli appear to be important contributors to individual differences in angry reactivity (Wilkowski & Robinson, 2008). The frontal cortex, especially the orbitofrontal cortex, plays a role in effortful control of anger and aggression (Blair, 2012). Furthermore, involvement of the orbitofrontal cortex and the amygdala have been reported in Intermittent Explosive Disorder, a mental disorder characterized by impulsive aggression (Coccaro, McCloskey, Fitzgerald, & Phan, 2007; McCloskey et al., 2016). Hyperactivation of the amygdala in response to angry faces was reported, as well as diminished OFC–amygdala coupling (Coccaro et al., 2007; McCloskey et al., 2016).

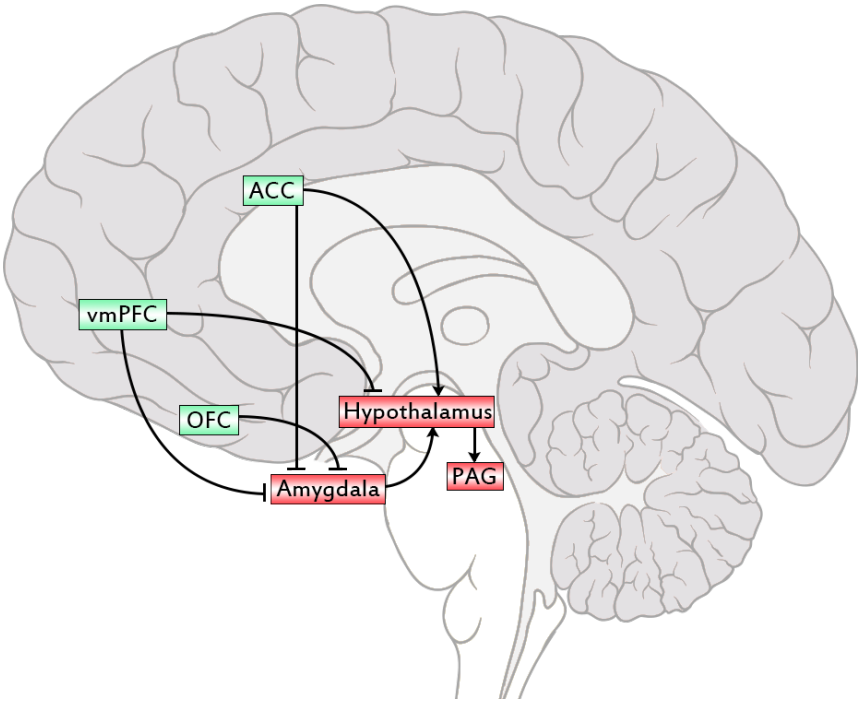

Figure 1.
Schematic overview of brain areas implicated in aggressive behavior.

MARS – Military Aggression Regulation Study

Since 1940, more than 650.000 Dutch soldiers have been involved in various missions and were deployed to various war zones. Currently, there are approximately 115.250 veterans in The Netherlands. Over the last decades, Dutch military personnel were deployed to a number of conflict regions in the world including (former) Yugoslavia (especially Bosnia-Hercegovina), Iraq and Afghanistan. The majority of military personnel reports no mental problems after home-coming. However, some veterans suffer from PTSD symptoms, fatique, depression and anger problems (Reijnen et al., 2015).

Most of the work described in this thesis are results from the Military Aggression Regulation Study (MARS). In 2012, the Dutch ministry of Defense decided to study the neurobiological and neuropsychological background of anger and aggression in military personnel. In this project, 52 deployed military veterans with anger and aggression problems, and 50 deployed control military veterans without mental disorders were recruited. They were interviewed and filled out questionnaires in order to gain insight into their problems with anger and aggression. Furthermore, blood samples were taken. Participants also underwent neuropsychological tasks and participated in a startle experiment.

Half of the participants were invited for a second appointment. During this appointment, participants underwent a magnetic resonance imaging (MRI)-scan. The MRI scan consisted of functional and structural scans. Among the functional scans were two tasks, which are described in this dissertation. Furthermore, the structural scans consisted a diffusion tensor imaging (DTI)-scan, a technique used to image the white matter connection in the brain.

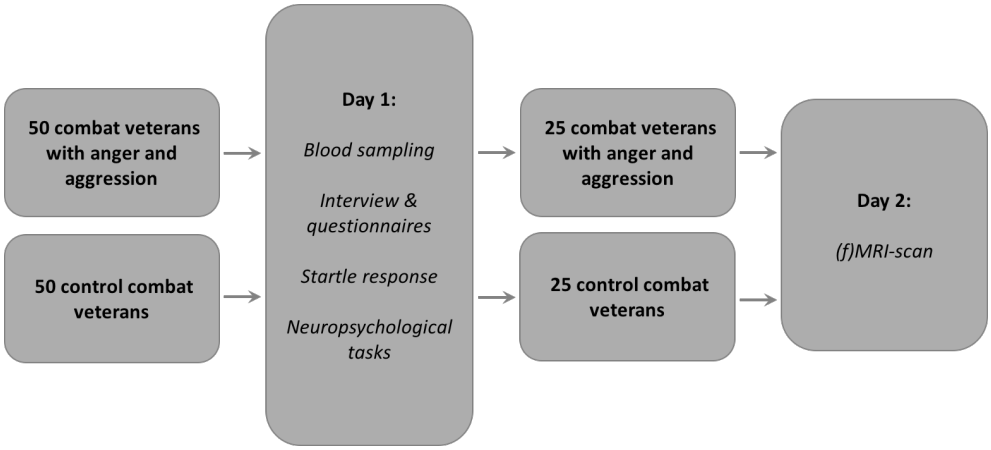

Figure 2.
Schematic overview of the Military Aggression Regulation Study (MARS)

Outline of the dissertation

The purpose of this dissertation is to examine the neurobiological background of anger and aggression in Dutch military personnel. We examined several underlying mechanisms, the specific aims were to:

- Investigate the trajectories of development of anger after military deployment;
- Test whether anger and aggression is accompanied by heightened vigilance;
- Measure brain activation in response to threat in anger and aggression;
- Measure brain activation in response to emotional stimuli in anger and aggression;
- Assess microstructure of white matter tracts that play a role in aggression, emotion and self-regulation.

In **chapter 2** the role of anger and aggression in PTSD is discussed. This chapter gives an overview of anger and aggression after trauma and how these phenomena are connected. In **chapter 3** it is tested whether veterans can be divided into subgroups based on their symptoms of anger before and after deployment. The trajectories of the development

of anger before and after deployment are described. This chapter also deals with the question which factors play a role in the development of anger. In **chapter 4** results of the startle response experiment are described. It is tested whether veterans with anger and aggression show a heightened startle response, which indicates heightened vigilance. **Chapter 5** describes the results of one of the fMRI tasks, in which heightened attention for features associated with threat is found. The second fMRI task points towards a stronger vigilance towards general stimuli. These results are reported in **chapter 6**. **Chapter 7** focuses on two white matter connections within the brain, the arcuate fasciculus and the uncinate fasciculus. These tracts play a role in self-regulation due to their connections with the frontal lobe. **Chapter 8** gives a summary and general discussion of this dissertation.

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2

PTSD, anger and aggression: Epidemiology, aetiology and clinical practice

Jan Rodenburg
Lieke Heesink
Boris Drožđek

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Abstract

Anger and aggression are common phenomena in PTSD, with many negative consequences as reduced physical health and poor family functioning. When PTSD is accompanied by anger and aggression, treatment outcome is worse. Anger and aggression itself are difficult conditions to treat. Given the negative consequences of anger and aggression, it is important to gain knowledge regarding the etiology of the complaints. The original focus on PTSD as an anxiety disorder is extended to emotion regulation, including anger and aggression. That is illustrated by the growing amount of research into the etiology of PTSD and the role of other stress responses to trauma, especially that of anger and aggression in PTSD. Anger and aggression seem to be related to the hyperarousal symptoms in PTSD, involving a lowered threshold for threat. Biologically, the close link between PTSD, anger and aggression can be found in brain regions that regulate aggression, hyperarousal and anxiety. Furthermore, the role of rumination, visual imagery and language processing will be discussed, as well as treatment directions.

Acknowledgment contribution authors
Designed research: J. Rodenburg, L. Heesink & B. Drožđek
Wrote the paper: J. Rodenburg, L. Heesink & B. Drožđek

Introduction

Although in the last decade the amount of research on posttraumatic stress disorder (PTSD) has been growing, only a small proportion of it focuses on anger and aggression and the related concept of hostility. Anger and aggression are common phenomena in different psychiatric diagnoses, and are most prevalent in- and associated with PTSD (e.g. Olatunji, Ciesielski, & Tolin, 2010)

In the past, the concepts of anger, aggression and hostility were often defined in different ways, making comparison and therefore understanding of these topics complicated. Anger and aggression are related, but not the same, as aggression is mostly accompanied by anger, but anger does not necessarily lead to aggression. This makes aggression rates in PTSD much lower than the fairly common anger problems in patients with PTSD. Failure to modulate anger is an important contributor to violence and aggression accompanying a subgroup of the patients with PTSD (Teten et al., 2010). Furthermore, anger is an important predictor of severity of PTSD symptomatology (McHugh, Forbes, Bates, Hopwood, & Creamer, 2012). The prognosis of the PTSD treatment outcome is worse in case of comorbid anger and aggression (McHugh et al., 2012). Furthermore, anger itself was found to be a difficult condition to treat (Shin, Rosen, Greenbaum, & Jain, 2012). This indicates the importance of attention to this phenomenon in both research and clinical practice.

Aggression and related concepts

Aggression is defined as "behavior carried out with the proximal (immediate) intention to inflict harm on another person who is motivated to avoid the harm" (DeWall, Anderson, & Bushman, 2011). Aggression includes verbal abuse, threats or violence (Taft, Creech, & Kachadourian, 2012). In literature, two distinct subtypes of aggression have been recognized. These are reactive and proactive aggression. Reactive aggression is an emotionally charged and uncontrolled aggressiveness, also called unintentional, affective or impulsive aggression. Proactive aggression is a planned, unemotional and goal-directed aggression, also called controlled, intentional, predatory or premeditated aggression. Recently, the need for a more precise definition of the PTSD-related aggression was underpinned (Teten et al., 2010). Impulsive aggression is suggested to be the predominant form of aggression in PTSD (Teten et al., 2010).

A widely-accepted definition of anger states that "anger is an emotional state that consists of feelings that vary in intensity, from a mild irritation or annoyance to fury and rage" (Spielberger, Jacobs, & Russell, 1983). An addition to this concise definition is made by noting that "angry feelings are connected with cognitions and their various associated verbal, facial, bodily and autonomic reactions" (Eckhardt, Norlander, & Deffenbacher, 2004).

Spielberger makes a distinction between anger domains (Spielberger, 1999; Spielberger & Sydeman, 1994), which is relevant to get a better understanding of the role of anger in PTSD. Anger is divided into state and trait, the first referring to the current intensity of angry feelings, and the latter referring to individual differences in the predisposition to react with anger.

Furthermore, a distinction is made in anger expression, consisting of anger-in and anger-out. The first refers to the extent that someone suppresses anger, while the latter refers to the extent that someone expresses anger outwardly. Anger control indicates the extent to which somebody monitors and controls physical or verbal expression of anger. It is divided in anger control-in and anger control-out, the first referring to the extent in which one attempts to relax, calm down, and reduce angry feelings, and the latter referring to extent that someone regulates the energy of physical or verbal expressions of anger (Spielberger, 1999). Trait anger, anger-in, anger-out and anger control are found to have a strong relationship with PTSD (Orth & Wieland, 2006).

Hostility is defined as an antagonistic attitude or evaluation of others and is associated with feelings of disgust, indignation and resentment (Teten et al., 2010). Hostility causes an increased frequency of anger and aggression, and these phenomena reciprocally activate each other (Orth & Wieland, 2006).

Table 1.
Important concepts

Concepts	
Aggression	
Impulsive	Emotionally charged, uncontrolled aggressiveness
Premeditated	Planned, unemotional, goal-directed aggressiveness
Anger	
State	Current intensity of angry feelings
Trait	Predisposition to react with anger
Anger Expression	
Anger-In	The suppression of anger
Anger-Out	The expression of anger outwardly
Anger Control	
Anger Control-In	Regulating angry feelings by relaxing and calming down
Anger Control-Out	Avoiding the expression of anger outwardly
Hostility	Negative attitude or evaluation of others

PTSD, anger and aggression in research and in the DSM classification

Anger and aggression are important in the treatment of PTSD, because anger seems to be the key predictor of treatment outcome (Forbes et al., 2008). Recent important

developments in research of anger and aggression in PTSD are still not part of the general knowledge in clinical practice. Anger problems may lead to poor family functioning (Taft, Schumm, Panuzio, & Proctor, 2008) and to poor physical health, both being common characteristics in PTSD patients (Ouimette, Cronkite, Prins, & Moos, 2004). These findings support the view that anger problems play an important role in the etiology of PTSD.

Novaco and Chemtob (2002) investigated the hypothesis that the correlation between anger and PTSD symptoms, as measured with the existing PTSD scales, is artificial. For the purpose of this research, the items measuring anger and irritability within the different PTSD scales were removed. The authors found that the correlation found was almost equally strong as it was with the complete PTSD scales, indicating that the correlation was not a methodological artefact (Novaco & Chemtob, 2002). In conclusion, the impact of anger on PTSD severity greatly exceeds the impact that may be expected because anger is also a part of the hyperarousal cluster in the PTSD diagnosis (Novaco & Chemtob, 2002).

Treatment of anger, when successfully implemented, seems to reduce PTSD symptoms as collateral gain (Novaco & Chemtob, 1998). Anger problems showed to be irrespective to gender, leaving anger as a common problem in both men and women with PTSD (Worthen et al., 2014). Furthermore, anger has been shown to be problematic in all PTSD affected populations irrespective of the types of traumatic events experienced, although, veterans show the highest levels of anger (Orth & Wieland, 2006).

Development of the section of 'Trauma and Stressor-Related Disorders' in the DSM-5 (American Psychiatric Association, 2013) may be an important contributor to the research into etiology of PTSD in the near future. The addition of this section is, in a certain way, a return to the classic conceptualization of the stress response syndromes. This was first described by Horowitz in his book Stress Response Syndromes (Horowitz, 1976). According to this theory, stress response syndromes start with an initial phase wherein one realizes that a stressful event has happened, followed by a phase of suppressing the disturbing news. Then, alternation of image intrusion and suppression take place, and finally in a processing phase, the disturbing information either gets integrated into the cognitive schemata or results in negative outcomes, such as development of psychiatric disorders and/or changes in personality.

Horowitz (1976) stated that the stressor related disorders are expressed with a heterogeneous amount of emotions, which are related to the traumatic event and to its reminders, changing over time both in characteristics and intensity. The disturbing information is accompanied with a wide variety of behaviors, cognitions and emotions, including anger. In essence, a failure in image control leads to development of posttraumatic symptomatology (Horowitz, 1976, 2011).

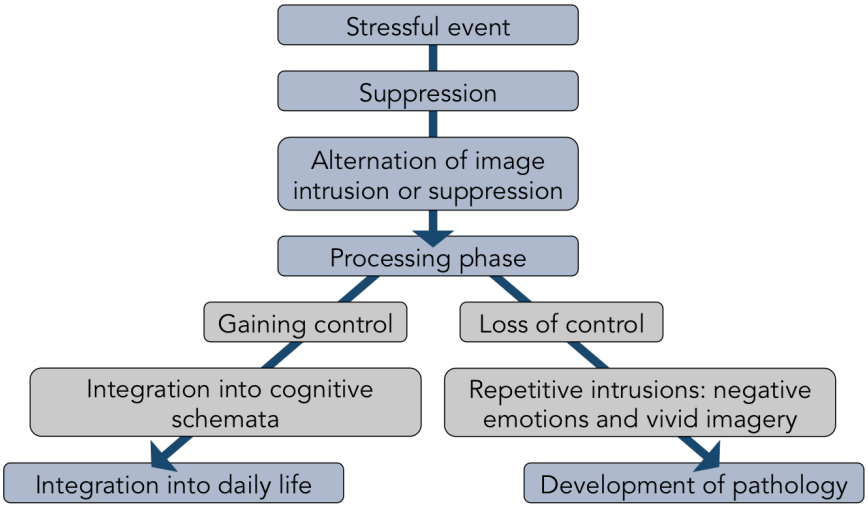

Figure 1.
Development of stress response syndromes; Horowitz, 1976; 2011.

The emphasis of multiple emotions in PTSD instead of on anxiety only, is made more explicit in the DSM-5 section of 'Trauma and Stressor-Related Disorders' which includes PTSD (American Psychiatric Association, 2013). This new section includes a revision of the PTSD diagnostic criteria, a decision explained by Friedman et al. stating that: "These variations of responses within PTSD highlight the heterogeneity of the condition, and different presentations are associated with distinct neural circuitries. This heterogeneity suggests that PTSD cannot be understood by a single model because different mechanisms are probably underpinning both the etiology and maintenance of the variants of PTSD" (Friedman et al., 2011).

The DSM-5 criteria for PTSD pay more attention to anger and aggression compared to the criteria in DSM-IV. In DSM-5 anger is included in the criterion D-4 ("Negative alternations in cognition and mood") as a "Persistent negative emotional state". Aggression is included in the criterion E-1 as "Irritable behavior and angry outbursts typically expressed as verbal or physical aggression". The inclusion of these criteria is supported by research findings, suggesting that the hyperarousal cluster in PTSD (according to the DSM-IV) is strongly correlated to anger and aggressive behavior (Elbogen et al., 2010; Jakupcak et al., 2007).

Theories and explanatory models regarding anger and aggression in PTSD:
Various phenomena and factors are associated with anger in PTSD, leading to different attempts made in order to explain this relationship. With regard to psychological processes, Orth and Wieland (2006) presented a 'survival mode theory' and a 'fear

avoidance' theory. The first theory hypothesizes that individuals suffering from PTSD have a lowered threshold for perception of threat, and when feeling threatened they activate a biologically predisposed survival mode, including fear and flight- and anger and fight reactions (e.g. Chemtob et al., 1997; Novaco and Chemtob, 1998). The second theory hypothesizes that PTSD patients want to avoid intrusions activated by trauma-related feelings of fear by shifting to trauma-related anger. Anger seems to be more acceptable for the PTSD patient than fear (e.g. Feeny, Zoellner, Fitzgibbons, & Foa, 2000).

The 'neo-associationist memory network theory' (Berkowitz, 1993) is an information processing model that, applied to PTSD and anger, focuses on associative networks between negative affect and anger related feelings, thoughts, memories and aggressive impulses (Taft, Vogt, Marshall, Panuzio, & Niles, 2007). According to this theory, the increased memory networking causes an all-consuming role of anger by dominating other emotions. This leads to a preoccupation with anger facilitated by a ruminative processing style and a vulnerability to triggering, because of the inability to discriminate between significant and non-significant triggers for anger. Furthermore, the probability that anger may result in aggression increases, as anger may be out of awareness.

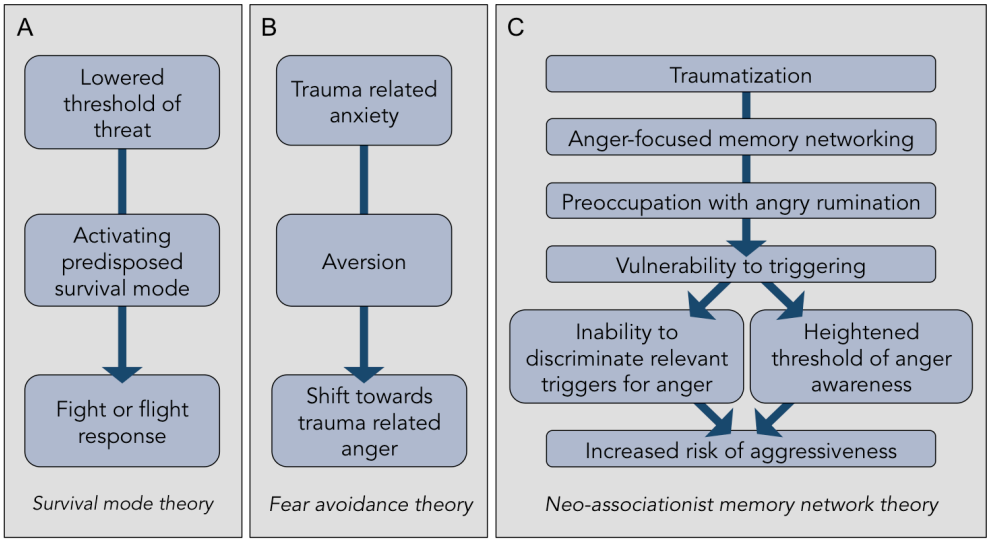

Figure 2.
Theories regarding anger and aggression in PTSD: A) Survival mode theory; Orth et al.., 2006. B) Fear avoidance theory; Orth et al.., 2006. C) Neo-associationist memory network theory; Berkowitz, 1993; Taft et al.., 2007.

Heightened arousal is known to increase aggressive behavior. The association between PTSD and aggression is linked to the common brain circuitries and neural systems that regulate aggression, hyperarousal and anxiety. The inhibiting role of the frontal cortex, the region primarily responsible for cognition, and the signaling role of the limbic structures, controlling autonomous arousal, play a significant role in regulating emotions and arousal (Davidson, Putnam, & Larson, 2000). In case of threat, signals are regarded as more threatening due to the overactive limbic system, whereas too little inhibition from the frontal areas leads to impulsive aggressive responding. These findings are in line with the survival mode theory.

Furthermore, neuromodulators tend to play a role in aggressive behavior. The facilitating role of serotonin on the frontal areas indicates that insufficient serotonergic activity enhances aggression. Additionally, GABAergic activity can reduce subcortical activity; thus, increased GABA activity increases aggressive behavior (Siever, 2008).

With regard to anxiety problems in PTSD, research suggested that anger relates to the approach motivational system, while anxiety relates to an aversive or avoidance motivational system. This division resembles the well-known fight or flight response to trauma exposure (Carver & Harmon-Jones, 2009).

Moreover, several other issues often present in PTSD patients may contribute to the development of anger and aggression. Mistrust, powerlessness, shame and guilt about the traumatic events experienced, can be externalized to other people in the form of irritability, hostility and aggression. Individuals with PTSD may not be perceived by their surroundings as having nice characters, and this opinion is often related to their irritability rooted in anger.

Anger and aggression in PTSD are moderated by different comorbid conditions, like substance abuse (Olatunji et al., 2010), personality characteristics connected to trait anger before trauma and is associated with an insecure attachment style (Troisi & D'Argenio, 2004), an externalizing personality style (type A personality), depression, and traumatic brain injury (increasing aggressive behavior in PTSD patients). Moreover, time elapsed since the original trauma with the oscillating phases of intrusion and avoidance and varying anger intensity and expression (Orth & Wieland, 2006) may also contribute to development of anger and aggression in PTSD.

Table 2.
Comorbid conditions moderating anger and aggression in PTSD

Comorbid conditions
Substance abuse
Personality characteristics (type A personality)
Insecure attachment
Depression
Traumatic brain injury

Orth & Wieland (2006) showed in their meta-analysis that war veterans show the highest level of anger, but that anger is also present in survivors of other types of traumatic experiences. Furthermore, it is suggested that higher military pre-deployment levels of hostility and trait anger predicted higher PTSD symptoms, which indicates that anger is a risk factor for the development of PTSD (Lommen, Engelhard, van de Schoot, & van den Hout, 2014; Van Zuiden et al., 2011).

However, none of the above-mentioned theories and explanations succeed in providing an all-encompassing explanation for the relationship between anger and PTSD. Therefore, further research is needed in order to generate new insights regarding this relationship.

The role of rumination in anger and aggression problems:
Rumination typically involves intrusive and repetitive thoughts about a distressing occurrence (Denson, Pedersen, Friese, Hahm, & Roberts, 2011). This description of rumination resembles the description of intrusion symptoms in PTSD, although an important difference is that intrusions are out of control and are accompanied with visual components. Both rumination and intrusions share the perseverance, but they differ in the way that rumination is not necessarily out of control and seems to be a mainly cognitive phenomenon. However, the latter is still a subject of debate, as will be discussed in the paragraph about visual imagery and PTSD.

It is important to take into account that the non-pathological development of anger upon trauma is characterized by its absence upon exposure to a traumatic experience, followed by its occurrence and raise to a significant level, and a gradual decrease over time. When this natural course of anger development does not take place and anger level is reduced or increases, we speak about angry rumination.

Conceptualization of the process of rumination originates from the depression and mood disorders research. The connection with trauma was established partially by coincidence in a study of Nolen-Hoeksema and Morrow (1991), when during their study into the role of emotional health and the role of rumination in depressive mood in a student population, the Loma Pieta Earthquake took place after the first measurement, giving a unique prospective opportunity to study the role of rumination in development of the traumatic stress symptoms (Nolen-Hoeksema & Morrow, 1991). It was found that students with ruminative response styles showed higher levels of symptoms associated with PTSD than those with a less ruminative style.

Conceptualization of the anger rumination was further influenced by the work of Averill (1983) and Spielberger et al. (1983). Especially the anger-in mode described by Spielberger (the suppression of anger) seems to result in angry rumination. Sukhodolsky et al. (2001) described anger rumination in more detail, defining it as ‘a tendency to

engage in unintentional and recurrent cognitive processes that emerge during, and continue after an episode of anger experience'. These authors separate anger from anger rumination and state that 'if anger is viewed as an emotion, anger rumination can be defined as thinking about this emotion' (Sukhodolsky, Golub, & Cromwell, 2001).

Ehlers and Clark (2000) defined rumination in relation to trauma as 'perseverative thinking about the trauma and its consequences, including thoughts about the past or present, as well as anxious thoughts about the future' (Ehlers & Clark, 2000). This definition stresses the perseverance of the process of rumination.

Meanwhile, research has proved that rumination increases anger and aggression, and more recent research focuses on the moderating effect of angry rumination in development of the PTSD symptomatology (Denson, Pedersen, Ronquillo, & Nandy, 2009). Since the ruminative style of emotion regulation is closely linked to the re-experiencing symptoms cluster in PTSD (Ehlers, Mayou, & Bryant, 1998), it remains important to address the role of rumination in connection to anger and PTSD both in research and clinical practice.

Research exploring the relationship between rumination, anger and traumatic stress is relatively scarce. However, strong indications were found that the effect of PTSD symptoms on anger was mediated by rumination (Orth & Wieland, 2006). When the mediating role of rumination was taken into account, the effect of PTSD symptoms on anger was not found to be significant, suggesting the crucial role of rumination in the development of anger problems. Based on this research, Orth & Wieland (2006) suggest that "rumination might be a psychological mechanism through which PTSD increases anger after a traumatic event".

Another recent study (Borders, McAndrew, Quigley, & Chandler, 2012) suggests that veterans with more severe PTSD and depressive symptomatology report more risky behavior. This relation shows to be moderated by rumination. This finding seems to support the earlier finding that PTSD severity is related to rumination (Orth, Cahill, Foa, & Maercker, 2008), especially when the strong correlation between anger-in and PTSD is taken into account. The hypothesis that a ruminative style of emotion regulation might be closely linked to the re-experiencing symptom cluster in PTSD fits to these findings (Orth & Wieland, 2006).

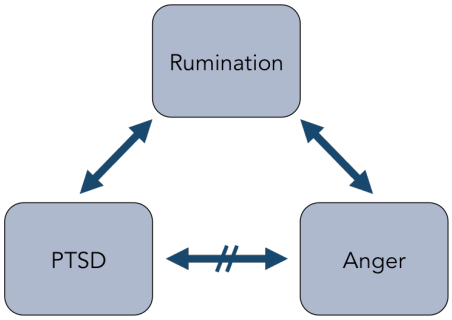

Figure 3.
The mediating role of rumination on anger problems in PTSD over time.

From the neurophysiological perspective, rumination is associated with regions involved in emotion regulation, such as the cingulate cortex, the mPFC, the lateral PFC, and the insula (Denson et al., 2009). In a study in which angry rumination, analytical rumination and reappraisal during an MRI-scan were compared, it was found that rumination lead to the highest levels of anger. Additionally, the functional connectivity between the frontal and the limbic areas was found to be the highest. This indicated that during angry rumination, top-down regulation of the limbic system was not effective enough (Fabiansson, Denson, Moulds, Grisham, & Schira, 2012). These findings imply that the underlying neural mechanisms of rumination contribute to the maintenance or aggravation of anger.

The role of visual imagery in anger and PTSD:
Visual imagery is described as the capacity to image visual mental phenomena (McHugh et al., 2012). According to McHugh et al. (2012), visual imagery may play a crucial role in development of anger problems in PTSD. This hypothesis is supported by the finding that there is a high level of overlap in the brain areas activated in angry emotion and visual imagery. Moreover, neural pathways link the processing of visual imagery with activation of defense emotions like anger. The processing of visual imagery and defense emotions together leads to rapidly responding to dangers or threats (McHugh et al., 2012).

Negative emotion and psychopathology is also associated with visual imagery. This can be explained with the direct effect of images on the emotional system in the brain. Images have a similar or even stronger effect than reality on emotion and images, and can reactivate feelings from the past. These associations closely resemble the intrusion symptoms of PTSD, in terms of visual imagery explained as experiencing repetitive traumatic imagery concomitant with high levels of negative emotions.

The influence of visual imagery on anger in PTSD is explained by a loss of control

caused by repetitive intrusions, leading to negative emotions and anger in particular. This is in accordance with the already discussed theory by Horowitz (1976), stating that the presence of traumatic information in active memory is in essence a failure in image control, which leads to a chain of emotions, including anger (Horowitz, 1976, 2011).

Moreover, repetitive intrusions lead to an increasing capacity to experience imagery and increase vividness of that imagery. The resulting distress intensifies intrusions, increasing the experience of anger. The attempts to suppress intrusive images leads to an unwanted increase of intrusions (McHugh et al., 2012).

With regard to the role of rumination in development of anger in PTSD, it can be hypothesized that repetitious and intrusive visual imagery characterizes angry rumination in PTSD. This hypothesis is underpinned by the finding that visual processing is more emotionally loaded than verbal processing (Holmes & Mathews, 2005). McHugh et al. (2012) state that in many disorders rumination may be verbal, but that in PTSD it may have a strong visual component leading to stronger emotions. The concept of visual imagery seems to be important as it may help in understanding the mechanisms underlying PTSD and the impact it has on anger in PTSD. However, research is still in its early stages. As stated by McHugh et al. (2012) 'visual imagery alone is unlikely to account for all presentations of anger in PTSD. At times, it may have little effect on anger in PTSD, interact with other cognitive mechanisms, or have a large, singular and direct effect on anger'.

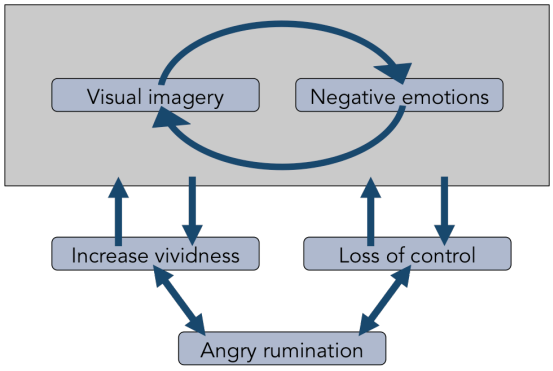

Figure 4.
Schematic depiction of the crucial role of visual imagery in the development of angry rumination in PTSD

Aggression and PTSD

The distinction between impulsive aggression and premeditated aggression depends on the aspects of control and concomitant emotion in aggression (Polman, Orobio de Castro, Koops, van Boxtel, & Merk, 2007). However, it is important to keep in mind that

the distinction between impulsive and premeditated aggression is partially artificial. In clinical practice persons can be separated as predominantly impulsive or predominantly premeditated with the majority of aggressive persons showing aspects of both types of aggression.

The knowledge about aggression in PTSD is based on relatively new research, which is at the stage that it is possible to draw conclusions about associations, but causalities are still hypothetical. Hypotheses that are based on the knowledge derived from neurobiological, neuropsychological and pharmacological knowledge on impulsive aggression are still subject of investigation. Nevertheless, this domain is extremely relevant for further development of interventions in clinical practice.

In order to understand the importance of impulsive aggression in PTSD, the current neurophysiological knowledge involved in impulsive aggression will be discussed. Furthermore, we will address related topics such as language impairment and impaired executive functioning. A comprehensive analysis and a model of impulsive aggression is given by Miller et al. (2008) in a recent overview of the functional anatomy of impulsive aggression. In the following section, the most relevant details of this analysis, helping to understand aggression in PTSD, will be discussed and explained.

Communication and information processing is impaired in patients with impulsive aggression. Perception of the context wherein the patient resides is biased towards interpretations of that context as threatening, victimizing and disrespectful. Giving calming feedback paradoxically fuels escalation instead of diminishing it. Afterwards, an aggressive person often feels guilty, reports loss of control and recognizes the disproportionality of his/her reaction to a trigger situation.

Functional MRI findings in studies of impulsive aggression show abnormalities in the language processing regions of the brain, the sections of the medial orbital prefrontal cortex and the lateral prefrontal cortex (Miller, Collins, & Kent, 2008; Teten, Miller, Bailey, Dunn, & Kent, 2008). The orbital and lateral prefrontal cortex have an important function in inhibiting aggression by their top-down regulatory function over the limbic system (Adams, 2006).

In animal research, defensive rage is a concept defined as an automatic and reflexive survival response to threat. In defensive rage, the medial nucleus of the amygdala, the medial hypothalamus and the dorsal periaqueductal grey are involved (Siegel, Bhatt, Bhatt, & Zalcman, 2007). When these regions are stimulated, defensive rage will occur. Human impulsive aggression resembles this defensive rage.

The amygdala plays a role in increasing and decreasing aggression (Davidson et al., 2000). Accurate interpreting of emotions in facial expression depends on intact amygdala and orbitofrontal cortical functioning, meaning that problems in these regions lead to problems in interpreting emotions, serving as the most important triggers for

impulsive aggression (Coccaro, McCloskey, Fitzgerald, & Phan, 2007). This finding is consistent with clinical knowledge suggesting that individuals presenting with impulsive aggression report misinterpretation of the intent of the other in impulsive aggressive episodes, and are interpreting cues more negatively than somebody without impulsive aggression. Furthermore, individuals with impulsive aggression have difficulties in labelling their own emotions, connected to abnormalities in the brain regions mentioned earlier (Denson et al., 2009).

Miller and colleagues (2008) summarized that 'dysfunction of key regions of the amygdala (or its prefrontal connections with the orbital prefrontal cortex) that modulate arousal and defensive rage, or that contribute to networks involved in the discrimination of emotional cues, may explain the importance of amygdala abnormalities in neuroimaging studies of impulsive aggression' (Miller et al., 2008).

The importance of language is supported by the finding that there is diminished verbal working memory and diminished syntactic processing. Both contribute to executive control problems, impairing the inhibition of emerging impulsive aggression. Bilateral abnormalities in language regions contribute to impulsive aggression in the way that they diminish the capacity of processing and interpreting complex linguistic stimuli.

Impulsive aggression in PTSD is studied by Teten and colleagues in a sample of traumatized war veterans (Teten et al., 2010, 2008). They conclude that 'language processing regions may mediate executive abilities important to the regulation of aggressive impulses, such as deductive reasoning, cognitive restraint of aggression (that may be separable from motoric inhibition of aggression), cognitive modulation of emotion, and/or reflective functioning'. They further suggest that alexithymia, a trauma related emotional awareness deficit defined as the inability to recognize and articulate one's own emotional experience despite an adequate emotional vocabulary, is uniquely associated with impulsive aggression (Teten et al., 2008). This deficit in processing and articulating emotional cues affects the ability to use language in emotion regulation, thus failing to inhibit aggressive outbursts.

Miller et al. (2008) conclude that the reduction of impulsive aggression is not achieved by the reduction of anger, and vice versa (Miller et al., 2008). Besides, pharmacological reduction of impulsive aggression (by using phenytoin, an anticonvulsant agent) did not result in reduction of anger, although there was a significant reduction of aggressive acts (Barratt, Stanford, Felthous, & Kent, 1997). Therefore, it can be argued that anger is necessary for the development of aggression, but that it is not sufficient to cause (impulsive) aggression.

Noteworthy is that some PTSD patients with aggression problems report becoming anxious upon being aggressive. They fear a loss of control during an aggressive outburst, and afterwards they become aware of the intensity of their anger and aggression. This is

typically referring to impulsive aggression instead of premeditated aggression. The latter does not seem to be accompanied with anxiety, on the contrary, it may even go together with feelings of pride. The notion that patients are anxious to become aggressive is supported by Forbes and colleagues by stating that individuals may be afraid to access traumatic memories, because of the fear of anger (Forbes et al., 2008). These memories might activate their anger and trigger aggressive behaviors (Forbes et al., 2008), giving support to the finding that impulsive aggression is uniquely connected to PTSD. The earlier mentioned PTSD E-1 criterion in DSM-5; "Irritable behavior and angry outbursts typically expressed as verbal or physical aggression", has to be understood as referring to impulsive, and not premeditated aggression. The latter is more often connected with other disorders, such as conduct disorder and antisocial personality disorder. The essence of aggression in PTSD is the loss of control and cognitive impairment.

Finally, it has to be acknowledged that the research focusing on aggression in PTSD that is presented in this section was predominantly carried out in veteran samples. Therefore, it is important to be careful in generalizing the research findings to other samples of PTSD patients.

Practice and procedures: assessment of anger, rumination and aggression

Several assessment instruments have been developed in the past decades, and can be used in assessing anger, aggression and rumination in clinical practice.

In assessment of anger, two instruments are highly recommended because of their capacity to discriminate between the different aspects of anger - the State Trait Anger Expression Questionnaire (STAXI-2) (Spielberger, Sydeman, Owen, & Marsh, 1999) and the Dimensions of Anger Reactions Scale (DAR) (Forbes et al., 2004). The STAXI-2 is a 57 item self-report questionnaire, measuring the dimensions of anger developed by Spielberger. The DAR is an instrument preliminary focusing on trait anger and, depending on the purpose of investigation, a good alternative to the STAXI-2. The DAR consists of 7 items, compared to the 57 items of the STAXI-2.

Assessment of rumination is possible with instruments developed out of different perspectives. The Ruminative Response Scale (RRS-R) (Nolen-Hoeksema & Morrow, 1991; Treynor, Gonzalez, & Nolen-Hoeksema, 2003) is a 26 item self-report questionnaire developed to measure rumination in mood disorders. Although well validated and documented, it is not originally meant to assess rumination in PTSD. Angry rumination can be measured with the 19 item Angry Rumination Scale (ARS) (Sukhodolsky et al., 2001). A third possibility is to use an instrument examining repetitive thinking, such as the Perseverative Thinking Questionnaire (PTQ). This is a 15-item instrument developed to assess a ruminative style, independent of the content of emotions as anger, depression, anxiety, etc. (Ehring et al., 2011). The instrument is based on the concept of Repetitive

Negative Thinking (RNT), defined as a trans-diagnostic process that shows the same characteristics across disorders, with only the content of thinking as disorder specific (Ehring & Watkins, 2008).

Aggression in PTSD can be assessed with the Impulsive Premeditated Aggression Scale (IPAS), a 30 item self-report scale (Stanford et al., 2003) with two subscales for premeditated aggression (12 items) and impulsive aggression (8 items). A good alternative is the Aggression Questionnaire (Buss & Perry, 1992), a 29-item questionnaire with four subscales for physical aggression, verbal aggression, anger and hostility.

It is also possible to assess aggression with a clinical interview, such as the Aggression Interview. This is a semi-structured interview designed to characterize the aggressive acts as either predominantly impulsive or premeditated in nature (Stanford et al., 2003).

Table 3.
Instruments for the assessment of anger, rumination and aggression.

Assessment	Instrument
Anger	State-Trait Anger Expression Questionnaire (STAXI-2)
	Dimensions of Anger Reactions Scale (DAR)
Rumination	Ruminative Response Scale (RRS-R)
	Angry Rumination Scale (ARS)
	Perseverative Thinking Questionnaire (PTQ)
Aggression	Impulsive Premeditated Aggression Scale (IPAS)
	Aggression Questionnaire

Practice and procedures: anger and aggression in clinical practice

Treatment strategies should address both impulsive aggression and angry emotion in PTSD. Although anger and aggression are connected, they are not the same. For this reason, treatment addressing only anger or only aggression is not enough. Treatment should address different pathways to diminish both anger and aggression.

Assessment should be carefully undertaken in order to find the most suitable pathway for treating PTSD patients with anger and aggression problems. It is important to know that patients who suppress anger experience higher physiological arousal (Chemtob, Novaco, Hamada, & Gross, 1997; McHugh et al., 2012). The focus of anger management programs should help patients moderate anger intensity and anger duration, and help them in facilitating a more appropriate expression instead of using catharsis or strengthening the capability to suppress anger (Mayne & Ambrose, 1999).

There are beliefs about anger and aggression widely supported by clinicians and thereby influencing treatment strategies, but not supported by research (Buss & Perry, 1992; Elbogen et al., 2010; Ouimette et al., 2004). The first belief is that expressing anger helps in reducing it. However, empirical studies show the contrary and suggest that

expression may increase anger intensity and expression. Another belief is that there is a gender difference in anger expression, and that males express anger outwardly while females direct their anger inwardly and get depressed. However, research showed that males and females experience anger with the same intensity and frequency, express it in the same way, and that depressed females are more angry than non depressed females. The confirmed gender difference is that angry males are more likely to express themselves though verbal and physical assault than females (Buss & Perry, 1992; Elbogen et al., 2010; Ouimette et al., 2004).

Development of treatment strategies of anger and aggression in PTSD is in its early stages. In a recent review of treatments targeting anger and aggression in PTSD, few interventions have been elaborated (Taft et al., 2012). Cognitive behavioral interventions, such as teaching relaxation skills and effective communication skills, improving coping skills and targeting the automatic anger-related thoughts, have shown to be effective in reducing anger and aggression problems in different populations. However, the effectiveness of cognitive behavioral interventions in the treatment of aggression is not established yet, as aggression was not included in the outcome measures in existing research.

As discussed earlier, language disturbances may play an important role in the development of impulsive aggression. Expressive writing is suggested to be an important strategy to improve the language impairment, enhance emotion regulation skills, and reduce physiological reactivity by attenuating cortisol levels (Lepore & Smyth, 2002; Pennebaker & Beall, 1986; Smyth, Hockemeyer, & Tulloch, 2008). Expressive writing reduces tension and anger in PTSD patients, and improves the capacity to regulate trauma-related intrusive thoughts, psychological distress and physical symptoms (Smyth et al., 2008). Although expressive writing does not decrease PTSD symptoms, the capacity to regulate them has been improved, enhancing the opportunity to be more effective with the usual PTSD treatment strategies afterwards.

Expressive writing is also important in reduction of rumination problems and depressive symptoms (Gortner, Rude, & Pennebaker, 2006). Given the important role of angry rumination in PTSD, the use of expressive writing in addressing this problem deserves further investigation both in research and in clinical practice.

More recently, the use of EMDR in anger management problems was reported, and an EMDR treatment protocol specifically targeting anger and revenge was developed (Veerbeek, 2014). In this protocol, the patient is, first, instructed to visualize a scenario including the subject of anger and revenge feelings. Next, the patient is asked to elaborate and visualize in detail the intended physical actions, targeting the physical arousal in the patient. During EMDR, the patient will continue visualizing physical and verbal actions towards the visualized other, until anger and revenge feelings are disappeared. The

author of this protocol argues that in patients where anger is most prominent, compared to other PTSD connected symptoms, anger should be targeted first. This hypothesis is supported by research discussed earlier in this chapter.

Pharmacological treatment of impulsive aggression has been studied with the anticonvulsant phenytoin (Stanford et al., 2001). It has been suggested that this agent has the potential to treat impulsive aggression, hypothesizing that phenytoin may help to regulate sensory and early attention processing, enhance the capacity to evaluate and react to eliciting stimuli. Also, Fluoxetine may be effective in treatment of impulsive aggression (Coccaro & Kavoussi, 1997), due to the inverse relationship between impulsive aggression and serotonin system functioning (Marazziti et al., 1993). It is important to mention that these research findings are based on non-PTSD samples.

An epilogue: morale in anger and aggression in PTSD

In research into anger and aggression in PTSD, the role of conscience and morale is almost entirely left out of consideration. This is remarkable because, except for natural disasters, most traumatic events are caused by aggressive acts, inflicted by others as a victim or performed to others as a perpetrator. The earlier discussed angry rumination often addresses repetitive thoughts about violation of deeply held moral beliefs and values. Especially combatants are frequently confronted with violations of their own expectancies, moral codes and values, leading to anger, shame, guilt and morality problems.

In research, morale connected to warzone trauma is addressed by the preliminary concept of moral injury (Litz et al., 2009), that is defined as 'the lasting psychological, biological, spiritual, behavioral, and social impact of perpetrating, failing to prevent, or bearing witness to acts that transgress deeply held moral beliefs and expectations'. Morally injurious experiences are recalled intrusively and often address anger and frustration about losses, sacrifices, and adversities. Rumination about moral injuries fosters distress, withdrawal, and reinforce destructive beliefs of being unforgiveable (Ehlers & Clark, 2000).

Related to moral injury is the effect of long term political violence and aggression on the development of children (Wainryb & Pasupathi, 2010). These circumstances can lead to disruptions in moral development and to acts of aggression, eventually resulting in traumatization of others. In addition, children can be affected by anger or aggression outbursts of their traumatized parents (Wainryb & Pasupathi, 2010). In clinical practice, this effect is known as the second-generation effect.

To get a better understanding of anger and aggression problems in PTSD, it is important to take into account the role of morality problems, both in the effect on the trauma survivor themselves as on the long-term effect on the raising of offspring.

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3

Longitudinal Measures of Hostility in Deployed Military Personnel

Lieke Heesink
Arthur Rademaker
Eric Vermetten
Elbert Geuze
Rolf Kleber

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Abstract

Increases in anger and hostility are commonly found after military deployment. However, it is unknown how anger and hostility develop over time, and which veterans are more at risk for developing these complaints. Data of 745 veterans one month before deployment to Afghanistan and one, six, twelve and 24 months after deployment were analyzed in a growth model. Growth mixture modeling revealed four classes based on their growth in hostility. Most of the participants belonged to a low-hostile group or a mild-hostile group that remained stable over time. Two smaller groups were identified that displayed increase in hostility ratings after deployment. The first showed an immediate increase after deployment. The second showed a delayed increase between twelve and 24 months after deployment. No groups were identified that displayed a decrease of hostility symptoms over time. Multinomial logistic regression was applied to predict group membership by age, education, early trauma, deployment stressors and personality factors. This study gains more insight into the course of hostility over time, and identifies risk factors for the progression of hostility.

Acknowledgment contribution authors
Designed research: L. Heesink, A. Rademaker, E. Vermetten & E. Geuze
Performed research: L. Heesink, A. Rademaker & E. Geuze
Analyzed data: L. Heesink, A. Rademaker & E. Geuze
Wrote the paper: L. Heesink, A. Rademaker, E. Vermetten, E. Geuze & R. Kleber

Introduction

During deployment, military personnel are often exposed to heightened stress and traumatic events. Mental health problems after returning from deployment, in particular (symptoms of) depression, anxiety and posttraumatic stress disorder (PTSD), have been identified in several studies (reviewed by Hoge et al., 2004) Furthermore, some studies point towards an increase in anger and hostility after deployment (Elbogen et al., 2010; Jakupcak et al., 2007; Reijnen, Rademaker, Vermetten, & Geuze, 2015; Worthen et al., 2014). However, many aspects such as the development over time and the risk factors of heightened anger and hostility after deployment remain unknown.

Anger and hostility are terms that partly overlap. Anger refers to the emotions and feelings, or the affective component of aggressive behavior, whereas hostility points towards the negative attitude or evaluation of persons or objects (Ramirez & Andreu, 2006). Anger can be divided into state and trait anger. State anger refers to a current emotional state, which can change over time. Trait anger can be described as a rather stable character trait (Spielberger, Sydeman, Owen, & Marsh, 1999). Both anger and hostility can lead to aggressive behavior, and anger and hostility are related to intimate partner violence (Birkley & Eckhardt, 2015). Anger and hostility are closely associated with a large number of disorders, including anxiety and depressive disorders (Painuly, Sharan, & Mattoo, 2005), intermittent explosive disorder (Coccaro, 2012), and PTSD (Orth & Wieland, 2006). In the DSM-5, an anger symptom has been added to the PTSD classification (American Psychiatric Association, 2013).

Anger and hostility may increase the risk of developing PTSD symptoms, whereas PTSD symptoms and exposure to traumatic events can lead to heightened anger and hostility (Heinrichs et al., 2005; Lommen, Engelhard, van de Schoot, & van den Hout, 2014; Meffert et al., 2008; van Zuiden et al., 2011). Anger and hostility is mainly treated using cognitive behavioral therapy (Chemtob, Novaco, Hamada, & Gross, 1997). Aggressive behavior is a difficult condition to treat due to a high drop-out (Chemtob et al., 1997) and number of treatment utilizations is not related to changes in aggression (Shin, Rosen, Greenbaum, & Jain, 2012). The presence of anger and hostility has been found to predict a worse course of psychiatric disorders and worsen the prognosis of psychotherapy (McHugh, Forbes, Bates, Hopwood, & Creamer, 2012; Painuly et al., 2005).

The course of anger and hostility over time has not been studied in a military sample before. One longitudinal study in a civilian sample revealed that hostility remained moderately stable into young adulthood (Hakulinen et al., 2014). Although exposure to traumatic events can lead to increased anger and hostility (Meffert et al., 2008), anger and hostility are more common after combat experience compared to any other type of major stress experience (Orth & Wieland, 2006). This suggests that combat experiences

may have a different effect on post-traumatic adjustment than other types of traumatic experiences. Alternatively, it is possible that military personnel are characterized by increased pre-trauma anger and aggression. Although heightened anger and hostility are commonly reported after deployment, it is still unknown how they develop over time and which factors affect the development and course of these symptoms.

Previous studies on the course of posttraumatic reactions over time in military samples (Berntsen et al., 2012; Bonanno et al., 2012; Orcutt, Erickson, & Wolfe, 2004) revealed different trajectories including chronic, new-onset, delayed-onset, recovery and benefit groups. Moreover, the majority of respondents was resilient and did not suffer from PTSD. Because anger and hostility in a deployed military sample are closely related to PTSD symptoms (Novaco & Chemtob, 2002), it is hypothesized that the progression of hostility symptoms over time is similar to the trajectories that are usually observed in PTSD symptom severity.

Heightened anger and hostility in military samples has been linked to increased reactivity to fearful or threatening distress (Chemtob et al., 1997). This increased reactivity might, at least partially, be attributed to individual differences in personality dimensions (Brandes & Bienvenu, 2006) as both general reactivity and behavior activation and inhibition reflect inherent dimensions of temperament (Cloninger, Svrakic, & Przybeck, 1993). Furthermore, the cognitive aspect of hostility, for example a negative attitude, is linked to personality as well (Ramirez & Andreu, 2006). Thus far, it remains largely unclear how personality factors may affect and shape the development of hostility symptoms after deployment over time (Orth & Wieland, 2006).

In the present study we used growth mixture modeling (GMM), to examine trajectories of hostility in military personnel from pre-deployment to two years after homecoming. GMM is a technique to identify homogenous groups within a larger heterogeneous sample (Jung & Wickrama, 2008). The first aim was the determination of the trajectories of hostility after deployment. The next aim was the identification of predictors of these trajectories, specifically age, education, early trauma, deployment stressors and personality.

Methods

Participants and procedure

The current study is part of a large prospective study on biological and psychological predictors of deployment-related disorders in the Dutch Armed Forces. The Dutch Armed Forces are a volunteer army. Participants included in this study consisted of 993 healthy veterans who were deployed for 4 months to Afghanistan as part of the

NATO International Security Assistance Force (ISAF). Duties during deployment included combat patrols, clearing or searching homes and buildings, participation in demining operations, and transportation across enemy territory. Participants were exposed to typical war-zone stressors such as enemy fire, armed combat, and seeing seriously injured fellow soldiers and civilians (including women and children). An overview of exposure to deployment stressors is presented in Table 1.

Questionnaires were administered one to two months prior to deployment to Afghanistan (T0) and one (T1), six (T2), twelve (T3) and 24 months (T4) after this deployment. Data of participants were only included in the analyses if data from at least three assessments were available. Therefore, 248 participants were excluded, leading to a final analysis sample of 745 participants (mean age = 29.5 years, 90.2% male). All participants gave written informed consent prior to the study. The study was carried out in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the University Medical Center Utrecht, the Netherlands.

Table 1.
Percent of sample endorsing each traumatic event during deployment.

	%
Enemy fire	62.3
Witnessed people suffering	60.1
Witnessed wounded	46.6
Colleague injured or killed	46.1
Incoming fire	38.3
Witnessed dead	37.4
Rejection by locals	33.9
Personal danger	29.2
Screaming of injured people	20.6
Witnessed people getting killed/injured	19.6
Insufficient means to intervene	17.1
Insufficient control over situation	13.5
Mission experienced as useless	12.9
Memories of former deployments	12.3
Traffic accident	9.1
Held at gunpoint	5.1
Being injured	2.5
Colleague held hostage	0.5
Held hostage	0.0

Measures

Hostility was measured at all time-points using the hostility scale of the Dutch version of the Revised Symptom Checklist-90 (SCL-90) (Derogatis & Unger, 2010). The SCL-90 has good reliability and has been used frequently in previous studies as well as in clinical

settings (Schmitz, Kruse, Heckrath, Alberti, & Tress, 1999). The hostility scale consists of six items, in which participants have to indicate whether they were bothered by the items in the last week, ranging from 1 (not at all) to 5 (extremely). The items on this scale measure both anger and hostile symptoms (Orth and Wieland, 2006). Scores on this scale range from 6-30 with higher scores reflecting more severe anger and hostility symptoms. The scale measures the current state of anger and hostility symptoms. Cronbach's α ranged from .63 till .82 on all time-points for this scale.

The Dutch short version of the Temperament and Character Inventory (TCI) (Duijsens, Spinhoven, Verschuur, & Eurelings-Bontekoe, 1999) was filled out prior to deployment to assess personality. This version of the TCI consists of 105 dichotomous 'true' or 'false' items. The questionnaire measures four temperament dimensions: novelty seeking, harm avoidance, reward dependence and persistence; and three character dimensions: self-directedness, cooperativeness and self-transcendence. 'Novelty seeking' is defined as impulsivity and activity in response to novelty. 'Harm avoidance' refers to inhibition of behavior and passive avoidant behavior. 'Reward dependence' is defined as maintenance of behavior and dependence on approval of others. 'Persistence' refers to perseverance. 'Self-directedness' is defined as self-determination. 'Cooperativeness' refers to empathy and helpfulness. 'Self-transcendence' refers to a spiritual union with one's surroundings. Cronbach's α ranged from .63 till .80 on all subscales.

Exposure to childhood trauma was assessed prior to deployment using the Dutch short-form self-report version of the Early Trauma Inventory (Bremner, Bolus, & Mayer, 2007; Rademaker, Vermetten, Geuze, Muilwijk, & Kleber, 2008). This checklist consists of 27 dichotomous items in order to assess exposure to traumatic experiences (general trauma, physical abuse, emotional abuse and sexual abuse) before the age of 18 years. The total score represents the number of different traumatic events experienced.

Exposure to traumatic events during deployment was assessed one month after homecoming using a 19-item checklist, the Deployment Experiences Scale (DES) (Reijnen et al., 2015). The items are depicted in Table 1.

Statistical analyses

Growth mixture modeling (GMM) is an explorative technique to estimate unobserved homogeneous subpopulations of trajectories within a larger heterogeneous sample (Jung & Wickrama, 2008). Using GMM, trajectories of hostility from predeployment to two years after deployment were modeled in models assuming 1 to 10 classes including the intercept, linear and quadratic terms. Fit indices as the log-likelihood, Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) and examination of the classes of the different models were used to decide on the final model (Nylund, Asparouhov, & Muthen, 2007; Ram & Grimm, 2009). The BIC has been found to be a good indicator for

deciding on the number of classes (Nylund et al., 2007). Besides the fit indices, further examination of the models was performed, with number of group members and plots of group trajectories taken into consideration (Ram & Grimm, 2009).

Next, predictors for class-membership were identified using multinomial logistic regression analyses (MLRA). Predictors in these models were age, education, early trauma, number of traumatic experiences during deployment and the subscales of the TCI (Cloninger et al., 1993).

All analyses were performed using Mplus version 6.11 for Macintosh (Muthén & Muthén, 2010). All models were estimated using full information maximum likelihood (FIML) with robust standard errors (MLR estimator) as implemented in Mplus (Muthén & Muthén, 2010). FIML produces unbiased parameter estimates and standard errors when data is missing at random (Graham, 2009).

Results

Growth mixture modeling

The fit indices for the models are depicted in Table 2. A four-class model that included a quadratic term was found to provide the best fit, based on the combination of fit indices, group sizes and group differences. The four-class model showed a high entropy of .95, indicating a confident group classification (Ram & Grimm, 2009). The AIC and BIC were lower in the four-class model compared to the models with one to three classes. Furthermore, the Vuong-Lo-Mendell-Rubin Likelihood Ratio Test nearly reached significance (p = .057), indicating that the four-class model was superior to the model with three classes. Models with more than four classes resulted in classes with insufficient group members (less than 1%) and much overlap. A description of the four subgroups is presented in Table 3.

The trajectories of the four groups are depicted in Figure 1. In the largest group, hostility scores remain low throughout all time-points, and is therefore described as a 'low-hostile group' (N=612). A second group shows a rather stable profile of hostility scores around the 80th percentile. This group is defined as a 'mild-hostile group' (N=95). Two smaller groups show a large increase in hostility scores over time, with scores above the 95th percentile. One of these groups is showing an increase immediate after deployment, and is defined as an 'early-hostile group' (N=22). In the last group the increase takes place with a delayed onset, between 1 and 2 years after deployment and is therefore described as a 'late-onset group' (N=16).

Table 2.
Fit indices for the latent growth models of hostility.

Number of classes	Log likelihood	AIC	BIC	BIC-ssa	Entropy	*p*-value VLMR
1	-6691.09	13398.17	13435.08	13409.68	*na*	*na*
2	-6172.14	12368.27	12423.63	12385.53	0.97	0.623
3	-5962.17	11956.34	12030.15	11979.35	0.95	0.225
4	**-5833.86**	**11707.73**	**11800.00**	**11736.49**	**0.95**	**0.057**
5	-5735.63	11519.26	11629.98	11553.77	0.96	0.187
6	-5668.03	11392.06	11521.24	11432.33	0.94	0.185
7	-5605.49	11274.98	11422.61	11321.00	0.95	0.473
8	-5561.46	11194.91	11360.99	11246.68	0.95	0.260
9	-5513.04	11106.08	11290.62	11163.60	0.94	0.686
10	-5470.37	11028.75	11231.73	11092.02	0.93	0.169

Note. AIC = Akaike information criterion; BIC = Bayesian information criterion; BIC-ssa = Sample-size-adjusted Bayesian information criterion; VLMR = Vuong-Lo-Mendell-Rubin Likelihood Ratio Test; *na* = not applicable; BOLD = model used in further analyse

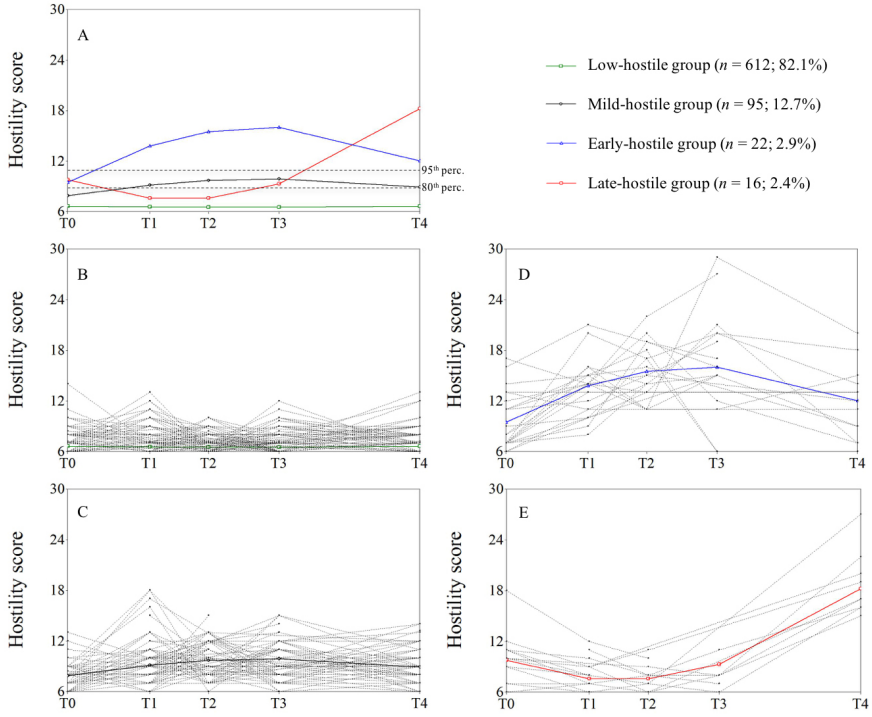

Figure 1.
Trajectories of hostility in the four groups identified with growth mixture modeling: A) The four-class model. B) Individual trajectories of the low-hostile group. C) Individual trajectories of the mild-hostile group. D) Individual trajectories of the immediate-hostile group. E) Individual trajectories of the late-hostile group. perc. = percentile score; T0 = one month prior to deployment; T1 = one month after deployment; T2 = 6 months after deployment; T3 = 1 year after deployment; T4 = 2 years after deployment.

Table 3.
Description of the four subgroups.

	Low-hostile group (*n* = 612)	Mild-hostile group (*n* = 95)	Early-hostile group (*n* = 22)	Late-hostile group (*n* = 16)
Gender (% male)	90.4%	91.6%	86.4%	81.3%
Age during deployment (SD)	30.18 (9.40)	26.45 (8.23)	24.86 (6.55)	26.56 (8.64)
Education				
% low	2.4%	5.5%	4.8%	0.0%
% moderate	82.3%	89.0%	81.0%	100.0%
% high	14.7%	5.5%	14.3%	0.0%
Early trauma (SD)	3.27 (2.85)	4.23 (3.59)	5.91 (3.35)	4.93 (5.01)
Trauma exposure (SD)	4.29 (3.08)	6.18 (3.07)	7.24 (3.11)	4.57 (3.61)
Hostility measures				
T0	6.59 (0.93)	7.77 (1.55)	9.60 (3.35)	9.79 (3.07)
T1	6.66 (1.05)	9.47 (2.49)	13.35 (3.40)	8.20 (1.82)
T2	6.44 (0.75)	9.75 (1.86)	15.37 (3.20)	7.60 (1.50)
T3	6.58 (0.92)	9.37 (2.25)	16.60 (6.52)	7.71 (1.70)
T4	6.62 (1.00)	9.10 (2.08)	11.85 (4.29)	18.50 (3.69)
Subscales of the TCI				
Novelty seeking (SD)	7.88 (2.81)	7.77 (3.15)	8.71 (2.41)	7.92 (1.78)
Harm avoidance (SD)	3.11 (2.81)	3.36 (2.97)	4.35 (3.60)	3.83 (2.59)
Reward dependence (SD)	8.49 (2.94)	7.97 (2.57)	7.05 (2.56)	9.37 (2.76)
Persistence (SD)	10.39 (2.70)	10.50 (2.66)	10.09 (3.28)	11.31 (2.91)
Self-directedness (SD)	13.8 (1.79)	12.92 (1.94)	11.99 (2.57)	13.42 (1.51)
Cooperativeness (SD)	12.35 (2.66)	10.57 (3.20)	8.76 (2.93)	10.32 (4.30)
Self-transcendence (SD)	2.53 (2.60)	3.42 (3.41)	4.16 (2.57)	4.08 (3.48)

Note. Education: low = primary education/four years of secondary education; moderate = Intermediate Vocational Education/five or six years of secondary education, high = higher vocational education/university; SD = Standard Deviation; TCI = Temperament and Character Inventory

Multinomial logistic regression analysis

The MLRA was first conducted using the low-hostility group as the reference group for comparisons with the other three groups. Veterans who reported more early trauma (odds = 1.092, $p < .05$), and/or who reported more deployment stressors (odds = 1.140, $p < .01$), and/or with a lower score on the subscale 'cooperativeness' (odds = 0.870, $p < .01$), had a higher chance to be in the mild-hostile group versus the low-hostility group (Table 4).

Lower education level (odds = 0.454, $p < .05$), more early trauma (odds = 1.159, $p < .05$), a higher score on TCI scale 'harm avoidance' (odds = 1.189, $p < .05$), and a lower score on TCI scale 'cooperativeness' (odds = 0.764, $p < .01$), were found to predict group membership of the late-hostile group versus the low-hostility group (Table 4).

Table 4.
Results of the multinomial logistic regression analysis.

Predictor	Mild vs. low			Late vs. low			Immediate vs. low			Late vs. immediate		
	Estimate (S.E.)	Odds	*p*	Estimate (S.E.)	Odds	*p*	Estimate (S.E.)	Odds	*p*	Estimate (S.E.)	Odds	*p*
Age	-0.261 (0.157)	0.972	0.096	-0.296 (0.305)	0.960	0.331	**-0.470 (0.148)**	**0.899**	***p*<0.01**	0.358 (0.295)	1.068	0.225
Education	-0.203 (0.130)	0.609	0.119	**-0.249 (0.123)**	**0.454**	***p*<0.05**	0.164 (0.121)	2.344	0.175	**-0.392 (0.149)**	**0.194**	***p*<0.01**
Early trauma	**0.272 (0.119)**	**1.092**	***p*<0.05**	**0.351 (0.173)**	**1.159**	***p*<0.05**	**0.330 (0.087)**	**1.255**	***p*<0.01**	-0.142 (0.177)	0.924	0.420
DES	**0.421 (0.116)**	**1.140**	***p*<0.01**	-0.074 (0.264)	0.971	0.780	**0.316 (0.122)**	**1.232**	***p*<0.05**	-0.447 (0.236)	0.788	0.058
Novelty seeking	-0.196 (0.134)	0.933	0.144	-0.086 (0.196)	0.961	0.661	0.026 (0.103)	1.020	0.798	-0.098 (0.191)	0.943	0.609
Harm avoidance	0.058 (0.154)	1.020	0.708	**0.382 (0.193)**	**1.189**	***p*<0.05**	**0.248 (0.123)**	**1.201**	***p*<0.05**	-0.017 (0.174)	0.990	0.924
Reward dependence	-0.017 (0.128)	0.994	0.891	0.438 (0.241)	1.215	0.069	-0.104 (0.119)	0.927	0.383	**0.461 (0.209)**	**1.311**	***p*<0.05**
Persistence	0.028 (0.132)	1.010	0.832	0.227 (0.248)	1.114	0.359	-0.035 (0.135)	0.973	0.795	0.216 (0.241)	1.145	0.370
Self-directedness	-0.130 (0.136)	0.934	0.341	0.273 (0.256)	1.207	0.287	-0.050 (0.101)	0.945	0.618	0.269 (0.231)	1.277	0.244
Cooperativeness	**-0.406 (0.117)**	**0.870**	***p*<0.01**	**-0.604 (0.220)**	**0.764**	***p*<0.01**	**-0.390 (0.104)**	**0.753**	***p*<0.01**	0.025 (0.237)	1.015	0.916
Self-transcendence	0.211 (0.147)	1.079	0.152	0.309 (0.192)	1.156	0.107	0.177 (0.097)	1.145	0.067	0.015 (0.199)	1.010	0.938

Note. Immediate = immediate-hostile group; Late = late-hostile group; Low = low-hostile group; Mild = mild-hostile group; SE = Standard Error; DES = Deployment Experiences Scale

Significant predictors of the early-hostility group versus the low-hostility group were lower age (odds = 0.899, $p < .01$), more early trauma (odds = 1.255, $p < .01$), more deployment stressors (odds = 1.232, $p < .05$), a higher score on TCI scale 'harm avoidance' (odds = 1.201, $p < .05$), and a lower score on TCI scale 'cooperativeness' (odds = 0.753, $p < .01$; Table 4).

Acute versus delayed onset of hostility

A second MLRA was performed in order to compare the early-hostility group with the late-hostility group, in order to identify differences between the two groups. In the immediate-increase group versus the late-increase group, lower education (odds = 0.194, $p < .01$), and the subscale 'reward dependence' of the TCI (odds = 1.311, $p < .05$), were found to be significant predictors (Table 4).

Discussion

This study aimed to identify distinct trajectories of hostility in a deployed military sample from 1 month prior to deployment until two years after returning home. Furthermore, predictors of class-membership were identified, in order to distinguish risk factors for groups with high hostility scores.

Using GMM, four trajectories of hostility were identified. These were a low-hostile group, a mild-hostile group, an immediate-increase group and a late-increase group. The majority of the respondents (82.1%) belonged to the low-hostile group, with hostility remaining low across all time points. 12.7% of the combat veterans were in the mild-hostile group. They showed slightly increased hostility scores across all time points, with scores above the 80th percentile (Arrindell & Ettema, 2003) at all time-points after deployment. Two small groups with an increase in hostility were identified, one with an immediate increase after deployment (2.9 % of the respondents), and one with a late-increase (2.4 % of the respondents). The scores of the early-hostile group are above the 95th percentile after deployment. The late-hostile group scores above the 80th percentile at T3, and increase to above the 95th percentile at T4 (Arrindell and Ettema, 2003). The increase-groups were only a small percentage of the total sample, thus these group should be replicated in the future to be more certain about the inferences.

To some extent, comparable latent classes were identified in studies regarding PTSD symptoms in a deployed military sample (Berntsen et al., 2012). In these studies, the majority of the veterans belonged to a resilient group, and a smaller amount to early and late increase groups. However, in these studies benefit-groups or recovery groups were also identified, in which the groups show a decrease of symptoms over time (Berntsen et

al., 2012; Bonanno et al., 2012; Orcutt et al., 2004). In the current study, these groups were not identified. The absence of a recovery group in the current study suggests that anger and hostility problems may rarely be targeted for interventions. In addition, it could also indicate that anger and hostility are resistant to change. It could also imply that individuals do not recognize symptoms of anger and hostility as psychological problems needing intervention. It is suggested that in order to avoid trauma-related feelings of fear, anger is used. The patient might more easily accept this emotion compared to fear (Foa, Riggs, Massie, & Yarczower, 1995).

The three hostile-groups were all characterized by more childhood trauma and less cooperativeness in comparison to the low-hostile group. This indicates that the experience of traumatic events early in life contributes to more hostility and symptoms of anger. This finding is comparable to findings concerning aggression in Vietnam veterans (Lenhardt, Howard, Taft, Kaloupek, & Keane, 2012); in that study pre-military traumatic events were related to more symptoms of anger. Furthermore, a link between early-life trauma and delinquency, violent behavior and aggression has been reported before (Chen, Coccaro, Lee, & Jacobson, 2012). Lower cooperativeness is associated to less empathic skills and being more self-centered (Cloninger et al., 1993). This finding is consistent with a previous study that has shown that deployed veterans with episodes of impulsive aggression reveal a lack of empathy (Teten, Miller, Bailey, Dunn, & Kent, 2008). Furthermore, lower cooperativeness was found as a predictor for hostility in patients with depressive disorder as well (Conrad, Wegener, Imbierowicz, Liedtke, & Geiser, 2009).

Membership of the mild-hostile and the early-hostile group versus the low-hostile group was also predicted by more stressful deployment experiences. Previous research in veterans with anger-related problems also reported an association with more traumatic events during deployment (Elbogen et al., 2010). Furthermore, high combat stress exposure has been related to more mental health problems (Hoge et al., 2004). However, deployment experiences were not found as a predictor in the late-hostile group. This suggests that experiences during deployment may have an immediate effect on hostility, whereas delayed hostility might be caused by other factors.

The two groups that showed an increase in hostility over time, i.e., the immediate-increase and late-increase groups, showed higher baseline scores on ‘harm avoidance’. This indicates that the people in these groups may show more passive avoidant behavior, for example fear of uncertainty (Cloninger et al., 1993). Elevated levels of harm avoidance were found in other psychiatric disorders such as depression (Abrams et al., 2004) and substance abuse (Hoge et al., 2004).

The last comparison, the late-hostile versus the early-hostile group showed lower education levels and higher scores on ‘reward dependence’ for the late-hostile group.

These higher scores on 'reward dependence' indicate that in the late-hostile group people are more dependent of approval of others (Cloninger et al., 1993). The people in the late-hostile group might be better able to control their anger because of this temperament factor. According to Pedersen (2004), one is less prone to aggressive behavior when interpersonal relationships are regarded as more important. When social attachment is higher, one might be more committed to control the anger. In case of lower attachment and less dependence of approval of others, this control might be considered as less important, leading to earlier complaints of anger and hostility.

Being the first of its kind, this study reveals trajectories of anger and hostility in a military sample and explored risk factors for these trajectories. However, some limitations must be mentioned. First of all, only data of deployed military personnel were taken into account, the percentage of woman in this sample was only 9.8%, and the increase-groups were rather small. This limits the generalizability of these results, and results should therefore be replicated. Second, anger and hostility symptoms were measured using the SCL-90 hostility subscale (SCL-hos). Although the use of this scale in GMM resulted in reliable distinction of different underlying groups, this six-item scale does not measure all aspects of anger and hostility symptoms. Third, in all the analyses, full information likelihood (FIML) was used. When missing data are missing at random, FIML produces unbiased parameter estimates (Graham, 2009). In this study, it is not completely certain whether the data are indeed not related to the outcome measures. Hostile respondents might be more prone to drop-out compared to respondents with low-hostility.

Our main finding is the identification of subgroups based on trajectories of anger and hostility symptoms. Because anger and hostility symptoms receive less attention compared to other psychological problems, it has been relatively unknown how they change over time. This study shows that an increase in anger and hostility symptoms does not only take place immediate after deployment, but even between one and two years after home-coming. Symptoms of anger and hostility are frequently reported by military personnel after deployment and seriously hamper the ability to reintegrate after deployment (Elbogen et al., 2012). Moreover, the present study demonstrates that hostility symptoms may easily become chronic. This underlines the necessity to follow military personnel for an extended period of time and when necessary, targeted intervention, such as cognitive behavioral therapy and group therapy, is offered to relieve these symptoms.

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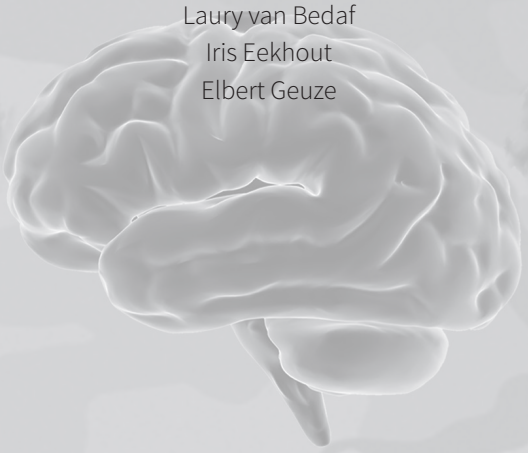
4

Anger and aggression problems in veterans are associated with an increased acoustic startle reflex

Lieke Heesink
Rolf Kleber
Michael Häfner
Laury van Bedaf
Iris Eekhout
Elbert Geuze



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Abstract

Anger and aggression are frequent problems in deployed military personnel. A lowered threshold of perceiving and responding to threat can trigger impulsive aggression. This can be indicated by an exaggerated startle response. Fifty-two veterans with anger and aggression problems (Anger group) and 50 control veterans were tested using a startle experiment with 10 startle probes and 10 prepulse trials, presented in a random order and with a random interval between the trials. Predictors (demographics, Trait Anger, State Anger, Harm Avoidance and Anxious Arousal) for the startle response within the Anger group were tested. Increased EMG responses were found to the startle probes in the Anger Group compared to the Control group, but not to the prepulse trials. Furthermore, Harm Avoidance and State Anger predicted the increased startle reflex within the Anger group, whereas Trait Anger was negatively related to the startle reflex. These findings indicate that threat reactivity is increased in anger and aggression problems. These problems are not only caused by an anxious predisposition, the degree of anger also predicts the startle reflex.

Acknowledgment contribution authors
Designed research: L. Heesink, M. Häfner & E. Geuze
Performed research: L. Heesink, L. van Bedaf & E. Geuze
Analyzed data: L. Heesink, L. van Bedaf, I. Eekhout & E. Geuze
Wrote the paper: L. Heesink, R. Kleber, M. Häfner, L. van Bedaf, I. Eekhout & E. Geuze

Introduction

Anger and aggression related problems have widespread consequences, ranging from partner/familial violence to a burden for society. These problems are frequently found in samples of deployed military veterans (Elbogen et al., 2010; Heesink, Rademaker, Vermetten, Geuze, & Kleber, 2015) and appear to be rather chronic (Heesink et al., 2015). In case of a psychiatric disorder with comorbid anger and aggression, treatment outcome is impaired (Forbes et al., 2008).

Definitions of anger and aggression are diverse. In short, aggression refers to behavior with the intention to harm, whereas anger refers to the emotion (Anderson & Bushman, 2002). Often, a distinction is made between the planned, premeditated form of aggression, and unplanned, impulsive aggression. The focus of this study is the impulsive form of aggression, in which anger plays an important role.

Dysregulated anger and aggression are symptoms of many disorders, such as posttraumatic stress disorder (PTSD; McHugh, Forbes, Bates, Hopwood, & Creamer, 2012), depression (Painuly, Sharan, & Mattoo, 2005) and Intermittent Explosive Disorder (IED; Coccaro, 2012). The importance of diagnostic criteria for dysregulated anger has been stated before, in order to recognize and study these problems (Del Vecchio & O'Leary, 2004; Morland, Love, Mackintosh, Greene, & Rosen, 2012). Since aggressive behavior is prevalent in many disorders, it is relevant to study it under NIMH's Research Domain Criteria (RDoC).

RDoC is a dimensional approach in which behavioural measures and neuroscience are integrated (Cuthbert, 2014). Within the RDoC framework, impulsive aggression fits into the negative valence domain. Part of the negative valence domain is the acute threat response. It is hypothesized that impulsive aggression is accompanied by a lowered threshold of perceiving situations as threatening, and threat activates a biologically predisposed survival mode, including fear and flight reactions as well as anger and fight reactions (Novaco & Chemtob, 2002). This defensive motivational system is related to activity in limbic brain structures. Furthermore, the domain of arousal within RDoC is an important construct in aggressive behavior, as it regulates the processes within the negative valence system. Arousal plays a role in the sensitivity to stimuli. For example, heightened arousal might lead to threat-related vigilance. Dysfunctional anger and aggression have been linked to heightened physiological arousal (Mackintosh et al., 2014).

The startle reflex is a response to a sudden, intense stimulus leading to a rapid muscle contraction. This can be measured by a facial electromyography (EMG) in response to a loud noise. An exaggerated startle reflex can indicate the lowered threshold of perceiving threat, due to the sudden and intense nature of the stimulus that leads to a

defensive response. Baseline startle reactivity is influenced by the activity of limbic brain structures (Baas, Milstein, Donlevy, & Grillon, 2006) as the amygdala, the bed nucleus of the stria terminalis (BNST) and the brainstem (Grillon & Baas, 2003). This reflex is thought to initiate the selection of an appropriate response to a certain threat. When the startling stimulus is presented several times, the startle reflex diminishes; this is known as habituation. Furthermore, when a less intense stimulus precedes the startle-eliciting stimulus, the response is inhibited. This prepulse inhibition (PPI) is thought to reflect low-level gating of information processing, or early attentional regulation (Christian Grillon & Baas, 2003). Deficits of PPI are an indication of the inability to filter out unnecessary information.

Mice genetically predisposed to aggression show an enhanced acoustic startle response and diminished PPI compared to controls (Naumenko, Kozhemyakina, Plyusnina, & Popova, 2014; Sallinen, Haapalinna, Viitamaa, Kobilka, & Scheinin, 1998). In humans with dysfunctional anger and aggression, the acoustic startle reflex has not been studied before in startle trials alone, without other stimuli as affective pictures or faces. Within a healthy population higher levels of aggressiveness as a personality trait were associated with a slower habituation rate (Blanch, Balada, & Aluja, 2014). This habituation is thought to reflect the biological background of judgment and motor or cognitive responses (Blanch et al., 2014).

An enhanced startle response was found in healthy participants during the viewing of angry faces (Dunning, Auriemmo, Castille, & Hajcak, 2010; Springer, Rosas, McGetrick, & Bowers, 2007). These angry face stimuli are classified as threatening stimuli and might therefore elicit a defensive response, measured by an enhanced startle response. Furthermore, angry faces might elicit angry feelings, which in turn can increase startle reactivity. Additionally, hyperactivity of the amygdala was found in a population of Intermittent Explosive Disorder (IED) patients, a disorder characterized by impulsive aggressive behavior, during aggressive faces viewing (Coccaro, McCloskey, Fitzgerald, & Phan, 2007). These aggressive faces are stated to be a paradigm for social threat. This hyperactivity of the amygdala might be linked to heightened arousal and a lower threshold for perceiving stimuli as threatening.

As stated before, dysfunctional anger and aggression have been linked to heightened arousal. Studying the startle response, including the habituation effect and prepulse inhibition, gives an objective, neurophysiological evaluation of regulation of arousal. It is hypothesized that military men with dysfunctional anger and aggression have an exaggerated startle response and show less PPI. Furthermore, we tested the influence of trait and state anger on the startle response within veterans with anger and aggression problems. In addition, given the link between anger, aggression and anxiety (i.e. Castillo *et al.* 2014) we also examined whether an exaggerated startle response is linked to underlying anxiety traits.

Methods

Participants

In this study, 52 veterans with dysregulated anger and aggression were included (Anger group). They were recruited via their psychologists/psychiatrists affiliated with Military Mental Health Care Institute and via advertisements in the waiting room and newsletters for veterans. Additionally, fifty control veterans without anger and aggression problems were also included. These were recruited by advertisements or had participated in previous studies. Inclusion criteria for the Anger group were based on the four research criteria for impulsive aggression described by Coccaro (2012): 1) Verbal or physical aggression towards other people occurring at least twice weekly on average for one month; or three episodes of physical assault over a one year period; 2) the degree of aggressiveness is grossly out of proportion; 3) the aggressive behavior is impulsive (not premeditated); 4) the aggressive behavior causes either distress in the individual or impairment in occupational or interpersonal functioning (Coccaro, 2012). Inclusion criteria for the Control group were 1) no current DSM-IV diagnosis; 2) no history of pathologic aggressive behavior.

The Ethics Committee of the University Medical Center Utrecht, The Netherlands, approved this study and all participants signed an informed consent before participation after having received a complete written and verbal explanation of the study. This study was carried out in accordance with the Declaration of Helsinki.

Interview and questionnaires

The Dutch version of the International Neuropsychiatric Interview (MINI) was used in order to screen for the presence of comorbid psychiatric disorders (Van Vliet, Leroy, & Van Megen, 2000). The complete MINI was administered. In this interview the following current or life-time disorders were screened: depressive disorder, dysthymia, suicidal risk, (hypo)manic disorder, panic disorder, anxiety disorder, agoraphobia, social phobia, obsessive compulsive disorder, PTSD, alcohol or drug dependence and/or abuse, psychotic disorders, anorexia nervosa, bulimia nervosa, generalized anxiety disorder, antisocial personality disorder, somatization disorder, hypochondria, body dysmorphic disorder, pain disorder, attention deficit hyperactivity disorder (ADHD) and adjustment disorder.

To measure anger and aggression, Dutch versions of the State-Trait Anger Expression Inventory-revised (STAXI-2; Hovens, Rodenburg, & Lievaart, 2015) and the Aggression Questionnaire (AQ; Meesters, Muris, Bosma, Schouten, & Beuving, 1996) were used. The STAXI-2 consists of 57 items on a 4-point Likert scale and is divided into two subscales; State Anger and Trait Anger. The AQ consists of 29 items on a 5-point Likert scale and is divided into 4 subscales; Physical Aggression, Verbal Aggression, Anger and Hostility.

The Mood and Anxiety Symptom Questionnaire (MASQ) Anxious Arousal subscale was used to measure current anxiety-specific symptoms (Watson et al., 1995). This scale consists of 17 items on a 5-point Likert scale. The Harm Avoidance subscale of the short version of the Temperament and Character Inventory (TCI; Cloninger, Svrakic, & Przybeck, 1993) was included to measure fearful, anxious personality characteristics and consists of 15 items on a dichotomous scale.

Exposure to childhood trauma was assessed using the Dutch short-form self-report version of the Early Trauma Inventory (Bremner, Bolus, & Mayer, 2007; Rademaker, Vermetten, Geuze, Muilwijk, & Kleber, 2008). This checklist assesses exposure to traumatic experiences (general trauma, physical abuse, emotional abuse and sexual abuse) before the age of 18 years using 27 dichotomous. The total score represents the number of different traumatic events experienced.

The Posttraumatic Stress Disorder Symptom Checklist (PSS; Foa et al., 1993) was used to measure PTSD symptoms. The PSS consists of 23 items on a 4-point Likert scale.

Experiment

The experiment consisted of 20 startle probes of 50 ms bursts of white noise of ~105 dB. Half of the probes were preceded by a 20 ms prepulse of ~70 dB with an inter-stimulus interval of 120 ms. During the experiment, background noise of ~60 dB was presented. All noises were delivered through headphones. The first probe was always a stand-alone startle probe, whereas all the other probes were randomly presented with an inter-trial interval of 15-25 seconds. The total duration of the experiment was 6.66 minutes. The participants focused on a white fixation cross on a dark grey background while sitting in a chair. They were instructed that they would hear some sounds through the headphones. Furthermore, they were asked to sit as still as possible and try not to laugh or talk during the experiment. The experiment was part of a larger study, which examined psychological and biological aspects of aggression in veterans.

Startle measures

Eye-blink responses were measured with two 6 mm silver chloride (AgCl) cup skin surface electrodes filled with high conductive recording gel. The electrodes were placed below the lower left eyelid in line with the pupil and separated by 15-20 mm (Blumenthal et al., 2005). A Biopac MP150 system with a sampling rate of 1000 Hz recorded the EMG signals.

Pre-processing

EMG responses were pre-processed using AcqKnowledge software version 4.3. An offline filter was used for the raw EMG signal. To filter out the high and low artefacts a Finite

Impulse Response (FIR) band-pass filter of 28 to 500 Hz was used. To filter out electrical noise, an Infinite Impulse Response (IIR) band stop filter was used. Next, the Root Mean Square (RMS) was calculated from the raw signal. The maximum value of the squared EMG signal within the time window between 20 and 120 ms after the startle probe onset was extracted from the data (Blumenthal et al., 2005). Furthermore, a baseline mean EMG response of two seconds before the onset of the startle probe was subtracted from the maximum value. This window of 2 seconds was divided into epochs of 100 milliseconds. Per epoch we measured the variation, and when this exceeded 0.0115 mV, we excluded this epoch from the baseline measurement in order to exclude artifacts as blinking or other movements. After visual inspection of the data, the most discriminative criteria were selected based on manual rejection of the trials. This baseline correction gives us the advantage of a large interval while constraining the risk of including artifacts.

Data analyses

First, to test for group differences in startle magnitude and in habituation, data of the 10 startle-alone trials were analyzed using a mixed model analysis with a random intercept at the subject level.

Next, an independent samples t-test was used in order to test whether the groups differed on prepulse inhibition (PPI). PPI was computed as the percentage reduction of the mean startle response (100 - (mean prepulse / mean startle) * 100). Prior to this analysis, multiple data imputation was performed to deal with missing values. 16.66% of the startle data was missing, due to voluntarily eye blinking or movement within the measuring window. Data-points were imputed when 3 or fewer data-points were missing for a subject. For each subject, the mean was then computed from the available data-points and the imputed data. This was done in 28% and 22% of the subjects, for the trials without and with prepulse, respectively. When more than three data-points were missing for one subject, the mean startle response was imputed directly. In both the trials with and without prepulse, this was done in 17% of the subjects. The imputation was done using predictive mean matching algorithm of the Multivariate Imputation by Chained Equations (MICE) package in R (Van Buuren & Groothuis-Oudshoorn, 2011), with 50 multiple imputations using 50 iterations.

In addition, using a linear regression, predictors for the mean startle response were tested per group. This analysis was performed within the imputed dataset. Age, education, early trauma, PSS score, trait anger, state anger, anxious arousal and harm avoidance were used in this model.

All analyses were performed using R software.

Sensitivity analysis

In order to evaluate the effect of the multiple data imputation, the linear regression was also performed as a complete-case analysis, i.e., including only the cases with completely observed startle responses. In 25 participants in the Anger group all startle responses were completely observed.

Results

Demographics

The demographics and characteristics of the two groups are depicted in Table 1. The groups did not differ significantly in age, education and number of deployments. The Anger group scored significantly higher on the anger and aggression measures; the STAXI-2 and the AQ (Table 1).

Table 1.
Demographics and characteristics of the Anger and the Control group.

	Anger (N=52)		Control (N=50)		
	Mean	SD	Mean	SD	Statistics
Age	35.26	6.81	34.67	7.30	t (1,100) = 0.419, *ns*
Education	4.04	0.64	4.27	0.74	t (1,100) = -1.668, *ns*
Number of deployments	2.30	1.37	2.52	1.60	t (1,100) = -0.740, *ns*
Years since last deployment	7.73	5.44	6.35	2.96	t (1,99) = 1.606, *ns*
Frequency of aggressive behaviour					
Verbal	4.68	1.39	0.38	1.21	t (1,100) = 16.673, $p < .001$
Physical	2.08	1.68	0.00	0.00	t (1,100) = 8.950, $p < .001$
Early Trauma	6.38	5.08	2.90	2.56	t (1,100) = 4.393, $p < .001$
PSS score	18.36	9.86	2.12	3.39	t (1,100) = 11.216, $p < .001$
STAXI-2					
State Anger	23.86	10.99	15.31	1.08	t (1,100) = 5.586, $p < .001$
Trait Anger	23.92	6.38	12.83	3.43	t (1,100) = 10.998, $p < .001$
Aggression Questionnaire					
Physical aggression	29.64	7.36	18.92	5.35	t (1,100) = 8.432, $p < .001$
Verbal aggression	15.26	3.44	11.62	1.68	t (1,100) = 6.839, $p < .001$
Anger	25.02	4.71	11.98	3.77	t (1,100) = 15.474, $p < .001$
Hostility	24.50	7.71	12.48	4.53	t (1,100) = 9.644, $p < .001$
MASQ Anxious arousal	12.12	10.14	1.42	1.94	t (1,100) = 7.471, $p < .001$
TCI Harm Avoidance	7.46	4.20	2.75	2.10	t (1,100) = 7.209, $p < .001$

Note. Education ranges from 1 to 8. Frequency of aggressive behaviour ranges from 1 to 8. ETI = Early Trauma Inventory; *ns* = not significant; MASQ = Mood and Anxiety Symptom Questionnaire; PSS = Posttraumatic Stress Disorder Symptoms Checklist; SD = Standard deviation; STAXI-2 = State-Trait Anger Expression Inventory revised. TCI = Temperament and Character Inventory, short version.

Startle reactivity and habituation test

The mixed model analysis in the startle-alone trials revealed a main effect of Time (Estimate = -4.41, SE = 0.95, t = -4.66, p < .001) and a main effect of Group (Estimate = 52.57, SE = 18.19, t = 2.89, p < .01), demonstrating higher EMG responses in general for the Anger group. No interaction effect of Group*Time was found (Estimate = -2.29, SE = 1.32, t = -1.74, p = .08), indicating no differences in change over time between the two groups. The data are depicted in Figure 1.-

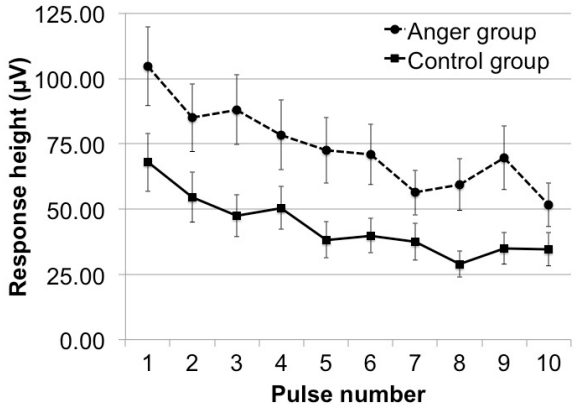

Figure 1.
The average startle response of the Anger and the Control group on the 10 startle pulses.

Prepulse inhibition

No differences were found in PPI between the Anger group (M = 67.44, SD = 30.45) and the Control group (M = 67.85, SD = 22.51; t = -0.07, p = 0.95).

Linear regression

To test which variables were significant predictors for a heightened startle response within the Anger group, a linear regression was used. Age, education, early life trauma (before the age of 18), trait anger, harm avoidance, state anger and anxious arousal were tested. The results of this general linear model are depicted in Table 3. Tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (Age, VIF = 1.29; Education, VIF = 1.25; Early Trauma, VIF = 1.25; Trait Anger, VIF = 2.24; Harm Avoidance, VIF = 1.88; State Anger, VIF = 2.04; Anxious Arousal, VIF = 2.20). Lower trait anger, higher scores on harm avoidance and higher state anger were found to be significant predictors of a heightened startle response, whereas age, education, early trauma and anxious arousal were not found to be significant. Furthermore, the same predictors were tested on the mean startle response on the trials with a prepulse.

Lower trait anger and higher harm avoidance were also found as significant predictors in these trials (Table 2). In the control group, none of these predictors were found to be significant predictors. The impact of the separate predictors is depicted in scatter plots in the supplemental material.

Table 2.
Predictors for the mean startle response within the Anger group.

Variable	Estimate	Std. Error	*t*	*p*
Intercept	193.73	74.67	2.59	**<.05**
Age	-1.92	1.49	-1.29	.21
Education	3.55	15.38	0.23	.82
ETI	-0.41	1.83	-0.22	.83
PSS Score	-2.29	1.23	-1.86	.07
Trait Anger	-4.80	1.67	-2.87	**<.01**
TCI harm avoidance	7.47	2.52	2.96	**<.01**
State Anger	2.28	1.07	2.12	**<.05**
MASQ anxious arousal	0.60	1.36	0.44	.66

Note. ETI = Early Trauma Inventory; MASQ = Mood and Anxiety Symptom Questionnaire; PSS = Posttraumatic Stress Disorder Symptoms Checklist; TCI = Temperament and Character Inventory, short version.

Sensitivity analysis

The general linear model was performed within the complete cases, to test the sensitivity of the multiple data imputation. These results are depicted in Table 3. Within the startle trials without prepulse, the predictors trait anger and harm avoidance remained significant, whereas state anger was no longer significant. Furthermore, the PSS score is a significant predictor. In the startle trials with prepulse, trait anger and harm avoidance also remained significant (Table 3).

Table 3.
Results of the sensitivity analysis.

Variable	Estimate	Std. Error	*t*	*p*
Intercept	191.30	83.18	2.30	**<.05**
Age	-3.31	1.65	-2.01	**<.05**
Education	17.57	17.35	1.01	0.31
ETI	0.04	2.19	0.02	0.99
PSS Score	-2.77	1.36	-2.04	**<.05**
Trait Anger	-4.58	1.88	-2.44	**<.05**
TCI harm avoidance	7.58	2.80	2.70	**<.01**
State Anger	1.37	1.29	1.06	0.29
MASQ anxious arousal	1.66	1.52	1.09	0.28

Note. ETI = Early Trauma Inventory; MASQ = Mood and Anxiety Symptom Questionnaire; PSS = Posttraumatic Stress Disorder Symptoms Checklist; TCI = Temperament and Character Inventory, short version.

Discussion

This study was carried out to examine whether the startle response in veterans with anger and aggression problems is different from control veterans. Furthermore, predictors of this exaggerated startle response were tested. The main finding of this study is that the startle response is increased in veterans with anger and aggression problems. No difference was found in startle probes preceded by a prepulse. Furthermore, no differences in habituation were found between the groups.

Our results on the heightened startle reflex in veterans with anger and aggression problems correspond to those of studies that show a heightened startle reflex during the viewing of negative pictures. These negative pictures are thought to induce a negative affective state (Christian Grillon & Baas, 2003). The current study indicates a lowered threshold for perceiving threatening stimuli in anger and aggression. It has been suggested before that impulsive aggression, originating from anger, is linked to the acute threat response system (Blair, 2012). Threatening stimuli can elicit a defensive response as measured by the acoustic startle reflex and in anger and aggression related problems this response is stronger. This indicates a stronger threat-sensitivity for veterans with anger and aggression problems. PTSD is related to a heightened startle response (Holstein, Vollenweider, Jäncke, Schopper, & Csomor, 2010; Pole, 2007), and the current study also shows a negative relation between PTSD score and startle magnitude in the complete cases analysis. An overlap between anger and aggression on the one hand and PTSD symptoms on the other hand has been reported before (McHugh et al., 2012; Orth & Wieland, 2006; Taft, Vogt, Marshall, Panuzio, & Niles, 2007). The PTSD score is a composite measure of heterogeneous symptoms. The negative relation as found in the current study might most likely be attributed to avoidance/numbing symptoms (see supplemental material).

Furthermore, the increased startle response found in the current study is consistent with findings in mice genetically predisposed to aggression (Sallinen et al., 1998). In that study, mice with altered α_{2C}-adrenoreceptor (α_{2C}-AR) expression show both an increased startle response and more aggressive behavior. This gives us indications for parallels between animal models and human studies on acoustic startle responses and aggression. Furthermore, it raises the question whether selective α_{2C}-AR agonists might have therapeutic effects in individuals with impulsive aggressive behavior.

No group differences were found in PPI. Deficits of PPI are an indication of the inability to filter out the unnecessary information and in veterans with aggression related problems this seems not disturbed. PPI deficits have been reported in several disorders such as schizophrenia, PTSD, obsessive compulsive disorder and ADHD (i.e. Braff, Geyer, & Swerdlow, 2001). In the current study the prepulse always had the same

intensity and interval between the startle pulses. It would therefore be interesting to test whether PPI differs between patients with anger and aggression problems and controls at other intensities and intervals of the prepulse stimulus. It could be that the current prepulse was not distinctive enough and that other variations in the characteristics of the prepulse do elicit differences between the two groups, as was found to vary in other disorders (Braff et al., 2001; Grillon, Ameli, Charney, Krystal, & Braff, 1992). It has been suggested that PPI deficits in PTSD have their origin in an attentional deficit. Due to distraction by for example thoughts or intrusions, the prepulse might lead to less inhibition compared to controls (Grillon, Morgan, Southwick, Davis, & Charney, 1996). This seems not the case in the current sample, although tests with variations in prepulse characteristics need to further support this.

Trait Anger negatively predicted the height of the startle response in the Anger group. Higher trait anger in combination with a lower startle response have been found before, but only to appetitive pictures (Amodio & Harmon-Jones, 2011). To negative pictures, no effects were found. This has been attributed to approach-related behavior associated with Trait Anger (Amodio & Harmon-Jones, 2011). Other studies show that higher Trait Anger was associated with higher startle responses (Cook, Hawk, Davis, & Stevenson, 1991). However, these findings come from a civilian sample without diagnosed anger and aggression problems. In the current control group of veterans, the personality trait of anger did not predict the height of the startle response; it was only a predictor within the Anger group. Participants in the current control group were selected after reporting no problems regarding anger or aggression, leading to lower Trait Anger in the current control group.

The Harm Avoidance personality trait on the other hand, predicted a higher startle response. This has been found before (Cook et al., 1991) and points towards an anxious predisposition underlying an exaggerated startle response in anger and aggression. In anxiety disorders, the startle response is also enhanced (Christian Grillon & Baas, 2003). However, the current study shows that the enhanced startle response in the Anger group likely cannot only be explained by an anxious predisposition. State anger also predicted an exaggerated startle response in the Anger group. This is comparable to studies in which negative affective pictures enhance the startle response (Anokhin & Golosheykin, 2010). Viewing negative pictures induces a negative affect, which leads to an enhanced startle response. The sensitivity analysis showed that when participants with missing startle responses were excluded, the effect of state anger diminished. This may be explained by the fact that participants with missing data on the startle responses had on average a higher score on state anger. Since we cannot be absolutely certain about missing observations, the effect of state anger should be interpreted with caution.

In this study, participants were included in the Anger group when they reported problems with Anger and Aggression. Although this is not a DSM diagnosis, the Anger group and the Control group showed major differences on the anger and aggression questionnaires. This underlines the discriminant value of these questionnaires. Furthermore, it shows that these questionnaires addressed the anger and aggression problems within the Anger group, demonstrating the serious problems in this group.

The current study only included male veterans. Although anger and aggression are also prevalent in women, the nature and symptoms can be different and therefore these findings cannot be generalized to a female population. Furthermore, impulsive aggression is not only reported within military populations, also in civilians these problems are frequently reported (van Gelderen, Bakker, Konijn, & Demerouti, 2011). Although the current study therefore carries significance beyond a military sample, it is not possible to generalize to the general population.

In the current study, only the basic acoustic startle response was measured, without inducing a negative or positive affective state. This needs to be disentangled in future research. It would be very informative to test whether inducing a positive affective state in individuals with anger and aggression related problems, would lead to a diminished startle response. This would give some pointers for treatment of these problems. Furthermore, the increased startle response in veterans with anger and aggression problems as seen in the current study might reflect the tendency to overreact in threatening situations. This leads to the speculation whether an increased startle response could provide useful information regarding the selection or exclusion of military personnel for certain duties.

The current study contributes to knowledge regarding the neurophysiological background of anger and aggression. Anger and aggression are associated with an increased startle response. The current study also shows that the increased startle response is the result of a complex interplay between anxious predisposition and state and trait anger. The neurobiological background of this exaggerated fear response needs to be disentangled in future research. For example, using fMRI techniques it could be discovered whether this difference in threat response can be found in corresponding brain areas. Furthermore, it raises questions whether the reaction to threat is a vulnerability factor to develop anger and aggression problems, or a consequence of these problems. It is therefore important to investigate whether the increased startle response remains after successful treatment of aggression or whether it diminishes.

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Supplementary material

Supplementary Table 1.
Univariate analyses per predictor for the mean startle response within the Anger group.

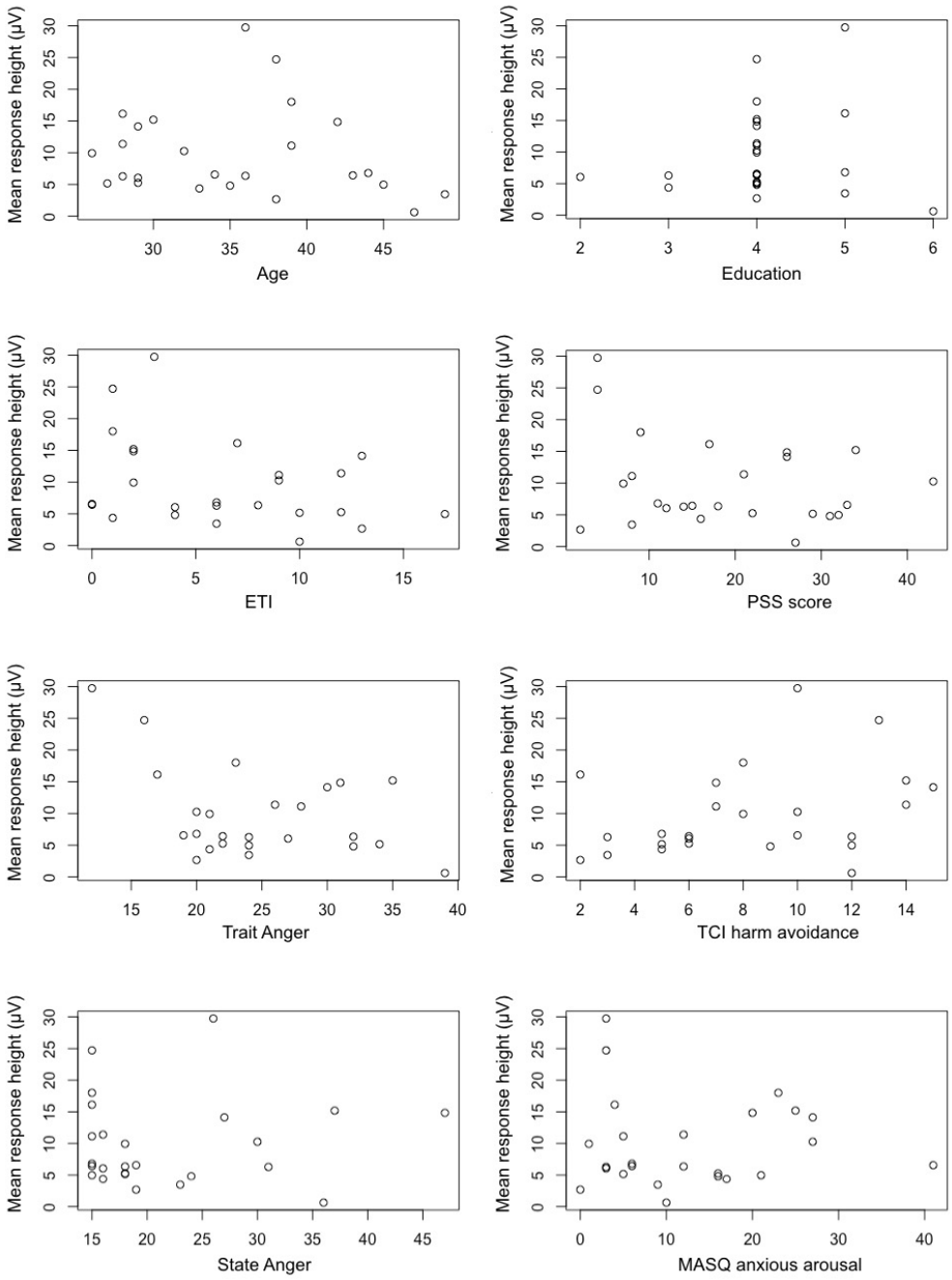
Variable	Estimate	Std. Error	*t*	*p*
Age	-2.29	1.48	-1.54	.13
Education	3.52	5.97	0.22	.83
ETI	0.22	2.08	0.11	.91
PSS Score	-1.08	1.02	-1.06	.30
Trait Anger	-2.10	1.58	-1.32	.19
TCI harm avoidance	4.76	2.27	2.10	<.05
State Anger	1.32	0.97	1.37	.18
MASQ anxious arousal	1.01	0.98	1.02	.31

Note. ETI = Early Trauma Inventory; MASQ = Mood and Anxiety Symptom Questionnaire; PSS = Posttraumatic Stress Disorder Symptoms Checklist; TCI = Temperament and Character Inventory, short version.

Supplementary Table 2.
Predictors for the mean startle response within the Anger group, with PTSD symptoms subdivided into avoidance, re-experiencing and arousal.

Variable	Estimate	Std. Error	*t*	*p*
Intercept	192.93	75.92	-2.54	**<.05**
Age	-1.80	1.53	-1.17	.25
Education	1.93	16.06	0.12	.90
ETI	0.10	1.94	0.05	.96
PSS Avoidance	-4.24	2.48	-1.71	.10
PSS Re-experiencing	-0.42	3.83	-0.11	.91
PSS Arousal	-0.10	3.96	-0.03	.98
Trait Anger	-5.29	1.79	-2.96	**<.01**
TCI harm avoidance	7.94	2.69	2.96	**<.01**
State Anger	2.38	1.09	2.19	**<.05**
MASQ anxious arousal	0.43	1.39	0.31	.76

Note. ETI = Early Trauma Inventory; MASQ = Mood and Anxiety Symptom Questionnaire; PSS = Posttraumatic Stress Disorder Symptoms Checklist; TCI = Temperament and Character Inventory, short version.

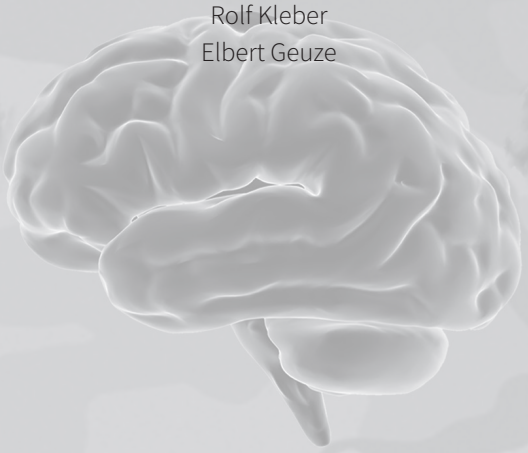


Supplementary Figure 1.
Scatterplots of the individual predictors.

5

Proximity Alert! Distance Related Cuneus Activation in Military Veterans with Anger and Aggression Problems

Lieke Heesink
Thomas Gladwin
David Terburg
Jack van Honk
Rolf Kleber
Elbert Geuze



Submitted

Abstract

Problems involving anger and aggression are common after military deployment, and may involve abnormal responses to threat. This study therefore investigated effects on neural activation related to threat and escapability among veterans with deployment experience. Twenty-seven male veterans with anger and aggression problems (Anger group) and 30 Control veterans performed a virtual predator-task during fMRI measurement. In this task, threat and proximity were manipulated. The distance of cues determined their possibility for escape. Cues signaled impending attack by zooming in towards the participant. If Threat cues, but not Safe cues, reached the participants without being halted by a button press, an aversive noise (105 dB scream) was presented. In both the Threat and the Safe condition, closer proximity of the virtual predator resulted in stronger activation in the cuneus in the Anger versus Control group. The results suggest that anger and aggression problems are related to a generalized sensitivity to proximity rather than preparatory processes related to task-contingent aversive stimuli. Anger and aggression problems in natural, dynamically changing environments may be related to an overall heightened vigilance, which is non-adaptively driven by proximity.

Acknowledgment contribution authors
Designed research: L. Heesink, D. Terburg & E. Geuze
Performed research: L. Heesink
Analyzed data: L. Heesink, T. Gladwin & D. Terburg
Wrote the paper: L. Heesink, T. Gladwin, D. Terburg, J. van Honk, R. Kleber, & E. Geuze

Introduction

Anger and aggression are feelings and behaviors involving the intent to harm a perceived threat (Anderson & Bushman, 2002). Disproportional anger and impulsive aggression can cause serious problems and danger to the individual and other people. Anger and aggression problems may occur after military deployment (Elbogen et al., 2010; Reijnen, Rademaker, Vermetten, & Geuze, 2015) due to the serious impact of a deployment (MacManus et al., 2015). These problems tend to persist over a long period of time, and can develop even after a substantial period of time after deployment (Heesink, Rademaker, Vermetten, Geuze, & Kleber, 2015).

Heightened anger and aggression have been linked to a lowered threshold of perceiving situations as threatening (Novaco & Chemtob, 2002). Animal research shows that distance is an important feature in risk assessment (Blanchard, Griebel, Pobbe, & Blanchard, 2011). When a possible threat is observed, a survival mode is activated, involving behavior ranging from freeze or flight when the threat is at a distance, to fight when threat is close by and more imminent (Blanchard, Blanchard, & Griebel, 2005). In humans, similar behavior in response to threat has been reported (Blanchard, Hynd, Minke, Minemoto, & Blanchard, 2001). In threatening situations, humans tend to respond faster (Nieuwenhuys, Savelsbergh, & Oudejans, 2012) and show increased response preparation in anticipation of avoidable threat (Gladwin, Hashemi, Van Ast, & Roelofs, 2016).

The fight-response in animals is mediated by a neural circuit including the amygdala, the hypothalamus and the periaqueductal gray (PAG; for review see Blanchard et al., 2005). This system appears to be involved with the response to threat in humans as well (Hermans, Henckens, Roelofs, & Fernández, 2013). In fMRI studies using threat paradigms, a shift was found from prefrontal activity during avoidable and distant threat, to brainstem activity (periaqueductal gray; PAG) during unavoidable, proximal threat (Coker-Appiah et al., 2013; Mobbs et al., 2007, 2009). Furthermore, exposure to threat is associated with activation in brain areas implicated in anxiety (Gold, Morey, & McCarthy, 2015).

The Fear-And-Escape Task was developed to investigate the response to threat in interaction with distance (Montoya, Van Honk, Bos, & Terburg, 2015). The task consists of a virtual predator in which the chance to escape the virtual predator varies with distance: it can be easily escapable, imminent (chance-level escapable) or inescapable. Further, threat is manipulated by using two predators, only one of which is associated with an aversive stimulus. The task shows a deactivation of the default mode network (parietal and prefrontal regions) and stronger activation within the midbrain due to threat imminence using a virtual predator (Montoya et al., 2015). This suggests that a shift from planning to impulsive (flight-fight) behavior takes place when threat approaches.

Reactions to threat, such as aggressive behaviors, can be adaptive and result in appropriate defensive responses, but aggression may also be dysfunctional. In individuals with aggression problems, stronger reactivity towards stressful or aversive stimuli has been reported (Patrick, 2008). For instance, individuals scoring high on aggressiveness react to avoidable threat with increased response preparation (Gladwin, Hashemi, et al., 2016). Furthermore, violent behavior in military veterans is associated with hyperarousal symptoms (Taft et al., 2015), also indicating stronger threat reactivity. Aggressive behavior in youths low in psychopathic traits is also linked to exaggerated activity in the PAG (White et al., 2016). In patient populations at risk for impulsive aggression (e.g., Intermittent Explosive Disorder (IED) and borderline personality disorder) heightened amygdala reactivity was found during the presentation of emotional faces compared to control participants (Coccaro et al., 2007; McCloskey et al, 2016; New et al, 2007). Again, this stronger reaction to aversive stimuli indicates a stronger reactivity to threat in anger and aggression.

The aim of the current neuroimaging study was therefore to investigate whether veterans suffering from anger and aggression problems, relative to veterans without these problems, show different neural responses to threat-related effects, as measured using the Fear-and-Escape Task (FAET). Based on the above literature, the primary hypothesis is that the anger group will show stronger activation reflecting the shift from escapable to inescapable threat. Further, differences between the two groups on the neural response to both threat and proximity were tested, as these factors may also play a role in abnormal responses to threat and perceived risk which may lead to aggressive behavior.

Materials and Methods

Participants

Twenty-seven male veterans with anger and aggression problems were included. All participants were right-handed and had normal or corrected-to-normal vision. They were recruited via their psychologists/psychiatrists at the Military Mental Health Care Institute and via advertisements in the waiting room and newsletters for veterans. Additionally, 30 control veterans without anger and aggression problems were included. Inclusion criteria for the Anger group were based on the four research criteria for impulsive aggression described by Coccaro (2012): 1) Verbal or physical aggression towards other people occurring at least twice weekly on average for one month; or three episodes of physical assault over a one year period; 2) the degree of aggressiveness is grossly out of proportion; 3) the aggressive behaviour is impulsive (not premeditated);

4) the aggressive behaviour causes either distress in the individual or impairment in occupational or interpersonal functioning (Coccaro, 2012). Inclusion criteria for the Control group were 1) no current DSM-IV diagnosis; 2) no history of pathologic aggressive behaviour.

All participants signed an informed consent before participation after a complete written and verbal explanation. The Ethics Committee of the University Medical Center Utrecht, The Netherlands, approved this study. This study was carried out in accordance with the Declaration of Helsinki.

Measures

Interview and questionnaires

All participants were screened for psychiatric diagnoses according to the DSM IV (American Psychiatric Association, 2000) using the MINI interview (Van Vliet, Leroy, & Van Megen, 2000). Anger and Aggression were measured using the Dutch version of the State-Trait Anger Expression Inventory revised (STAXI-2; Hovens, Rodenburg, & Lievaart, 2015) and the Dutch version of the Aggression Questionnaire (Meesters, Muris, Bosma, Schouten, & Beuving, 1996).

Fear-and-Escape Task

A virtual-predator task, the Fear-and-Escape Task, (FAET; Montoya, Van Honk, Bos, & Terburg, 2015) was used. An outline of the task is depicted in Figure 1 (for a complete description of the task see Montoya et al., 2015). The task consists of a Threat condition and a Safe condition, indicated by a yellow and a blue pictogram, respectively. The pictograms were presented either at a small size, of full-screen divided by 16 (in the escapable condition), full-screen divided by 2 (in the imminent condition) or at actual full-screen size (in the inescapable condition). The sizes visually represented distance. The duration of presenting these pictograms was randomized and counterbalanced across conditions and lasted 3, 4.5 or 6 seconds. The pictograms in the escapable and imminent conditions could increase in size ('Attack'), visually nearing the participant. During this Attack, participants could press a button to halt this approach. If this was not done in time and the pictogram reached full size in the Threat condition, an aversive noise (AN) in the form of a female scream at 110 dB for the duration of 1 second, was presented through MR-compatible headphones. The large picture (full-screen size) in the Threat condition could also be followed by the AN in 20% of the trials, however this could not be prevented (unavoidable). The trials in the Safe condition were never followed by the AN, but participants were requested to also push the button when these cues increased in size. Between trials, a resting phase, indicated by a black fixation cross, displayed for 3 or 4 seconds. The durations were randomized and counterbalanced between conditions.

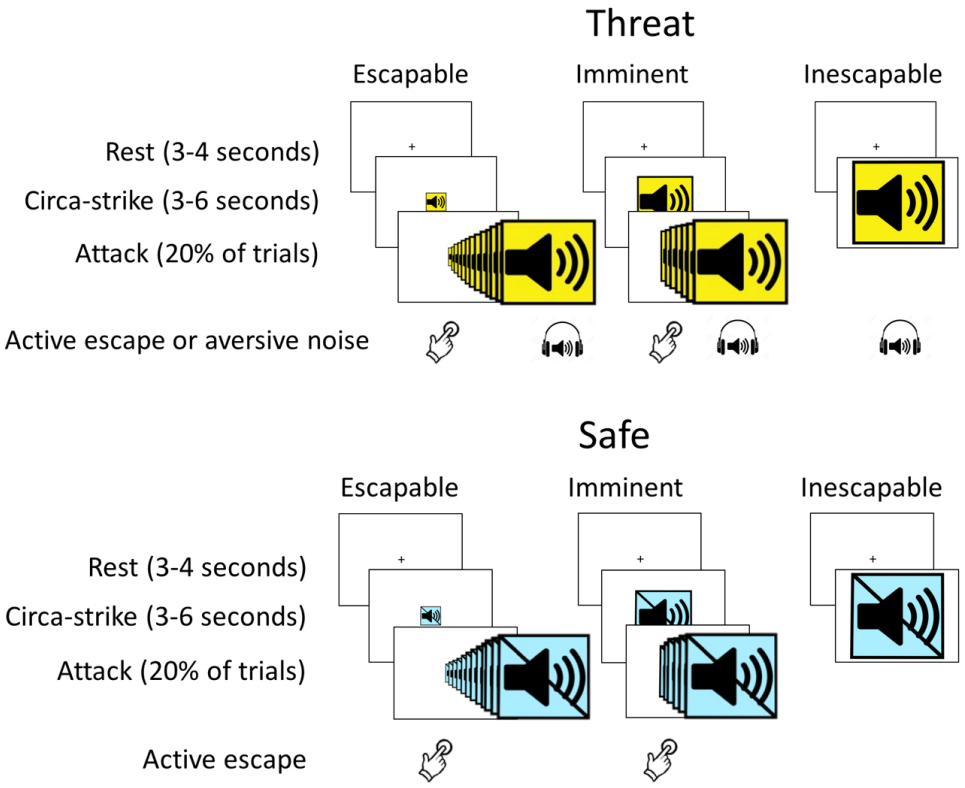


Figure 1.
Outline of the Fear-and-Escape Task (FAET). The task consists of 3 blocks of 29 trials. The Threat condition consists of 5 Escapable trials, 5 Imminent trials and 4 Inescapable trials. In 20% of the Escapable and Imminent (escapable at chance-level) trials the cue attacked the participant by rapidly increasing in size. This could be halted by pushing a button. When this was not done in time, a highly aversive noise was presented. The procedure was exactly the same in the Control condition, only without the threat of the aversive noise.

fMRI acquisition and preprocessing

Using a 3T magnetic resonance imaging scanner (Philips Medical System, The Netherlands) 622 functional images were acquired during the task. A two-dimensional echo planar imaging-sensitivity encoding (EPI-SENSE) sequence was used with the following parameters: voxel size = 4 mm isotropic; repetition time (TR) = 1400 ms; echo time (TE) = 23 ms; flip angle = 70°; 4 mm slice thickness; field of view (FOV) 208 × 119 × 256 mm; 30 slices; SENSE-factor R = 2.4 (anterior-posterior). For within subject registration, a T1-weighted image (200 slices; TR = 10 ms; TE = 3.8 ms; flip angle = 8°; FOV = 240 × 240 × 160 mm, matrix of 304 × 299) was used. The images were obtained in a single run with a duration of 14 minutes and 30 seconds.

All fMRI data was preprocessed using statistical parametric mapping (SPM8; Wellcome Trust Centre for Neuroimaging, www.fil.ion.ucl.ac.uk), and visualized using hiro3 (Gladwin, Vink, & Mars, 2016). Preprocessing started with motion-correction of the functional scans to the first dynamic scan and slice-time correction to the middle slice. Next, the anatomical scan was coregistered to the mean functional scan. Subsequently, the structural scan was segmented and normalization parameters were estimated. Using these normalization parameters, all volumes were normalized to a standard brain template (MNI) and resliced at 2.0 mm isotropic voxelsize. Smoothing (8.0 mm full width at half maximum Gaussian kernel) was applied to the normalized functional volumes.

Statistical analyses

Mann-Whitney U Tests were used to test whether the groups show differences in the proportion of attempted and successful escapes, and for the difference scores between the Threat and Safe condition. Furthermore, it was tested whether the two conditions, Threat and Safe, differ in attempted and successful escapes using a Wilcoxon Signed Rank Test.

General Linear Models (GLM) were used to model BOLD-responses to various events. Six trial types were distinguished: Threat-Escapable, Threat-Imminent, Threat-Inescapable, Safe-Escapable, Safe-Imminent and Safe-Inescapable. In the first-level GLM, the following regressors were used: six for the onsets of each trial type, six for the trial-offsets, four for the attacks of each relevant trial type, one for the AN-onset and one for the responses. Due to previous found activation in response to trial-offsets (Klumpers et al., 2010), these were also modeled, but where not of interest in the current study. Furthermore, to reduce variance due to noise caused by movement and drifts in the signal, realignment parameters and a discrete cosine transform high-pass filter (1/128 Hz cut-off frequency) were entered into the analyses. Maps of the regression coefficients for the model were computed for each participant.

Effects on activation at stimulus onset were tested using a full-factorial 2 × 2 × 3 ANOVA design (Anger/Control × Threat/Safe × Escapable/Imminent/Inescapable) with group as between-subjects factor and the conditions as within-subjects factors. A threshold of $p < 0.05$ family-wise error (FWE)-corrected was used in all contrasts. Small volume corrections were applied for regions of interest (ROIs), $p < 0.05$, FWE-corrected. The ROIs used were based on the findings in Montoya et al. (2015) in the placebo condition, and included the anterior insular cortices, dorsal anterior cingulate cortices and the midbrain.

Results

Demographics

Demographic information is depicted in Table 1. The groups did not significantly differ on age, education and number of deployments. The anger and aggression measures all showed a significant difference between the groups.

Table 1. Description of the Anger group and the Control group.

	Anger group (N=27)	Control group (N=30)	
	Mean (SD)	Mean (SD)	Statistics
Age	36.37 (6.54)	34.53 (7.59)	t (1,55) = 0.97, *ns*
Education	4.22 (0.64)	4.2 (0.81)	t (1,55) = 0.11, *ns*
Number of deployments	2.07 (1.17)	2.37 (1.25)	t (1,55) = -0.91, *ns*
Frequency of aggressive behaviour			
Verbal	4.44 (1.55)	0.3 (0.99)	t (1,55) = 12.15, $p < 0.001$
Physical	2.22 (1.65)	0.00 (0.00)	t (1,55) = 7.39, $p < 0.001$
STAXI-2			
State Anger	23.33 (10.08)	15.20 (0.76)	t (1,55) = 4.41, $p < 0.001$
Trait Anger	22.44 (6.88)	12.13 (2.47)	t (1,55) = 7.68, $p < 0.001$
Aggression Questionnaire			
Physical aggression	29.26 (7.10)	18.47 (4.55)	t (1,55) = 6.91, $p < 0.001$
Verbal aggression	15.41 (3.99)	11.3 (1.54)	t (1,55) = 5.23, $p < 0.001$
Anger	24.26 (5.47)	11.17 (2.49)	t (1,55) = 11.83, $p < 0.001$
Hostility	24.04 (7.22)	11.87 (3.41)	t (1,55) = 8.27, $p < 0.001$

Behavioral data

Table 2 shows the behavioral results of the FAET. Participants succeeded in escape more often in the Imminent Threat condition compared to the Imminent Safe condition (Wilcoxon Signed Rank test, $p < 0.01$). The data thus indicate that participants were motivated to avoid the aversive scream. Mann-Whitney U tests revealed no significant differences between the two groups (all p's > 0.234). Furthermore, the difference between the two conditions in proportion attempted escapes and succeeded escapes did not differ between the two groups (Mann-Whitney U test, $p = 0.557$ and $p = 0.434$, respectively).

Table 2.
Behavioral data from the FAET.

Condition	Attempted escapes (SD)		Succeeded escapes (SD)	
	Anger	Control	Anger	Control
Escapable				
Threat	100% (0.0)	100% (0.0)	100% (0.0)	100% (0.0)
Safe	100% (0.0)	100% (0.0)	100% (0.0)	99% (6.1)
Imminent				
Threat	91% (14.9)	87% (20.7)	43% (29.0)	46% (28.3)
Safe	89% (16.0)	89% (16.0)	27% (33.4)	34% (29.7)

Note. Significant differences were found in succeeded escapes in the Imminent Threat condition compared to the Imminent Safe condition (Wilcoxon Signed Rank test, $p < 0.01$). Mann-Whitney U tests revealed no significant differences between the two groups (all p's > 0.234).

fMRI results

Task effects. The Threat versus Safe contrast revealed a comparable pattern to that described by Montoya et al. (2015), see Figure 2 and Table 3. Several regions, among which the hippocampus, insula and the supplementary motor cortex, were active during observation of the threat-indicating stimulus compared to the control stimulus, many of them part of the salience network. Furthermore, deactivation was found in regions that are part of the default mode network, such as prefrontal and parietal cortices.

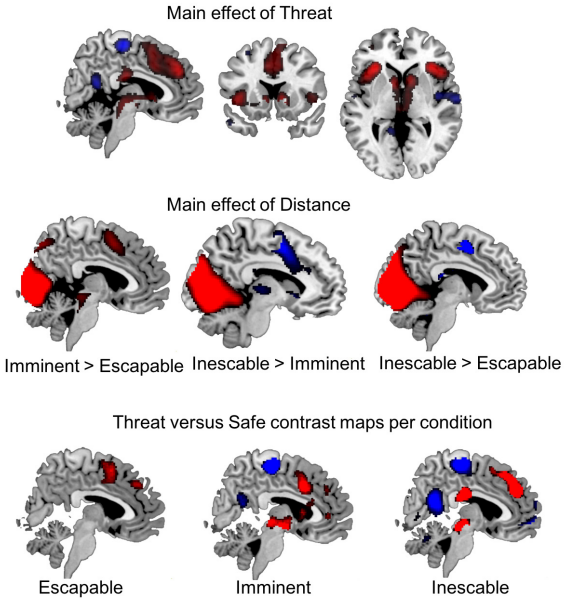


Figure 2.
Brain activation during onset of the cues. The statistical map is overlaid on a template brain in MNI-space, thresholded at $p < 0.05$, FWE-corrected (t=4.49).

Table 3.
Task effect threat onset

Region	Side	x	y	z	n voxels	Center of mass, *t* or *F*
Main effect of Threat onset						
Threat > Safe						
Insula	L	-32	24	-2	694	9.60
Insula	R	40	24	-2	793	9.55
Frontal superior medial cortex	R	6	40	38	351	7.10
Cingulum mid	L	0	-18	30	270	6.26
Caudate	R	12	12	2	66	6.01
Supramarginal gyrus	R	58	-42	28	231	5.88
Caudate	L	-8	10	2	50	5.83
Thalamus	R	2	-22	-6	154	5.83
Cingulum mid	R	2	12	46	467	5.75
Supramarginal gyrus	L	-56	-42	30	162	5.59
Frontal mid	R	30	50	20	67	5.19
Superior frontal cortex	R	14	10	66	23	4.94
Safe > Threat						
Hippocampus	L	-26	-24	-16	1125	-8.11
Hippocampus	R	28	-16	-18	699	-7.98
Supplementary motor area	R	6	-22	64	513	-7.26
Thalamus	L	0	-24	20	1707	-6.79
Superior frontal cortex	L	-18	34	48	602	-6.42
Thalamus	R	18	-28	12	1735	-6.44
Middle temporal gyrus	L	-58	-6	-8	191	-6.27
Angular gyrus	R	50	-62	24	264	-5.91
Postcentral gyrus	L	-54	-6	26	287	-5.70
Inferior orbitofrontal cortex	L	-38	36	-16	48	-5.44
Lingual gyrus	R	24	-58	-8	46	-5.31
Precentral gyrus	R	44	-16	58	166	-5.29
Insula	L	-36	-12	12	39	-5.13
Cerebellum	L	-14	-50	-20	39	-5.03
Superior medial frontal cortex	L	-8	64	18	85	-4.83
Middle occipital gyrus	R	42	-76	14	41	-4.79
Middle occipital gyrus	L	-42	-74	8	32	-4.72
Postcentral gyrus	R	46	-26	48	61	-4.74
Main effect of Distance						
Calcarine cortex	R	2	-76	4	26253	573.18
Supplementary motor area	R	4	8	50	2696	74.96
Postcentral gyrus	L	-38	-18	50	3497	56.44
Thalamus	R	24	-24	-2	153	45.01

Insula	R	34	24	6	238	28.48
Inferior frontal gyrus	L	-48	30	0	454	27.56
Precentral gyrus	L	-56	6	28	71	25.35
Insula	L	-30	20	4	290	24.92
Precuneus	R	22	-40	14	122	24.52
Insula	L	-42	0	12	131	23.36
Cerebellum	R	22	-50	-26	114	22.26
Posterior cingulum	L	-18	-42	12	81	20.37
Caudate	R	12	16	0	72	19.36
Caudate	L	-10	18	-2	37	19.60
Midbrain	R	2	-46	-26	77	16.99
Midbrain	R	2	-26	-10	173	17.71
Cingulum mid	R	2	-22	24	218	18.24
Middle frontal gyrus	L	-32	38	32	55	16.74
Inferior frontal gyrus	R	56	30	0	28	15.34
Imminent > Escapable						
Calcarine cortex	R	2	-76	8	19475	30.56
Hippocampus	L	-20	-26	-4	171	8.64
Thalamus	R	22	-26	-2	184	8.55
Middle frontal gyrus	L	-32	-4	52	957	6.43
Supplementary motor area	R	12	6	54	1630	6.44
Brainstem	R	2	-26	-10	281	5.87
Insula	L	-36	16	4	29	4.75
Escapable > Imminent						
Inferior occipital cortex	R	32	-90	-6	420	-21.78
Inferior occipital cortex	L	-30	-88	-10	303	-18.97
Middle occipital gyrus	L	-46	-68	26	838	-8.82
Angular cortex	R	54	-64	28	399	-7.30
Superior medial frontal cortex	L	-8	56	32	27	-4.71
Inescapable > Imminent						
Lingual cortex	R	2	-70	4	15468	20.10
Inferior frontal gyrus	L	-48	30	0	682	7.41
Inferior frontal gyrus	R	54	30	0	75	5.54
Middle frontal gyrus	L	-44	18	44	64	5.32
Middle temporal gyrus	L	-48	-56	22	24	4.75
Imminent > Inescapable						
Cingulum mid	L	-2	0	44	2931	-11.97
Postcentral cortex	L	-42	-20	50	3152	-10.59
Inferior occipital cortex	R	30	-90	-6	437	-8.18
Insula	R	34	24	6	315	-7.50
Precentral cortex	L	-56	6	28	103	-6.96
Insula	L	-40	2	12	209	-6.78

Putamen	L	-24	20	4	458	-6.61
Cerebellum	R	20	-50	-26	128	-6.33
Caudate	R	12	16	2	177	-6.12
Thalamus	L	-8	-18	6	268	-6.13
Cingulum mid	R	2	-22	24	347	-6.00
Midbrain	R	4	-48	-26	95	-5.42
Middle frontal gyrus	L	-30	36	30	82	-5.33
Thalamus	R	10	-18	8	21	-4.70
Inescapable > Escapable						
Lingual gyrus	R	2	-72	6	22824	31.82
Hippocampus	R	24	-26	-4	113	7.96
Superior parietal cortex	L	-20	-60	54	167	5.77
Escapable> Inescapable						
Inferior occipital cortex	R	32	-90	-6	543	-23.83
Inferior occipital cortex	L	-30	-88	-10	399	-21.86
Postcentral cortex	L	-46	-22	50	1224	-8.45
Precuneus	R	22	-40	14	224	-6.99
Supplementary motor area	L	-4	4	52	318	-6.89
Posterior cingulum	L	-18	-42	12	147	-6.35
Midbrain	R	2	-44	-26	109	-5.76
Angular cortex	R	48	-70	36	64	-5.82
Rolandic operculum	L	-40	-2	12	60	-5.49
Insula	R	32	22	12	34	-5.11
Thalamus	R	10	-24	20	103	-5.14
Thalamus	L	-6	-26	20	47	-5.02
Caudate	L	-14	18	22	158	-5.15
Interactions: Threat × Distance						
Hippocampus	L	-28	-22	-12	295	20.48
Postcentral cortex	R	64	-16	36	127	19.90
Hippocampus	R	30	-18	-16	130	18.88
Inferior parietal cortex	L	-52	-22	42	189	18.11
Amygdala	L	-26	-2	-20	65	16.74
Postcentral cortex	R	48	-28	50	122	15.83
Anterior cingulum	R	16	32	-4	20	15.61
Middle temporal gyrus	L	-50	-68	0	64	15.31
Insula	L	-34	-2	14	30	15.57
Precentral cortex	L	-36	-12	62	43	15.13
Supplementary motor area	R	2	-20	64	45	14.73
Postcentral cortex	L	-38	-34	54	29	14.38
Escapable, Threat > Safe: no supratreshold voxels						
Escapable, Safe > Threat: no supratreshold voxels						
Imminent, Threat > Safe						

Insula	L	-32	22	-2	481	6.77
Inferior orbitofrontal cortex	R	34	24	-6	206	6.16
Thalamus	R	4	-8	-8	28	5.11
Cingulum mid	L	0	14	40	56	4.82
Imminent, Safe > Threat						
Supplementary motor area	R	4	-22	64	210	-5.68
Inescapable, Threat > Safe						
Insula	R	40	26	0	453	7.87
Insula	L	-32	24	0	352	7.58
Superior medial frontal cortex	R	6	42	36	159	6.50
Cingulum mid	R	2	-18	28	189	6.23
Thalamus	R	2	-24	-6	40	5.26
Superior medial frontal cortex	R	4	34	48	28	4.87
Inescapable, Safe > Threat						
ParaHippocampal_R	R	30	-18	-18	1226	-8.34
Supplementary motor area	R	6	-22	66	648	-6.90
Superior temporal cortex	L	-54	-2	-10	681	-6.62
Thalamus	L	-12	-12	0	2669	-8.54
Rolandic operculum	R	38	-22	26	5146	-7.11
Middle occipital gyrus	L	-40	-68	18	1864	-6.13
Inferior frontal gyrus	R	50	40	8	133	-5.88
Middle frontal gyrus	L	-22	24	50	710	-5.89
Middle temporal gyrus	R	48	-62	10	1224	-5.77
Insula	L	-36	-8	10	185	-5.66
Postcentral cortex	L	-52	-16	34	559	-5.64
Postcentral cortex	L	-38	-32	48	294	-5.29
Caudate	L	-22	-2	24	101	-5.12
Middle occipital gyrus	R	26	-74	34	123	-5.12
Superior parietal cortex	R	24	-52	58	121	-5.03
Inferior orbitofrontal cortex	R	18	34	-4	26	-5.01
Inferior frontal gyrus	L	-48	36	10	39	-5.00
Inferior orbitofrontal cortex	L	-38	36	-16	27	-4.97
Superior medial frontal cortex	L	-8	66	22	97	-4.98
Caudate	R	20	6	24	26	-4.77
Superior parietal cortex	L	-24	-52	60	24	-4.68

Note. Table shows anatomical region, MNI coordinates of the center of the cluster, and *F* or *t*-values for the main effect of Threat onset, Distance and the interaction effect of Threat × Distance. Clusters with more than 0.10 proportion overlap were combined. Clusters consisting of at least 20 voxels are reported. All analyses are conducted at the voxel-level, whole-brain p-value < 0.05, FWE-corrected.

The main effect of Distance is also shown in Figure 2 and Table 3. Results show stronger activation in the occipital cortex during the onset of cues in the Imminent versus the Escapable condition, in the Inescapable versus the Imminent condition, and the Inescapable versus the Escapable condition.

The interaction between Threat and Distance is shown in Figure 2 and Table 3. Stronger activation during Threat cues was found in the insula, brainstem and the cingulum, whereas deactivation of the supplementary motor area was found.

Group effect. The Group*Threat and the Group*Threat*Distance interaction revealed no significant results. Small volume correction within the ROI based on the activation found in Montoya et al. (2015) in the control (placebo) condition also showed no significant differences between the Anger and the Control group on these contrasts.

The Group*Distance interaction revealed significant differences with peaks at the right calcarine cortex (x=8, y=-80, z=10) and the left occipital superior cortex (x=-8, y=-96, z=10). T-tests revealed that the occipital superior cortex was more active in the Anger group compared to the control group during viewing of inescapable stimuli versus escapable stimuli (Figure 3 and Table 4). Furthermore, the cuneus was more active in the Anger group compared to the control group during viewing of imminent stimuli versus escapable stimuli. Figure 3 and Table 4 show these effects.

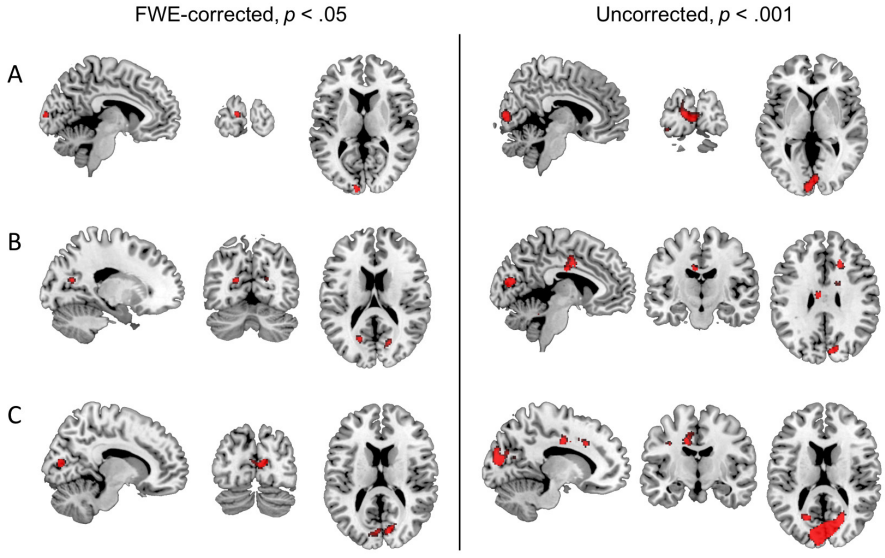


Figure 3.
A) Stronger activation in imminent versus escapable stimuli in the Anger group compared to the Control group. B) Stronger activation in inescapable versus imminent stimuli in the Anger group compared to the Control group. C) Stronger activation in inescapable versus escapable stimuli in the Anger group compared to the Control group.

Table 4.
Interaction effect of Group and Distance

Region	Side	x	y	z	*n* voxels	Peak, *T*	*p*
Imminent > Escapable							
Cuneus	L	-8	-96	8	57	5.65	<0.05, FWE-corr.
	L	-8	-96	8	230	5.65	<0.001
Cuneus	R	4	-84	6	84	3.87	<0.001
Inferior occipital gyrus	L	-30	-84	-8	45	3.76	<0.001
	L	-36	-92	-12	same cluster	3.28	<0.001
Lingual gyrus	L	-14	-92	24	1	3.10	<0.001
Inescapablle > Imminent							
Sub-gyral	L	-20	-66	16	7	4.70	<0.05, FWE-corr.
Precuneus	R	18	-70	18	2	4.52	<0.05, FWE-corr.
Sub-gyral	L	-20	-66	16	1431	4.70	<0.001
Precuneus	R	18	-70	18	same cluster	4.52	<0.001
Cuneus	R	12	-76	24	same cluster	4.39	<0.001
Cingulate gyrus	L	-10	-8	40	256	3.98	<0.001
	L	-8	-10	32	same cluster	3.89	<0.001
	L	-14	0	34	same cluster	3.17	<0.001
Cingulate gyrus	R	18	26	30	78	3.83	<0.001
Fusiform	L	-22	-44	-18	76	3.55	<0.001
Cingulum mid	L	-16	-34	42	44	3.44	<0.001
	L	-10	-38	48	same cluster	3.31	<0.001
Cingulate gyrus	R	14	4	28	17	3.32	<0.001
	R	16	-4	32	same cluster	3.18	<0.001
Fusiform	L	-22	-32	-22	9	3.31	<0.001
Cingulate gyrus	R	12	-38	26	6	3.27	<0.001
Cerebellum	L	-6	-46	-24	3	3.24	<0.001
Fusiform	R	28	-54	-18	3	3.22	<0.001
Extra-nuclear	L	-30	-28	24	1	3.20	<0.001
Inescapable > Escapable							
Cuneus	R	8	-80	10	216	5.62	<0.05, FWE-corr.
Cuneus	L	-6	-82	14	same cluster	4.89	<0.05, FWE-corr.
Cuneus	R	8	-80	10	2084	5.62	<0.001
Cuneus	L	-6	-82	14	same cluster	4.89	<0.001
	L	-4	-92	14	same cluster	4.38	<0.001
Cingulate gyrus	L	-12	-8	34	145	3.90	<0.001
	L	-14	0	36	same cluster	3.33	<0.001
Inferior occipital gyrus	L	-30	-84	-8	33	3.88	<0.001
Cingulate gyrus	L	-14	18	34	54	3.74	<0.001
Precentral gyrus	L	-36	-12	34	32	3.48	<0.001
Cingulate gyrus	R	18	26	32	19	3.45	<0.001

Fusiform	L	-28	-72	-10	4	3.34	<0.001
Cerebellum	L	-6	-66	-6	12	3.31	<0.001
Cingulate gyrus	L	-12	6	38	4	3.29	<0.001
Extra-nuclear	L	-32	-28	24	8	3.25	<0.001
Sub-gyral	L	-36	-66	10	9	3.25	<0.001
Sub-gyral	R	24	-52	38	5	3.22	<0.001
Hippocampus	L	-30	-28	-12	4	3.21	<0.001
Fusiform	R	30	-50	-18	1	3.14	<0.001
Inferior occipital gyrus	L	-34	-92	-12	1	3.14	<0.001
Sub-gyral	L	-38	-24	-10	1	3.14	<0.001

Note. Table shows anatomical region, MNI coordinates and T-values for the main effect of Threat onset. All analyses are conducted at the voxel-level, both whole-brain p-value < 0.001 and <0.05, FWE-corrected.

Discussion

The current study used the Fear-And-Escape Task (FAET) to determine abnormal neural responses to threat related to anger and aggression in military veterans. The main finding was the significantly stronger activation in the cuneus in the Anger group compared to the Control group with increasing proximity. The cuneus is involved in motivated attention (Bradley et al., 2003), which facilitates the perceptual processing of motivationally relevant stimuli or stimulus features (Edmiston et al., 2013; Lang et al., 1998; Lee, Sakaki, Cheng, Velasco, & Mather, 2014; Satpute et al., 2015). The stimulus size indicates proximity, and therefore makes stimuli more salient. Motivated attention refers to the attentional processing of motivationally relevant stimuli or stimulus features, such as proximity. The size of the stimuli not only reflects saliency, it also reflects threat. A larger cue can attack and is harder to escape from. This might be perceived as more threatening by the Anger group leading to more extensive processing of stimulus features. Proximity thus appears to evoke increased motivated attention in the Anger group. This may be related to the fundamental role distance plays in defensive responses to threat (Fanselow, 1994; Mobbs et al., 2007). Future study is needed to determine whether the group by proximity effect reflects a more general tendency to be vigilant towards stimuli or features relevant for defensive responses, in particular those such as proximity that have a "hard-wired" relationship to defensive responses. If so, aggression in the complex, dynamic environment of daily life could be related to attention that is automatically biased towards threat-relevant signals, which could increase the likelihood of false positives in the detection of actual threat.

Further, the results confirmed that the paradigm activates a similar pattern in this population as shown by Montoya et al. (2015): Proximal and escapable threat activated

areas that are part of the salience network, and deactivated areas that are part of the default mode network, in line with the literature on the threat system (McNaughton & Corr, 2004). The overall effect of anticipatory threat was thus replicated, but this effect did not differ between the anger group and the control group. This contrasts with previous studies in patients with anger and aggression problems, which show increased reactivity to facial threat stimuli in passive viewing paradigms (Coccaro et al., 2007; McCloskey et al., 2016; New et al., 2007). This might indicate that the processing of anticipated threat is not affected in veterans with anger and aggression problems. Further, military personnel is required to respond differently compared to civilians in similar situations. This might also explain the different results in reactivity to threat. Whether unanticipated threat is affected or not in anger and aggression, needs to be explored in future studies.

Visual threat processing has been studied in anxiety, with studies among others showing that in anxiety, perception of threat is increased (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & Van IJzendoorn, 2007; Fox, Russo, Bowles, & Dutton, 2001; Sussman, Szekely, Hajcak, & Mohanty, 2016). A perceptual bias toward potential threat in anxiety is also seen in the current sample. However, anticipatory processing in threat has been found to showed no differences with regard to visual stimuli in anxiety disorder compared to controls (Mills, Grant, Judah, & White, 2014). These corresponding results might be explained by the high overlap between aggression and anxiety (Pinna et al., 2016).

The stimuli used in the current task were clearly differentiable task-contingent threat and safe cues, without any ambiguity. Differences in response to threat associated with aggression problems might be more related to a hostile attribution bias, in which in particular ambiguous situations are more easily coded as threatening (Anderson & Bushman, 2002). Indeed, increased partner violence was found in military veterans who interpret all kinds of situations in an overly hostile manner (Taft et al., 2015). Perception also plays a role in the effect of deployment on the brain: the neural coupling between the amygdala and the insula/dorsal anterior cingulate cortex in deployed veterans is mainly influenced by perceived threat rather than by actual threat exposure (Van Wingen, Geuze, Vermetten, & Fernández, 2011). Whether reactivity to ambiguous situations is indeed distinctly different from non-ambiguous threat reactivity in veterans with an aggression disorder, should be addressed in future research.

Note however that the Anger group might also be more impulsive relative to the control group, and it is not possible to disentangle effects of impulsivity. Furthermore, the experienced anger during the task was not measured, thus, it could not be tested whether subjective feelings of anger influenced the activation.

Since the participants in this study were all male veterans, generalization of the results to females, other professions, or civilians, is difficult. However, anger and aggression

are common problems that are not only reported within military veterans. For instance, heightened anger has also been described in police personnel (Meffert et al., 2008). The results from this study therefore have a wider significance beyond the current sample. Threat-related motivated attention in dynamically changing situations involving threat could play a role in other populations as well. Future research could focus on whether training can reduce increased motivated attention in anger and aggression. Decreasing this attention might lead to fewer situations perceived as provocative or threatening. Furthermore, when patients recognize these situations earlier, it might lead to more appropriate behavior.

In conclusion, while no differences related to anticipatory threat were found, individuals with anger and aggression showed a sensitivity to proximity of the virtual predator. Future research is needed to confirm whether anger and aggression are related to abnormal responses to fundamental stimulus features such as proximity in threatening contexts, as opposed to more contingent forms of threat. Moreover, the role of ambiguity in contingent threat remains an important direction for future research. Such research might help to develop methods for clinical interventions aimed at reducing aggression-related threat reactivity.

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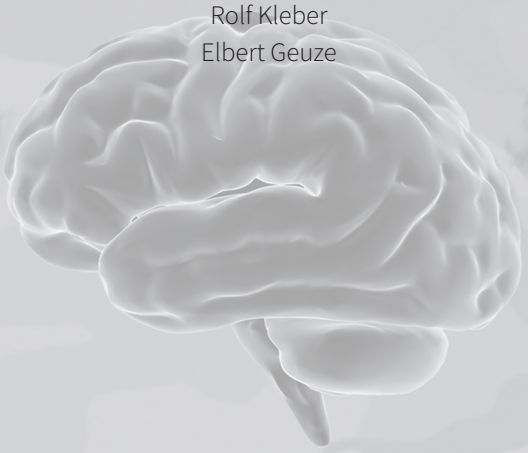
6

Neural activity during the viewing of emotional pictures in veterans with pathological anger and aggression

Lieke Heesink
Thomas Gladwin
Matthijs Vink
Jack van Honk
Rolf Kleber
Elbert Geuze



Submitted

Abstract

Anger and aggression are common mental health problems after military deployment. Anger and aggression have been associated with abnormalities in subcortical and cortical levels of the brain and their connectivity. Here, we tested brain activation during the processing of emotional stimuli in military veterans with and without anger and aggression problems. 30 military veterans with anger and aggression problems and 29 veterans without a psychiatric diagnosis (all males) participated in this study. During an fMRI scan 32 negative, 32 positive and 32 neutral pictures from the IAPS were presented in intermixed order. The Aggression group showed heightened activity in brain areas including the supplementary motor area, the cingulum and the parietal cortex, in response to stimuli, regardless of category. Furthermore, the Aggression group showed stronger connectivity between the dorsal anterior cingulate cortex (dACC) and the amygdala during the viewing of negative stimuli, and weaker connectivity between dACC and medial prefrontal cortex during the viewing of positive stimuli. Veterans with anger and aggression problems showed enhanced brain response to all stimuli during the task, irrespective of valence and they rated the pictures more likely as negative. We take this to indicate enhanced preparation for action and attention to the presentation of stimuli that could prove to be threatening. Further, group differences in functional connectivity involving the dACC reveal abnormal processing of stimuli with negative and positive valence. In sum, the results point towards a bias towards an enhanced sensitivity to perceived or potential threat in aggression.

Acknowledgment contribution authors
Designed research: L. Heesink, M. Vink & E. Geuze
Performed research: L. Heesink
Analyzed data: L. Heesink & T. Gladwin
Wrote the paper: L. Heesink, T. Gladwin, M. Vink, J. van Honk, R. Kleber, & E. Geuze

Introduction

Millitary deployment is often a stressful period and regularly leads to mental and social difficulties after homecoming (Fear et al., 2010). Frequently occurring problems, besides symptoms of posttraumatic stress disorder and depression, are anger and aggression (Heesink, Rademaker, Vermetten, Geuze, & Kleber, 2015; Reijnen, Rademaker, Vermetten, & Geuze, 2015). Emotional and behavioral manifestations of these problems can be very disabling for the individual as well as their surroundings (Anderson & Bushman, 2002). Anger and aggression problems have been linked to disturbed emotional processing (Davidson, Putnam, & Larson, 2000). That is, stimuli are more easily perceived as negative or threatening, which might lead to reactive or impulsive aggression.

An important brain area in emotional processing is the amygdala (Etkin, Büchel, & Gross, 2015; Janak & Tye, 2015). The amygdala consists of distinct subnuclei (Hrybouski et al., 2016; Janak & Tye, 2015). The basolateral amygdala (BLA) plays a role in differentiating responses to stimuli currently evaluated to have biologically significant outcomes (Balleine & Killcross, 2006; Baxter & Murray, 2002; Murray, 2007). The BLA is reciprocally connected with a wide range of brain areas, including medial and orbitofrontal prefrontal cortex and has projections to the central medial amygdala (CMA). The CMA in turn projects to areas such as the hypothalamus and brainstem, including the periaqueductal gray, thereby activating appropriate physiological responses such as freezing (Hermans, Henckens, Roelofs, & Fernández, 2013).

In patients diagnosed with Intermittent Explosive Disorder (IED) hyperactivity of the amygdala has been reported in response to angry faces (Coccaro, McCloskey, Fitzgerald, & Phan, 2007; McCloskey et al., 2016). Furthermore, the circuitry of the amygdala, including the orbitofrontal cortex and the anterior cingulate cortex, has been implicated in disorders characterized by aggressive behavior such as IED and borderline personality disorder (Adams, 2006; Best, Williams, & Coccaro, 2002; Davidson et al., 2000).

Post-traumatic stress disorder (PTSD) is a common mental disorder after deployment and also associated with aggression (Jakupcak et al., 2007; Taft, Vogt, Marshall, Panuzio, & Niles, 2007). Although in PTSD no evidence was found for amygdala dysfunction in relation to general, non-facial, emotional stimuli (Van Rooij et al., 2015), it was found that patients with PTSD who did not respond to therapy show heightened amygdala activation to such stimuli before treatment (Van Rooij, Kennis, Vink, & Geuze, 2016). Furthermore, stronger activation in the dorsal anterior cingulate cortex (ACC) is implicated in the processing of negative emotional stimuli in PTSD (Van Rooij et al., 2015). Increased attention to negative emotions has been related to dACC activity (Etkin, Egner, & Kalisch, 2011) and might therefore be of interest in aggression as well.

Differences in the processing of emotional stimuli in anger and aggression are mostly tested using facial stimuli (Coccaro et al., 2007; McCloskey et al., 2016), but general non-facial negative emotional stimuli also elicit amygdala activation (Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002). However, whether such stimuli also result in enhanced responses in the amygdala related to anger and aggression is not yet known. Therefore, it is important to investigate the neural response to emotional stimuli in anger and aggression.

Here, we investigate brain responses to general, non-facial, emotional stimuli, in military veterans with and without anger and aggression problems. To this aim, 28 military veterans with anger and aggression problems and 28 veterans without a psychiatric diagnosis (all males) rated 32 negative, 32 positive and 32 neutral pictures from the IAPS while being scanned with fMRI. We studied both brain activity and the connectivity of the amygdala and the dACC with other areas of the brain in relation to the task. Based on previous studies in patients with aggressive behavior, we hypothesize that amygdala and dACC activation will be higher in the impulsive aggression group during the viewing of negative emotional pictures, in comparison to the control group. We expected that the functioning of the amygdala and dACC connectivity is also disturbed in aggression.

Methods

Participants

In this study, 30 male veterans with anger and aggression problems were included (Aggression group). They were recruited via their psychologists/psychiatrists at the Military Mental Health Care Institute and via advertisements in the waiting room and newsletters for veterans. Additionally, 29 male control veterans without anger and aggression problems were also included. It was attempted to include participants in the control group such that this group did not differ on age, education and number of deployments. These participants were recruited by advertisements in magazines for veterans or had participated in previous studies. After analysing the behavioural data of the task, two participants in the Aggression group and 1 participant in the Control group were excluded because they rated too few trials congruently (i.e., according to the IAPS-rating, see below for further details) to include them in the analyses. Inclusion criteria for the Aggression group were based on the four research criteria for impulsive aggression described by Coccaro (2012): 1) Verbal or physical aggression towards other people occurring at least twice weekly on average for one month; or three episodes of physical assault over a one year period; 2) the degree of aggressiveness is grossly out of

proportion; 3) the aggressive behaviour is impulsive (not premeditated); 4) the aggressive behaviour causes either distress in the individual or impairment in occupational or interpersonal functioning (Coccaro, 2012). Inclusion criteria for the Control group were 1) no current DSM-IV diagnosis; 2) no history of pathologic aggressive behaviour.

The Ethics Committee of the University Medical Center Utrecht, The Netherlands, approved this study and all participants signed an informed consent before participation after having received a complete written and verbal explanation of the study. This study was carried out in accordance with the Declaration of Helsinki.

Interview and questionnaires

The Dutch version of the International Neuropsychiatric Interview (MINI) was used in order to screen for the presence of comorbid psychiatric disorders (Van Vliet, Leroy, & Van Megen, 2000). The complete MINI was administered. In this interview the following current or life-time disorders were screened: depressive disorder, dysthymia, suicidal risk, (hypo)manic disorder, panic disorder, anxiety disorder, agoraphobia, social phobia, obsessive compulsive disorder, PTSD, alcohol or drug dependence and/or abuse, psychotic disorders, anorexia nervosa, bulimia nervosa, generalized anxiety disorder, antisocial personality disorder, somatization disorder, hypochondria, body dysmorphic disorder, pain disorder, attention deficit hyperactivity disorder (ADHD) and adjustment disorder.

To measure anger and aggression, the Dutch version of the State-Trait Anger Expression Inventory-revised (STAXI-2; Hovens, Rodenburg, & Lievaart, 2015, Spielberger, 1999) was used. The STAXI-2 consists of 57 items on a 4-point Likert scale and is divided into two subscales: State Anger and Trait Anger.

Furthermore, the Dutch translation of the Buss-Perry Aggression Questionnaire (AQ) (Buss & Perry, 1992; Meesters, Muris, Bosma, Schouten, & Beuving, 1996) was administered. The AQ consists of 29 items on a 5-point Likert scale and is divided into 4 subscales: Physical Aggression, Verbal Aggression, Anger and Hostility.

Task

The task (Van Rooij et al., 2015; Vink, Derks, Hoogendam, Hillegers, & Kahn, 2014) consisted of 96 pictures from the IAPS (Lang, Bradley, & Cuthbert, 1997). These pictures elicit general emotional experience (Lang et al., 1997). The pictures were categorized as neutral, positive, or negative based on the IAPS rating. The pictures were presented for 2 seconds, after which an evaluation screen was presented. By pressing a button with the thumb of their right hand, participants could give their rating (positive, negative or neutral) of the picture within 2 seconds. After each rating period, a fixation cross appeared for the remaining trial duration. The task consisted of four blocks, each with

24 pictures in pseudo-randomized order (8 neutral, 8 positive, 8 negative). Between the blocks, a fixation cross was presented for 32 seconds. For a schematic overview of the task, see Figure 1.

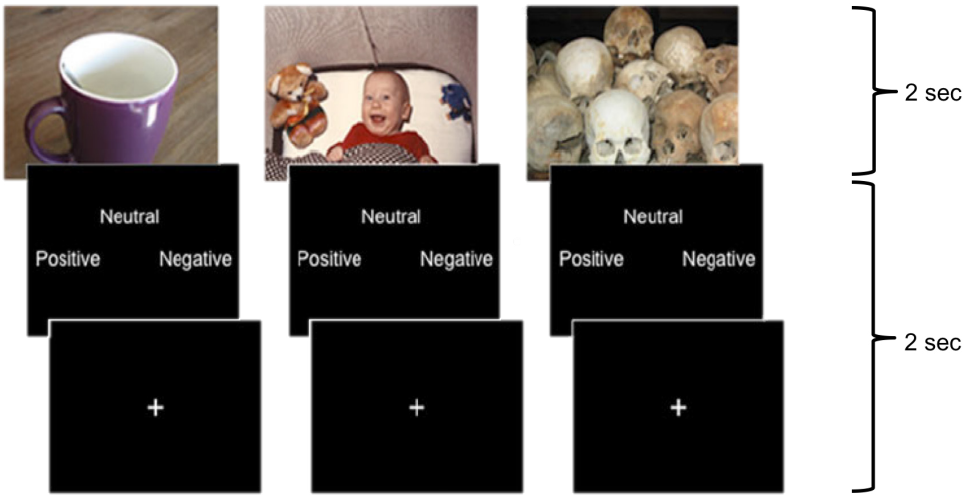


Figure 1.
Outline of the task. Pictures from three categories (Neutral; left, Positive; middle, Negative; right) were presented in an intermixed order for two seconds. After that, an evaluation screen was shown until the participant pressed a button to indicate their evaluation or for a maximum of two seconds. Next, a fixation cross was presented for the remaining duration of the trial.

MRI acquisition

A 3.0 T whole-body magnetic resonance imaging scanner (Philips Medical System, The Netherlands) was used to acquire the functional images during the task, and a T1 weighted image for within-subject registration. An EPI-SENSE sequence scan acquired 322 functional images during the task, with the following parameters: repetition time (TR) = 1600 ms; echo time (TE) = 23 ms; flip angle = 72.5°; 64 x 51 matrix; 4 mm slice thickness; field of view (FOV) = 256 x 204 mm. For within subject registration, a T1 weighted image was used (200 slices, TR = 10 ms; TE = 3.8 ms; flip angle = 8°; FOV = 240 x 240 x 160 mm).

Preprocessing

Preprocessing and analyzing the data was done using SPM 12 (http://www.fil.ion.ucl.ac.uk/spm) and hiro3, a Matlab tool for visualizing and analyzing fMRI data (Gladwin, Vink, & Mars, 2016). Volumes were slice-time corrected to the middle slice and realigned to the first acquired volume. The data were spatially normalized to an MNI T1-weighted template. Smoothing was done using an 8 mm full-width-at-half-maximum (FWHM) Gaussian kernel.

Data Analyses

FMRI data were analyzed using a general linear model regression analysis. Trials were only included when the participants rated the picture congruent to the IAPS rating. For each participant, first-level analyses were performed with the predictors: Neutral stimulus (2 s boxcar), Positive stimulus (2 s boxcar), Negative stimulus (2 s boxcar), response (stick function) and motion parameters. The used contrasts were Negative minus Neutral and Positive minus Neutral stimulus presentation. Further, overall activation due to stimulus presentation was tested, contrasting all stimuli against the implicit baseline. A whole-brain corrected threshold was used such that the family-wise error rate was controlled at 5%; that is, the chance of any voxel showing a false positive was 5%.

In order to investigate differences in amygdala activation during the viewing of emotional pictures, an ROI analysis was performed. The CMA and BLA were defined based on the probabilistic cytoarchitectonic areas from the SPM anatomy toolbox (Eickhoff et al., 2007). When the probability of a certain voxel was higher for the CMA than for the BLA, it was included in the CMA-map and vice versa. The dACC was defined based on the WFU Pick atlas, by using Brodmann's area 32. The same ROI's were used in psychophysiological interaction (PPI) analyses (O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012). In the first analyses, familywise error rate correction was again used. However, after failing to find effects strong enough to survive this correction, exploratory analyses were added in order to show weaker but possibly informative effects. The used threshold was $p < .001$, uncorrected, with an extent of $k \geq 20$ voxels (Lieberman & Cunningham, 2009). As has been pointed out before (Eklund, Nichols, & Knutsson, 2016; Gladwin, Vink, et al., 2016; Lieberman & Cunningham, 2009), this heuristic measure does not (and does not claim to) provide whole-brain corrected results. In order to at least provide an indication of the level of whole-brain significance, permutation tests were used to acquire the null-hypothesis distribution of cluster extents over the chosen threshold.

Results

Demographics

Demographic information is depicted in Table 1. The groups did not differ on age, education and number of deployments. The Aggression group scored significantly higher on all anger and aggression measures.

Table 1.
Description of the Anger group and the Control group.

	Anger group (N=28)	Control group (N=28)	
	Mean (SD)	Mean (SD)	Statistics
Age	36.29 (6.43)	34.21 (7.75)	*ns*
Education	4.21 (0.63)	4.21 (0.79)	*ns*
Number of deployments	2.07 (1.18)	2.29 (1.24)	*ns*
STAXI-2			
State Anger	24.29 (11.45)	15.21 (0.79)	t (1,54) = 4.18, p < .001
Trait Anger	22.71 (6.92)	12.07 (2.49)	t (1,54) = 7.66, p < .001
Aggression Questionnaire			
Physical aggression	30.11 (7.62)	18.46 (4.55)	t (1,54) = 6.94, p < .001
Verbal aggression	15.54 (3.99)	11.36 (1.42)	t (1,54) = 5.23, p < .001
Anger	24.46 (5.43)	11.18 (2.45)	t (1,54) = 11.80, p < .001
Hostility	24.07 (7.07)	12.07 (3.43)	t (1,54) = 8.08, p < .001

Note. SD = standard deviation, ns = not significant

Behavioral data

Table 2 shows the results of the ANOVA. The Aggression group rated significantly more pictures incongruently to the IAPS rating compared to the Control group for both the Positive (F(1,56) = 10.21, p < .01, partial η^2 = .16) and the Neutral picture categories (F(1,56) = 5.43, p < .05, partial η^2 = .09). The Aggression group rated the neutral pictures more often as negative (F(1,56) = 10.11, p < .01, partial η^2 =.16), and the positive pictures more often as neutral (F(1,56) = 5.93, p < .05, partial η^2 = .10) and negative (F(1,56) = 6.37, p < .05, partial η^2 = .11).

fMRI results

Task effect. Brain areas involved in emotional processing were activated by the task, in both the Negative minus Neutral contrast and the Positive minus Neutral contrast, see Figure 2 and Table 3. For the Negative minus Neutral contrast and the Positive minus Neutral contrast, these regions included the amygdala, hippocampus and orbitofrontal cortex.

Table 2.
Behavioral data of the task.

		IAPS rating								
		Neutral			*Positive*			*Negative*		
		Aggression (SD)	Control (SD)	*F*	Aggression (SD)	Control (SD)	*F*	Aggression (SD)	Control (SD)	*F*
Subjects' rating	*Neutral*	**0.77 (0.16)**	**0.86 (0.13)**	**5.43***	**0.25 (0.17)**	**0.15 (0.14)**	**5.93***	0.11 (0.17)	0.05 (0.06)	2.8
	Positive	0.09 (0.09)	0.07 (0.11)	0.01	**0.70 (0.17)**	**0.84 (0.14)**	**10.21****	0.02 (0.03)	0.01 (0.02)	0.52
	Negative	**0.12 (0.14)**	**0.04 (0.05)**	**10.11****	**0.03 (0.05)**	**0.00 (0.02)**	**6.37***	0.87 (0.17)	0.93 (0.07)	3.06

Note. * indicates significance at the .05 level; ** indicates significance at the .01 level.

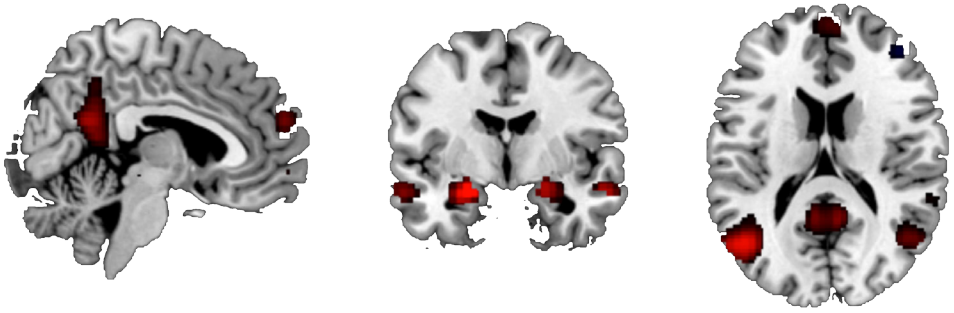


Figure 2.
Brain activation during the Negative minus Neutral contrast, showing the task effect. $p < .05$, FWE-corrected.

Table 3.
Whole-brain activation within subjects during the negative and positive contrast.

Brain area	L/R	Peak value	x	y	z	N voxels
Negative > Neutral						
Medial temporal	R	8.41	52	-52	10	1235
Medial temporal	L	8.28	-46	-60	14	1372
Amygdala	L	6.62	-24	-6	-16	628
Posterior cingulum	L	5.69	0	-50	26	1354
Medial temporal	R	5.35	56	2	-16	219
Hippocampus_L	L	5.16	-6	-2	-16	706
Medial temporal pole	R	4.69	46	16	-26	216
Superior medial frontal cortex	R	4.39	2	58	22	430
Medial orbitofrontal cortex	L	4.27	0	56	-2	161
Superior temporal pole	L	3.84	-40	20	-28	67
Inferior parietal cortex	R	-4.20	50	-46	46	189
Medial frontal cortex	R	-3.80	42	46	18	154
Inferior parietal cortex	R	-3.71	50	-54	42	144
Positive > Neutral						
Anterior cingulum	L	6.45	2	6	16	5579
Medial temporal	L	6.21	-44	-64	16	894
Medial temporal	R	5.98	48	-58	10	490
Medial temporal	L	4.39	-58	-4	-16	99
Caudate nucleus	L	3.96	-6	18	-6	65
Superior temporal pole	L	3.82	-38	22	-28	46
Superior frontal cortex	L	3.67	-18	36	50	58
Medial temporal	R	3.65	60	0	-18	54
Amygdala	L	3.58	-22	-2	-18	55
Hippocampus	L	3.54	-24	-14	-18	62
Superior temporal pole	R	3.45	46	20	-28	43

Note. Clusters $k > 20$ were reported.

Whole brain group differences. The whole brain analyses revealed no differences between the two groups on the Negative minus Neutral contrast or the Positive minus Neutral contrast. However, whole brain group differences were found in activation due to stimulus presentation in general, regardless of the valence of the stimuli. Among other regions, stronger activation was found in the supplemental motor area, frontal cortex, inferior parietal cortex and the anterior cingulum. All differences are depicted in Table 4 and Figure 3.

Table 4.
Stronger brain activity during all stimuli in the Aggression group compared to the control group.

Brain area	L/R	Peak value	x	y	z	N voxels
Precentral gyrus	L	7.3554	-40	-4	56	153
Medial frontal cortex	R	6.8658	46	4	54	147
Superior frontal cortex	R	6.638	20	32	52	101
Precentral gyrus	R	6.6167	44	-8	42	394
Caudate nucleus	L	6.3178	-14	2	18	94
Supplemental motor area	R	6.2	12	2	68	77
Inferior parietal cortex	R	6.134	34	-52	50	195
Supplemental motor area	L	6.1327	0	12	64	71
Medial frontal cortex	R	5.9376	44	38	20	110
Putamen	R	5.8881	28	-12	4	36
Cuneus	L	5.8793	-8	-84	32	27
Medial temporal	R	5.8435	50	-44	0	144
Paracentral lobule	L	5.6892	-18	-30	64	43
Mid cingulum	R	5.6208	10	20	36	22
Supramarginal gyrus	R	5.6199	50	-40	46	145
Inferior temporal cortex	R	5.6061	56	-34	-16	21
Precentral gyrus	R	5.5744	24	-22	58	127
Postcentral gyrus	R	5.5012	44	-12	28	86
Precentral gyrus	L	5.3306	-28	-18	64	25
Caudate nucleus	L	5.2511	-10	-6	18	60
Medial temporal	R	5.2364	54	-40	-8	77
Medial frontal cortex	R	5.2077	48	34	36	23
Paracentral lobule	L	5.2073	-16	-30	68	42
Medial temporal	R	5.1408	46	-44	8	52
Calcarine	L	5.1341	0	-66	14	16
Precentral gyrus	R	5.0847	32	-28	68	21
Postcentral gyrus	L	5.0589	-62	-2	20	15
Precentral gyrus	R	4.9903	36	-26	58	21
Anterior cingulum	L	4.9282	-2	40	16	21
Putamen	L	4.8814	-26	-18	6	16
Supramarginal gyrus	R	4.8627	44	-38	34	16

Note. Activation clusters are reported when $k > 15$.

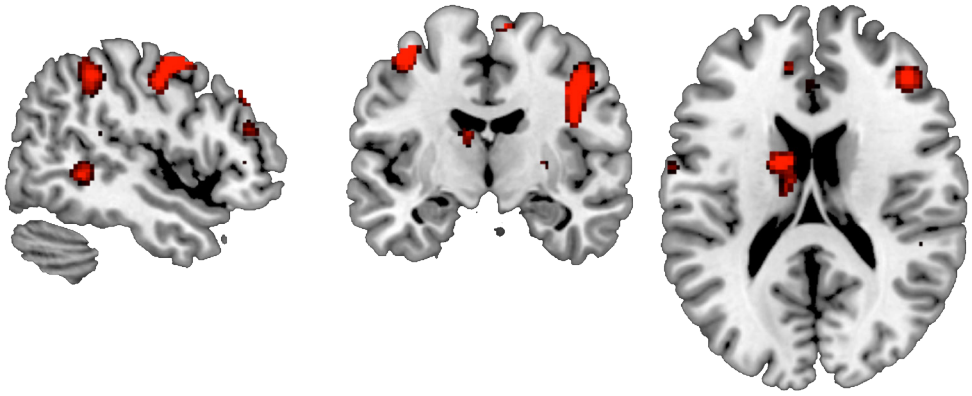


Figure 3.
Stronger brain activation in the Aggression group during the viewing of the pictures, regardless of category. $p < .05$, FWE-corrected.

ROI analyses. Activation of the basolateral and the centromedial amygdala and the dorsal ACC did not differ between the two groups (all p's > .10, uncorrected).

PPI analyses. PPI analyses using the BLA and the CMA as seed regions, did not reveal differences in task-related changes in functional connectivity, both within and between the two groups, using a threshold of $p < .001$, uncorrected.

PPI analyses using the left and right dACC as seed regions, revealed stronger connectivity with the amygdala in the Aggression group compared to the control group during the Negative minus Neutral contrast, using a threshold of $p < .001$, uncorrected. The Positive minus Neutral contrast revealed diminished connectivity with the (orbito) frontal cortex in the Aggression group. All differences are shown in Table 5.

Table 5.
Group differences in dACC coupling during negative versus neutral picture viewing.

Seed region	Brain area	L/R	Peak value	x	y	z	N voxels	Whole-brain *p*
Negative minus Neutral contrast								
Left dACC	Transverse temporal gyrus	L	4,90	-34	-32	10	152	.11
	Frontal Superior cortex	R	4,36	32	4	80	22	.87
	Amygdala	L	4,30	-22	-10	-12	32	.72
	Parahippocampal area	R	3,98	16	-18	-20	36	.66
	Putamen	R	3,90	34	-2	6	28	.77
	Rolandic operculum	R	3,81	46	-2	14	28	.77
	Hippocampus	L	3,68	-26	-6	-18	33	.71
Right dACC	Thalamus	L	4,61	-20	-20	12	77	.29
	Inferior frontal gyrus	R	4,05	2	58	-24	26	.70
	Amygdala	L	3,93	-20	2	-22	32	.70
	Transverse temporal gyrus	L	3,90	-34	-30	10	29	.74
	Putamen	L	3,74	-26	-24	8	56	.43
	Hippocampus	L	3,59	-22	-14	-12	27	.78
	Cuneus	L	-3,64	-6	-94	28	33	.69
Positive minus Neutral contrast								
Left dACC	Mid orbitofrontal cortex	R	-3,56	4	70	-14	35	.66
	Posterior cingulum	R	-3,58	6	-44	28	56	.43
	Medial frontal cortex	R	-3,68	40	52	20	92	.22
	Medial frontal cortex	R	-3,85	34	36	46	43	.57
	Medial temporal cortex	R	-3,91	58	-12	-22	50	.49
	Medial frontal cortex	R	-4,30	48	54	10	255	.039 *
	Posterior cingulum	R	-4,25	4	-34	22	112	.17
	Inferior frontal gyrus	L	-4,28	-6	74	-32	27	.78
	Medial frontal cortex	R	-4,50	46	66	26	46	.54
	Medial frontal cortex	R	-4,74	48	32	32	123	.15
	Superior frontal cortex	R	-4,79	32	62	14	173	.081
	Precentral gyrus	L	6,06	-44	-10	82	85	.26
	Postcentral gyrus	L	4,80	-60	-14	54	87	.24
	Inferior temporal cortex	L	4,12	-70	-24	-24	42	.58
	Superior frontal cortex	L	3,85	-38	52	46	22	.85
Right dACC	Inferior orbitofrontal cortex	R	-4,17	32	36	-6	26	.96
	Medial occipital lobe	R	5,08	64	-92	32	22	.98
	Inferior temporal cortex	L	4,45	-66	-26	-24	59	.69
	Medial occipital lobe	R	4,21	64	-94	32	32	.92
	Orbitofrontal cortex	L	3,65	-50	48	-28	30	.93
	Postcentral gyrus	L	3,76	-36	-22	30	37	.88
	Inferior parietal cortex	R	3,58	70	-48	54	22	.98

Note. Activation clusters are reported when $k > 20$ and $p < .001$. For each cluster, the whole-brain *p* values give the probability of at least one cluster of its size occurring. This was determined by permutation tests of the beta maps of the given contrast, in which group membership was randomly permuted on each of 1000 iterations.

Discussion

In this study we examined whether veterans with anger and aggression problems show different brain activation and functional connectivity in response to general, non-facial emotional stimuli. To test this, positive, negative and neutral pictures were shown during an fMRI scan. It was found that the groups showed no differences either on the negative minus neutral contrast or the positive minus neutral contrast. However, a main effect of picture presentation was found, with stronger activation in motor areas and the parietal cortex evoked by stimuli in the Aggression group compared to the Control group.

These group differences in the parietal cortex point towards increased attention to the stimuli in general, regardless of their valence in the Aggression group, possibly due to the context in which every stimulus had the potential to be negative. Indeed, attentional problems have been reported in aggression and emotion regulation before (Jaworska et al., 2012; Ochsner & Gross, 2005). In individuals reporting dysfunctional anger, differences in levels of oscillatory EEG activity were found that were interpreted as a chronic hypervigilant state (Jaworska et al., 2012), which may lead to an overreaction to non-harmful situations. The increased cue reactivity as found in the current study might also reflect a general heightened arousal level. In line with this possibility, in an earlier study we showed that military veterans with aggression had a heightened startle response (Heesink et al., 2016).

Furthermore, stronger activation in motor areas points was found in the Aggression group. This could be related to impulsivity and reduced inhibition (Bari & Robbins, 2013), which are strongly associated with aggression (Ramirez & Andreu, 2006). The concept of impulsivity refers to the tendency to act quickly, without thinking or planning. Furthermore, individuals with higher trait anger show impaired response inhibition in a Go/NoGo task (Pawliczek et al., 2013), and individuals with higher trait aggression showed a combination of reduced orienting but enhanced preparation for action in a threat-anticipation task (Gladwin, Hashemi, van Ast, & Roelofs, 2016). The motor-related activation in the Aggression group might therefore be related to impulsiveness and preparation to respond quickly, prior to proper stimulus discrimination.

Using the dACC as a seed region, differences in functional connectivity between the two groups were found. During the viewing of negative pictures, the Anger group show stronger connectivity between the left amygdala and both the left and right dACC. This is similar to a previous finding in which participants with an anxiety disorder showed increased dACC-amygdala connectivity during the viewing of negative facial stimuli (Robinson et al., 2014). Because the dACC is involved with responses to stimuli requiring control or adaptation (Bush, Luu, & Posner, 2000), this effect might indicate a tendency to attend to negative stimuli and respond to them via up-regulation of their

emotional processing (Robinson et al., 2014). Furthermore, the diminished connectivity of the dACC with frontal areas as observed in the Aggression group, might point towards reduced attention to positive stimuli or their evaluation (Etkin et al., 2011; Kanske, Heissler, Schönfelder, Bongers, & Wessa, 2011). Taken together, the connectivity results therefore suggest a negative bias in attentional processes that could skew the perception of situations as threatening. We note however that these results were not generally whole-brain significant. Future studies need to confirm the valildy of our findings and interpretations.

The behavioral data in the current study show that the participants in the Aggression group were more likely to rate the positive pictures as neutral or negative, and the neutral pictures more likely as negative. This is in line with the finding that people with anger regulation deficits show a hostile attribution bias. According to the hostile attribution bias, ambiguous situations are more easily interpreted as hostile (Wilkowski & Robinson, 2008). In individuals with aggression problems it is often reported that they tend to interpret cues and situations as hostile (Schönenberg & Jusyte, 2014), from which dysfunctional behavior could follow. This tendency could be related to the findings showing abnormal connectivity discussed above: If individuals are highly sensitive to negative information but fail to pay attention to positive information, this would be expected to negatively bias their interpretations of situations.

The finding that amygdala activation did not differ between the two groups, is not in line with previous studies (Coccaro et al., 2007; McCloskey et al., 2016), possibly due to the use of different stimuli or the military versus non-military populations. In the previous studies, heightened amygdala activation was found in Intermittent Explosive Disorder in response to angry faces. Also in an anger-inducing experiment, stronger activation of the amygdala has been reported (Dougherty et al., 2004). Furthermore, individuals scoring high on trait anger, show a stronger bias for angry faces (Van Honk, Tuiten, de Haan, Van den Hout, & Stam, 2001). These studies evoked negative emotions with different stimuli compared to the current study. In the current study, general, non-facial, emotional stimuli were used, and although the task did reveal amygdala reactivity, this reactivity did not differ between the two groups. Facial expressions are rather homogeneous in comparison to IAPS pictures, and might represent danger more consistently than non-facial stimuli (Hariri et al., 2002). Thus, the current task might induce different emotions compared to previous studies, which do not distinguish the Aggression group from the control group.

A limitation of the current study is that the task we used does not actively require regulation of emotions. It remains unknown whether participants used strategies in order to regulate or suppress evoked emotions and whether this differed between the two groups. In future studies, it might be relevant to study emotion regulation

instead of a passive viewing task. Furthermore, in this study only military veterans were compared; therefore, the effects of military training and deployment cannot be excluded. For example, brain activation of combat veterans with PTSD was only different compared to civilian controls and not compared to combat controls (Van Rooij et al., 2015). The common military training and experience may have diminished symptom-related group differences. The 8 mm smoothing kernel used in the current study might have limited detection of group differences in the PPI analyses using parcellations of the amygdala. However, in studies using similar analyses, differences were detected (Stock et al., 2015; Yoder, Porges, & Decety, 2015), indicating that subdivisions of the amygdala are indeed sufficiently parcellated using this smoothing method. Another limitation is that the stimuli were presented in a pseudo-random order, thus participants could not predict the valence of the stimuli. This may have resulted in effects related to potentially threatening or negative stimuli, instead of reactions actual negative stimuli. In future studies, it would be interesting to compare trials on which participants can versus cannot predict the valence of the upcoming stimulus, providing potentially interesting comparisons involving processes such as vigilance, uncertainity and reactivity.

In conclusion, the findings in the current study indicate a valence-aspecific increase in arousal and impulsivity in veterans with impulsive aggression in response to non-facial emotional stimuli. Furthermore, effects on functional connectivity involving the dACC, amygdala and medial prefrontal cortex point towards attentional abnormalities involving positive and negative stimuli. Impulsive aggression may emerge from a combination of negative biases in attention and interpretation, the consequences of which are exacerbated by impulsivity. These findings may provide targets for interventions, for example neurostimulation or biofeedback methods to decrease impulsivity and hypervigilance.

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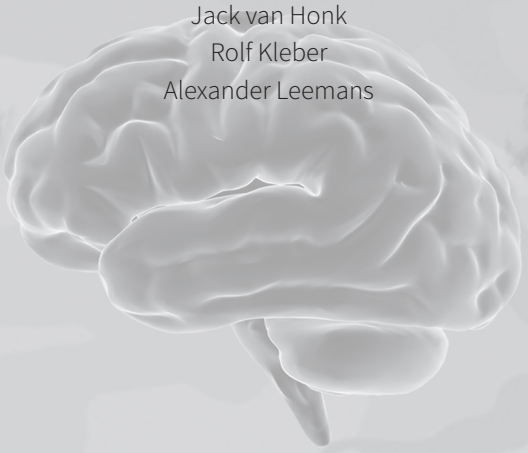
7

White matter structural abnormalities in veterans with aggressive behavior: A diffusion tensor imaging and fiber tractography study

Lieke Heesink
Elbert Geuze
Thomas Gladwin
Szabolcs David
Jack van Honk
Rolf Kleber
Alexander Leemans



Submitted

Abstract

Aggression is a common complaint after a military deployment and is associated with a dysfunction in a network connecting brain regions implicated in threat processing and emotion regulation. The uncinate and arcuate fasciculi form an integral part of the emotion regulation circuit, thus studying potential abnormalities in these white matter connections can further our understanding of anger and aggression problems in military veterans. In this study, we use diffusion tensor imaging tractography to investigate white matter microstructural properties of the uncinate fasciculus and the arcuate fasciculus in veterans with and without anger and aggression problems. More specifically, fractional anisotropy (FA) estimates are derived along the trajectory of both fiber tracts and compared between both groups. While no between-group FA differences are observed for the uncinate fasciculus, there are parts of the arcuate fasciculus that show a significantly lower FA in the group with veterans who have aggression and anger problems. These findings provide further insights into the etiology of anger and aggression in military veterans. Abnormalities in arcuate fasciculus white matter connectivity that are related to self-regulation may play an important role in these problems.

Acknowledgment contribution authors
Designed research: L. Heesink & E. Geuze
Performed research: L. Heesink
Analyzed data: L. Heesink, T. Gladwin, S. David & A. Leemans
Wrote the paper: L. Heesink, E. Geuze, T. Gladwin, S. David, J. van Honk, R. Kleber, & A. Leemans

Introduction

Anger and aggression problems are frequently reported in veterans after military deployment (Heesink, Rademaker, Vermetten, Geuze, & Kleber, 2015; Reijnen, Rademaker, Vermetten, & Geuze, 2015). The problems hardly diminish over time (Heesink et al., 2015) and even often remain after treatment (Shin, Rosen, Greenbaum, & Jain, 2012). These findings underline the importance of research into the etiology of anger and aggression in order to improve treatment strategies.

Functional connectivity studies in populations with anger and aggression have found evidence of reduced inhibitory interactions between frontal brain areas and the amygdala (Best, Williams, & Coccaro, 2002; Coccaro, McCloskey, Fitzgerald, & Phan, 2007). Furthermore, brain systems involved in emotional processing, cognitive control and attention are implicated in anger and aggressive behavior (Blair, 2016). These functional differences might involve structural abnormalities in white matter connectivity. Diffusion tensor imaging (DTI) studies in impulsive aggression are scarce. The available data suggest a role for the uncinate fasciculus (UF) and bundles in the superior longitudinal fasciculus (SLF). The UF connects the frontal lobe and temporal pole structures including the amygdala (Catani, Howard, Pajevic, & Jones, 2002; Schmahmann et al., 2007) and is related to the use of social-emotional information in decision making (Von Der Heide, Skipper, Klobusicky, & Olson, 2013). A recently published systematic review showed that in adults with antisocial disorder, the integrity of the UF is diminished (Waller, Dotterer, Murray, Maxwell, & Hyde, 2017). Furthermore, lower white matter integrity of the UF is linked to aggressive behavior in non-clinical populations of adults (Peper, De Reus, Van den Heuvel, & Schutter, 2015).

The SLF is a white matter tract that connects frontal and posterior regions and has been found to be related to attention (Kamali, Sair, Radmanesh, & Hasan, 2014; Schmahmann et al., 2007). In a population with intermittent explosive disorder (IED), lower white matter integrity, expressed in fractional anisotropy (FA) values, was found in an area linked to the SLF (Lee et al., 2016). In a non-clinical adolescent sample, lower FA values in this tract were linked to aggressive acts (Karlsgodt et al., 2015). One bundle in the SLF, the arcuate fasciculus (AF), is of particular interest to the current study. The AF is related to cognitive functioning and language (Kamali et al., 2014; Schomers, Garagnani, & Pulvermüller, 2017), while deficits in language are a risk factor for anger and aggression problems (Miller, Collins, & Kent, 2008; Teten et al., 2010). Lower FA values in the AF were linked to mood disorders (Spitz, Alway, Gould, & Ponsford, 2017). To our knowledge, DTI studies on aggression focusing on the AF have not yet been performed.

The aim of the current study is to determine whether the FA of the AF and the UF is related to anger and aggression problems. Tracts were reconstructed using tractography, and comparisons of the FA of whole tracts and segments of tracts were compared between veterans with anger and aggression and a control group of veterans who had also been in combat but did not suffer from anger and aggression problems.

Methods

Participants

This study included 29 male veterans with anger and aggression (Aggression group) and 30 control veterans (Control group). Participants in the Aggression group were recruited via their psychologists/psychiatrists at one of the outpatient clinics of the Military Mental Health Care Institute or via advertisements in the waiting room and newsletters for veterans. Control participants were recruited by advertisements or had participated in previous studies. The two groups were matched on number of deployments, education and age. Inclusion criteria for the Aggression group were based on the four research criteria for impulsive aggression described by Coccaro (2012): 1) Verbal or physical aggression towards other people occurring at least twice weekly on average for one month; or three episodes of physical assault over a one year period; 2) the degree of aggressiveness is grossly out of proportion; 3) the aggressive behavior is impulsive (not premeditated); 4) the aggressive behavior causes either distress in the individual or impairment in occupational or interpersonal functioning (Coccaro, 2012). Inclusion criteria for the Control group were 1) no current DSM-IV diagnosis; 2) no history of pathologic aggressive behavior.

All participants signed an informed consent form before participation and after complete written and verbal explanation of the study. This study was approved by the Medical Ethical Committee of the University Medical Center Utrecht and was performed in accordance with the Declaration of Helsinki.

Interview and questionnaires

The Dutch version of the International Neuropsychiatric Interview (MINI) was used in order to screen for the presence of comorbid psychiatric disorders (Van Vliet, Leroy, & Van Megen, 2000). The complete MINI was administered. In this interview the following current or life-time disorders were screened: depressive disorder, dysthymia, suicidal risk, (hypo)manic disorder, panic disorder, anxiety disorder, agoraphobia, social phobia, obsessive compulsive disorder, PTSD, alcohol or drug dependence and/or abuse, psychotic disorders, anorexia nervosa, bulimia nervosa, generalized anxiety disorder,

antisocial personality disorder, somatization disorder, hypochondria, body dysmorphic disorder, pain disorder, attention deficit hyperactivity disorder (ADHD) and adjustment disorder.

To measure anger and aggression, two questionnaires were administered. First, the Dutch version of the State-Trait Anger Expression Inventory-revised (STAXI-2; Hovens, Rodenburg, & Lievaart, 2015, Spielberger, 1999) was used. The STAXI-2 consists of 57 items on a 4-point Likert scale and is divided into two subscales: State Anger and Trait Anger. Furthermore, the Dutch translation of the Buss-Perry Aggression Questionnaire (AQ) (Buss & Perry, 1992; Meesters, Muris, Bosma, Schouten, & Beuving, 1996) was administered. The AQ consists of 29 items on a 5-point Likert scale and is divided into 4 subscales: Physical Aggression, Verbal Aggression, Anger and Hostility.

Data acquisition

All datasets were acquired using a 3.0 T MRI scanner (Philips Medical System, Best, The Netherlands). Two DTI scans were collected; one with posterior-anterior (PA) and one with anterior-posterior (AP) phase-encoding direction each with one non-diffusion weighted image (b = 0 s/ mm^2) and 30 diffusion-weighted images (b = 1000 s/ mm^2), where the distribution of the diffusion- weighted gradient were based on (Jones, Horsfield, & Simmons, 1999). The acquisition settings were: TR = 7057 ms, TE = 68 ms, voxel size = 1.875 x 1.875 x 2 mm^3, 75 slices, slice thickness = 2 mm without gap, FOV = 240 x 240 mm^2, matrix size = 128 x 128. Details of the T1 weighted anatomical scan: TR = 10 ms, TE = 4.6 ms, flip angle = 8°, voxel size = 0.8 x 0.8 x 0.8 mm^3, FOV = 240 x 240 mm^2, matrix size = 304 x 299.

Data processing

The diffusion MRI data sets were processed using *FSL* (v5.0.9) (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012) and *ExploreDTI* (v4.8.6) (Leemans, Jeurissen, Sijbers, Jones, & Jones, 2009). First, susceptibility distortions were estimated with *topup* (Andersson, Skare, & Ashburner, 2003) which was an input for *eddy* (Andersson & Sotiropoulos, 2016) to correct for eddy-current distortions and subject motion using the Jacobian modulation and rotation of the diffusion gradient orientations (Leemans & Jones, 2009). Other settings of the *eddy* step (interpolation, number of voxels for hyperparameter estimation, etc.) were left at default values. Robust extraction of brain tissue was executed with BET (Smith, 2002). Whole brain tractography was performed with the following default parameter settings: seed FA threshold = 0.2, angle threshold = 30°, linear interpolation method (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000).

Reconstruction of the UF (left and right) was performed by placing two "AND" regions of interest (ROIs) on the most posterior coronal slice were the temporal and frontal lobes

were separated. The first ROI included the entire temporal lobe, and the second ROI included all pathways running towards the frontal lobe. Obvious artifacts (lines running towards the occipital lobe or lines over the midline) were removed by "NOT" ROIs. Figure 1 (A, B) shows the positions of the ROIs for the reconstruction of the UF.

Reconstruction of the AF (left and right) were performed by placing two AND ROIs. The first ROI was placed on the most posterior coronal slice showing the fornix on the midline in order to include the pathways laterally to the corona radiata trajectories running towards the frontal lobe. The second ROI was placed on a sagittal slice to include the pathways going towards the temporal lobe. Figure 1 (C, D) shows the positions of the ROIs for the reconstruction of the AF.

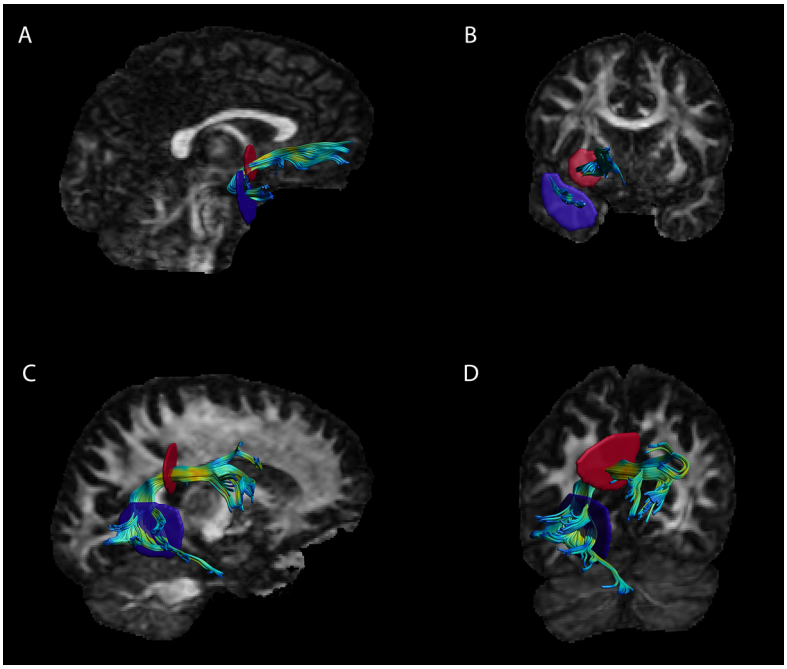


Figure 1.
Used ROIs for tractography of the uncinate (A and B) and the arcuate (C and D) fasciculus.

The mean FA values over the whole tracts were computed. Furthermore, an along-tract analysis was performed in order to investigate the properties of the tracts along the entire path. This was done by resampling the fiber bundles with a number of points based on the mean tract length in mm divided by the voxel size (2 mm). The mean FA values at all segments of the tract were computed. In both the AF and UF, the first and last three positions were excluded from the analyses due to partial volume effects.

Statistical analyses

Mean FA values of the left and right UF and AF were compared between groups using the following two-step approach. First, between-group t-tests were performed for each position along the tract separately. Second, permutation tests were performed in order to test whether the length of sequences of consecutive nominally significant positions was above chance level. The null-hypothesis distribution of this nominally-significant sequence length was determined using permutation tests as in a previous study (Gladwin, Hashemi, van Ast, & Roelofs, 2016). Permutation tests allow a simple and valid method to estimate distributions involving non-independent tests (Eklund, Nichols, & Knutsson, 2016; Nichols & Holmes, 2002), such as those for different positions in the current analyses. Permutation consisted of randomizing group assignment, and was done for 10000 permutations. From the permutations, a null-hypothesis distribution of the longest sequence of consecutive nominally significant segments over the whole tract was computed and used to test observed sequence lengths. Using this approach, false positive ratio is controlled over the whole tract.

Results

Demographics

The groups did not differ in age, education, number of deployments and time since last deployment (all p's > .10). As expected, the Aggression group showed significantly higher scores on all anger and aggression measures compared to the Control group. Table 1 shows statistics of the demographic data and questionnaire data.

Mean FA values per tract

Reconstruction of the left and right UF was possible in all participants. Tracking of the left AF failed in six participants and tracking of the right AF in one participant. Figure 2 shows the tracking results of ten representative subjects. No differences were found between the groups on mean FA values per tract (UF right: $T(57) = 0.120$, $p = .91$; UF left: $T(57) = 0.193$, $p = .85$; AF right: $T(56) = 1.123$, $p = .27$; AF left: $T(51) = 0.934$, $p = .36$).

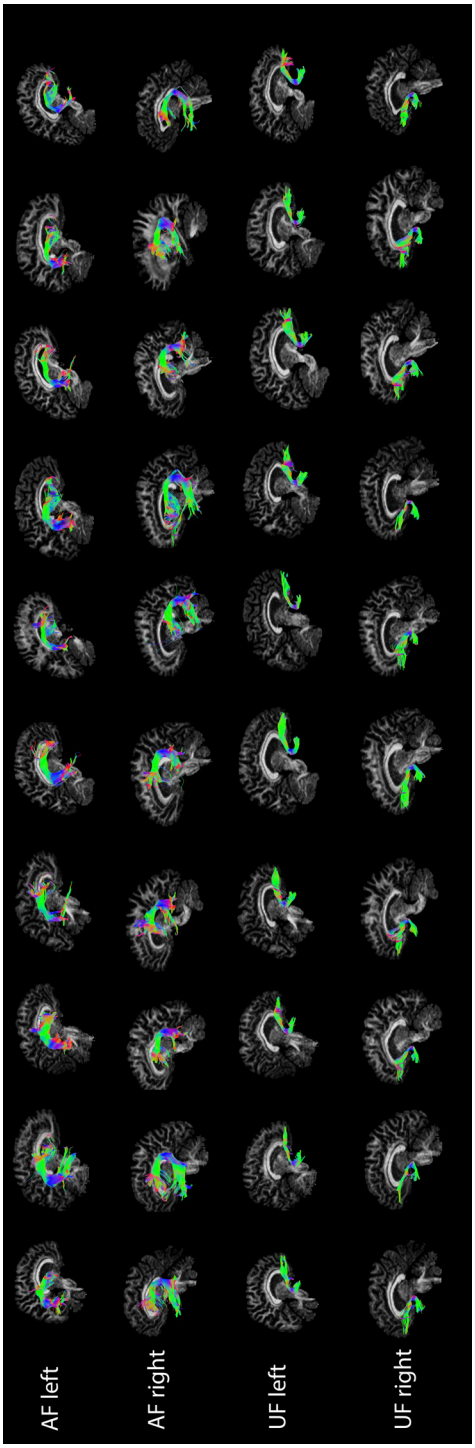


Figure 2.
Reconstructed fibre bundles of both the uncinate and arcuate fasciculus of ten representative subjects.

Table 1.
Demographics of the Anger and the Control group

	Anger group (N=29) Mean (SD)	Control group (N=30) Mean (SD)	Statistics
Age	36.28 (6.31)	34.53 (7.59)	t (1,57) = 0.96, *ns*
Education	4.21 (0.62)	4.2 (0.81	t (1,57) = 0.04, *ns*
Number of deployments	2.07 (1.16)	2.37 (1.25)	t (1,57) = -0.95, *ns*
STAXI-2			
State Anger	24.07 (11.30)	15.20 (0.76)	t (1,57) = 4.29, p < .001
Trait Anger	23.03 (7.01)	12.13 (2.47)	t (1,57) = 8.02, p < .001
Aggression Questionnaire			
Physical aggression	30.07 (7.48)	18.47 (4.55)	t (1,57) = 7.22, p < .001
Verbal aggression	15.66 (3.97)	11.3 (1.54)	t (1,57) = 5.60, p < .001
Anger	24.48 (5.34)	11.17 (2.49)	t (1,57) = 12.35, p < .001
Hostility	24.24 (7.00)	11.87 (3.41)	t (1,57) = 8.68, p < .001

Note: SD = standard deviation; STAXI-2 = State Trait Aggression Inventory-revised.

Along-tract analyses

Uncinate fasciculus. Between group t-tests showed one significant difference along the right UF tract (T(57)= 2.05, p = .045, uncorrected). This was not sufficient to achieve whole-tract significance using the permutation test. The left UF showed no significant differences along the tract (all p's > .20). The FA values along the right and left UF are depicted in Figure 1A and B, respectively.

Arcuate fasciculus. Between group t-tests showed significant differences along both the right and left AF tract. Significant differences on the left AF were found on point 34 (T(51) = 2.196, p = .03), point 35 (T(51) = 2.301, p = .03), point 36 (T(51) = 2.124, p = .04), point 38 (T(51) = 2.107, p = .04), point 39 (T(51) = 2.569, p < .01), point 40 (T(51) = 2.910, p = .005) and point 41 (T(51) = 2.615, p < .01). Permutation tests showed that this number of consecutive significant points was significant (p = .019). The FA values along the right and left AF are depicted in Figure 1C and D, respectively. Significant differences on the right AF were found on point 17 (T (56) = 2.170, p = .03), point 18 (T (56) = 2.536, p = .01), point 19 (T (56) = 2.782, p = .01), point 20 (T (56) = 2.647, p = .01) and point 21 (T (56) = 2.167, p = .03). Permutation tests showed that this number of consecutive significant points did not reach the threshold for significance (p = .091).

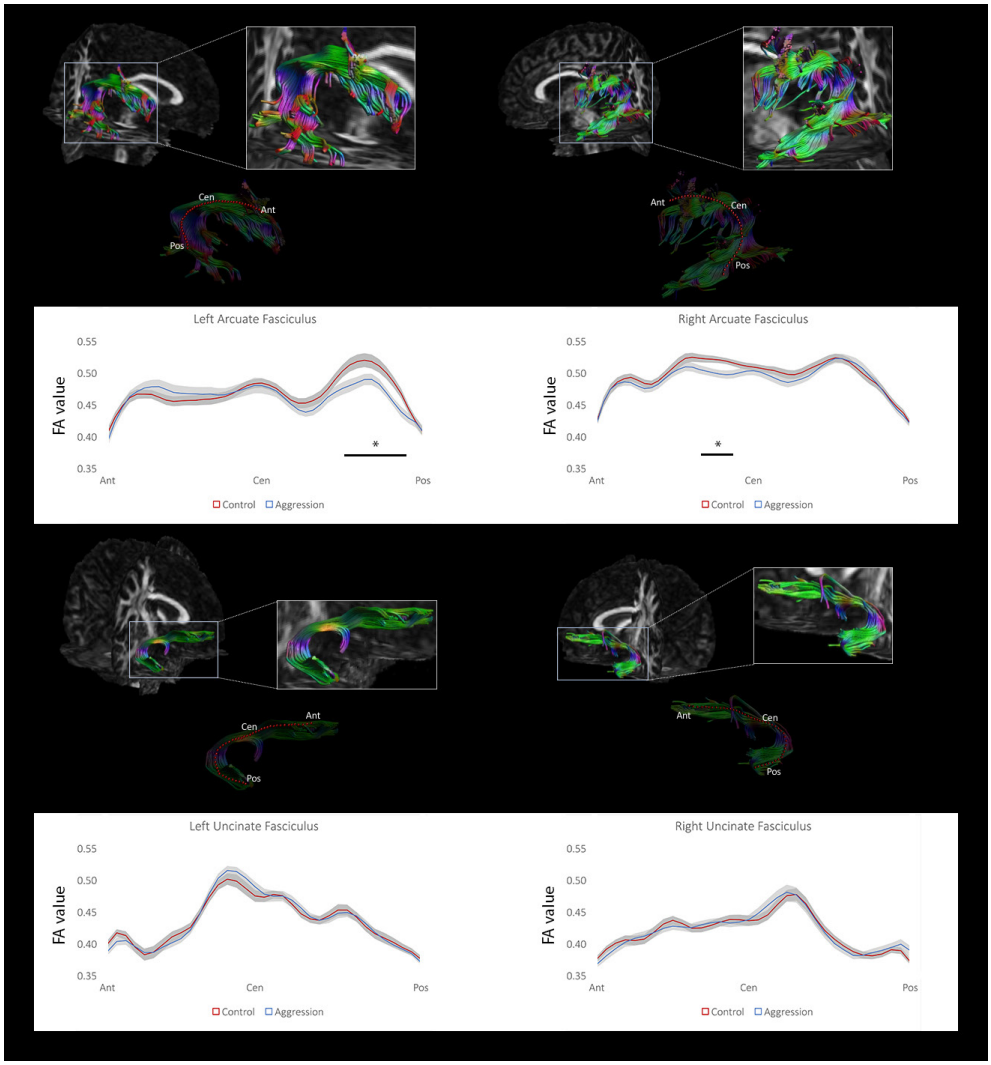


Figure 3.
Schematic overview of the along tract analysis. FA values along the right (A) and left (B) arcuate fasciculus and the right (C) and left (D) uncinate fasciculus.

Discussion

This study was performed to test whether combat veterans with anger and aggression problems differed in white matter structure in the UF and AF from combat veterans without these problems. These two tracts play a role in the regulation of emotion and attention and are therefore of interest in anger and aggression. No differences between

the two groups were found in the UF, whereas evidence for reduced FA in the AF was found in the anger and aggression group.

The AF connects the dorsolateral prefrontal cortex with posterior parietal regions, the fibers running alongside the SLFII (Makris et al., 2005). The frontal cortex receives visuospatial information from the parietal cortex through this tract and this information plays a role in memory, attention and cognitive control (Makris et al., 2005). Using tract-based spatial statistics, reduced white matter integrity in a similar area as the current study was reported in Intermittent Explosive Disorder (IED), a psychological disorder characterized by impulsive aggression (Lee et al., 2016). The lower FA values within the AF in the current study strengthen the impression that white matter integrity within this area plays a role in anger and aggression.

The role of the arcuate is primarily related to cognitive functioning and language (Schomers et al., 2017). One study related diminished lower FA values in the AF to alexithymia, a condition characterized by reduced emotional self-awareness (Kubota et al., 2012). Anger and aggression in veterans have been linked to alexithymia as well (Miller et al., 2008; Teten, Miller, Bailey, Dunn, & Kent, 2008). Furthermore, in autism a link between diminished FA values in the AF and mentalizing systems was reported (Kana, Libero, Hu, Deshpande, & Colburn, 2014). Together, these findings point towards disturbances in insight and interpretation of feelings and emotions in veterans with anger and aggression. Further, weak verbal abilities may reduce an individual's ability to deal with problems in a non-violent manner.

No differences in FA values along the UF were found in the current study. Also in a previous study in healthy individuals no link was found between UF integrity and trait aggressiveness (Beyer, Münte, Wiechert, Heldmann, & Krämer, 2014). Further, in a study with IED patients, no differences in white matter in brain areas corresponding to the UF were found as well (Lee et al., 2016). Reduced UF integrity is however related to antisocial behavior (Waller et al., 2017) and psychopathy (Craig et al., 2009). The relationship between UF integrity and aggressive behavior appears to be dependent on whether the aggression is antisocial or impulsive in nature. The current population of veterans is characterized by impulsive rather than antisocial behavior, possibly explaining the absence of effects on the UF.

The cross-sectional nature of the current study gives no information regarding whether the poorer integrity of the AF in veterans with anger and aggression is a cause or a consequence of the problems with anger and aggression. This needs to be addressed in future studies. Furthermore, research into the etiology of anger and aggression needs to be extended beyond fronto-limbic dysfunction. Brain networks involved in attention and executive functioning, including prefrontal and parietal cortex (Van Hecke et al., 2013; Wager & Smith, 2003), might play an important role as well, as shown by decreased

white matter integrity in parietal regions of the SLF (Karlsgodt et al., 2015). The current study also shows that analysis of values along the tract, instead of one measure per tract, are important, as this kind of analysis appears more sensitive in detecting differences in the integrity of a tract.

Some limitations must be addressed. First, only FA values were studied, and although this is a measure for white matter integrity (lower FA values are found in damaged, atrophied or badly organized white matter), it is an indirect measure. Lower FA values are also found in areas with many crossing fibers. Second, tractography of the arcuate fasciculus was not possible in all participants due to the signal-to-noise ratio in this tract. This led to a loss of six participants in the left AF analyses and one in the right AF analyses.

This study contributes to the understanding of disturbed information processing of veterans with anger and aggressive behavior. Disturbances in networks responsible for attention, understanding and verbal working memory may render individuals more vulnerable to anger and aggression. Such knowledge could ultimately be used to better target interventions of such vulnerabilities.

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8

Summary and general discussion

Summary

Chapter 2 gives an overview of anger and aggression, common phenomena in Posttraumatic Stress Disorder (PTSD). These problems have many negative consequences as reduced physical health and poor family functioning. When PTSD is accompanied by anger and aggression, treatment outcome is worse. Anger and aggression itself are difficult conditions to treat. Given the negative consequences of anger and aggression, it is important to gain knowledge regarding the etiology of the complaints. The original focus on PTSD as an anxiety disorder is extended to emotion regulation, including anger and aggression. That is illustrated by the growing amount of research into the etiology of PTSD and the role of other stress responses to trauma, especially that of anger and aggression in PTSD. Anger and aggression seem to be related to the hyperarousal symptoms in PTSD, involving a lowered threshold for threat. Biologically, the close link between PTSD, anger and aggression can be found in brain regions that are regulating aggression, hyperarousal and anxiety.

Increases in anger and hostility are commonly found after military deployment. However, it is unknown how anger and hostility develop over time, and which veterans are more at risk for developing these complaints. In **chapter 3**, data of 745 veterans one month before deployment to Afghanistan and one, six, twelve and 24 months after deployment were analyzed in a growth model. Growth mixture modeling revealed four classes based on their growth in hostility. Most of the participants belonged to a low-hostile group or a mild-hostile group that remained stable over time. Two smaller groups were identified that displayed increase in hostility ratings after deployment. The first showed an immediate increase after deployment. The second showed a delayed increase between twelve and 24 months after deployment. No groups were identified that displayed a decrease of hostility symptoms over time. Multinomial logistic regression was applied to predict group membership by age, education, early trauma, deployment stressors and personality factors. This study gains more insight into the course of hostility over time, and identifies risk factors for the progression of hostility.

A lowered threshold of perceiving and responding to threat can trigger impulsive aggression. This can be indicated by an exaggerated startle response. In **Chapter 4** 52 veterans with anger and aggression problems (Anger group) and 50 control veterans were tested using a startle experiment with 10 startle probes and 10 prepulse trials, presented in a random order and with a random interval between the trials. Predictors (demographics, Trait Anger, State Anger, Harm Avoidance and Anxious Arousal) for the startle response within the Anger group were tested. Increased EMG responses were found to the startle probes in the Anger Group compared to the Control group, but not to the prepulse trials. Furthermore, Harm Avoidance and State Anger predicted

the increased startle reflex within the Anger group, whereas Trait Anger was negatively related to the startle reflex. These findings indicate that threat reactivity is increased in anger and aggression problems. These problems are not only caused by an anxious predisposition; the degree of anger also predicts the startle reflex.

Problems involving anger and aggression may involve abnormal responses to threat. **Chapter 5** describes the effects on neural activation related to threat and escapability among veterans with deployment experience. Twenty-seven male veterans with anger and aggression problems (Anger group) and 30 Control veterans performed a virtual predator-task during fMRI measurement. In this task threat and proximity were manipulated. The distance of cues determined their escapability. Cues could attack by zooming in towards the participant. If Threat cues, but not Safe cues, reached the participants without being halted by a button press, an aversive noise (105 dB scream) was presented. In both the Threat and the Safe condition, closer proximity of the virtual predator resulted in stronger activation in the cuneus and the cingulate cortex in the Anger versus Control group. The results suggest that anger and aggression problems are related to a generalized sensitivity to proximity rather than preparatory processes related to task-contingent aversive stimuli. Anger and aggression problems in natural, dynamically changing environments may be related to an overall heightened vigilance, which is non-adaptively driven by proximity.

Chapter 6 describes that anger and aggression are common mental health problems after military deployment. Anger and aggression are related to differences in social emotional processing. During the viewing of angry faces, heightened amygdala activity has been found in patients with impulsive aggression. However, in patients with anger and aggression problems, it is unknown whether general non-facial negative emotional pictures will also elicit a stronger amygdala response. 28 military veterans with anger and aggression problems and 28 veterans without a psychiatric diagnosis (all males) participated in this study. During an fMRI scan 32 negative, 32 positive and 32 neutral pictures from the IAPS were presented for two seconds. After that, participants rated the pictures by pressing a button. During stimulus presentation, averaged over categories, the Aggression group show heightened activity in brain areas such as the supplemental motor area, the cingulum and the parietal cortex. No significant differences were found between the Aggression and the Control group on amygdala activity. Amygdala reactivity to general emotional stimuli in veterans with impulsive aggression does not appear to be abnormal. The heightened overall neural response to stimuli in general might reflect increased impulsivity in veterans with impulsive aggression, resulting in a tendency towards motor preparation and attention.

Chapter 7 diffusion tensor imaging (DTI) tractography of two white matter tracts was performed. Integrity of the Uncinate Fasciculus (UF) and the Arcuate Fasciculus

(AF) were studied. Differences in white matter integrity were found along the AF. The arcuate fasciculus connects frontal areas of the brain with parietal areas and has been linked to processes related to understanding, attentional and emotional control. The current results thus provide further insight into anger and aggression in military veterans. Abnormalities in white matter connectivity related to self-regulation may play an important role in these problems.

General discussion

Anger and aggression are common in military populations, with a high impact on the individual and their surroundings. Violent offending is frequently reported in US military personnel after deployment to Iraq and Afghanistan (Elbogen et al., 2012, 2014). An image of short-tempered veterans is picked up easily by the media, leading to public debate. Research into prevalence of psychological symptoms shows that about 6.6% of the Dutch military personnel deployed to Afghanistan develop problems with anger (Reijnen, Rademaker, Vermetten, & Geuze, 2015). Therefore, the Dutch Ministry of Defense decided to gather information concerning these difficulties, in order to find markers for the prevention and treatment of anger and aggression. To this aim, this dissertation is focused on the prevalence and trajectories of the development of anger problems after military deployment and on the neurobiological background of anger and aggression in military personnel.

Characteristics and prevalence of anger and aggression in military personnel

Chapter 2 discussed the problems of anger, aggression and hostility in relation to post-traumatic stress disorder (PTSD). Prevalence of PTSD after deployment is about 3 percent (Engelhard et al., 2007), PTSD symptoms are reported in 6-9% of deployed veterans (Reijnen et al., 2015) and these can develop even after a long period of time after combat (Eekhout et al., 2016). Chapter 2 showed that anger and aggression are common in PTSD and that the presence of anger and aggression is important in treatment outcome. Further, this chapter showed that anger and aggression receive less attention compared to anxiety within psychotraumatology research. Anger refers to the emotion, while aggression refers to behavior with the intention to bring harm and hostility is defined as a negative attitude or evaluation of others (Anderson & Bushman, 2002; Ramirez & Andreu, 2006). These definitions show overlap.

Problems with aggressive behavior are common in many mental disorders: They have been reported in depression (Painuly, Sharan, & Mattoo, 2005), anxiety disorders (Makin-Byrd, Bonn-Miller, Drescher, & Timko, 2012) and schizophrenia (Bulgari et al., 2016). In DSM-5 (American Psychiatric Association, 2013) problems with aggressive behavior are also described as a distinct disorder: Intermittent Explosive Disorder. However, since aggressive behavior is prevalent across many disorders, it is highly suitable to study difficulties with aggression under the RDoC system. RDoC (Research Domain Criteria) is a recently developed framework for research into the mechanisms underlying mental disorders and is based on dimensions of neurobiology and observable behavior. These dimensions cut across the current heterogeneous disorder categories (Cuthbert, 2014; Insel et al., 2010). Within the RDoC framework, anger and aggressive

behavior fit into several domains: negative valence systems (increased responses to threat and potential harm), cognitive systems (attention, cognitive control) and arousal (sensitivity to stimuli). Because the RDoC system is an important framework for research into the neurobiological mechanisms underlying mental disorders, this framework is also relevant for the neurobiology of anger and aggression as investigated in the studies in this dissertation.

In chapter 3 the trajectories of anger and hostility before and after deployment were revealed. Four trajectories were found: a low-hostile (remaining low over time), a mild-hostile (remaining mildly hostile over time), an early hostile group (increases in hostility immediately after deployment) and a late-hostile group (hostility rises 2 years after deployment). It is remarkable that no trajectories with decreases in hostility were found. Similar analyses after deployment described decreases in PTSD symptoms over time (Berntsen et al., 2012; Bonanno et al., 2012; Eekhout et al., 2016; Orcutt, Erickson, & Wolfe, 2004). This raises several important questions on why aggression appears to be so persistent. The first is whether symptoms such as anger, hostility and aggression are sufficiently recognized as psychiatric problems in military personnel. If the focus of research and clinical practice after deployment is overly focused on PTSD symptoms, the risk of the development of psychological complaints as anger and aggression (although to some extent part of the hyperarousal criterion of PTSD), might receive less attention. Furthermore, dealing with aggression is a significant part of the military profession, and difficulties in handling this behavior and the resulting emotions might therefore not be acknowledged as a problem needing intervention, leading to persistence of these problems. Another question has to do with intervention: even when these difficulties are recognized, is treatment of these symptoms effective enough? These questions need to be addressed in future research. Also, they show that awareness of the risk of the development of problems regarding anger and aggression is important, not only to start interventions when necessary, but also to create awareness of acknowledgement of these problems.

Further, this study shows that increases in anger and hostility do not only take place immediately after deployment, but also between one and two years after home-coming. Important in this context is that delayed PTSD has been found to be more common among combat veterans compared to people exposed to other traumatic events (Smid, Mooren, Van der Mast, Gersons, & Kleber, 2009). There are several explanations for this late increase. A possible cause is the loss of structure after leaving military service, leading to a slow but steady increase in complaints. Another explanation might be that the time of deployment leads to a suppression or decrease in complaints and that veterans eventually return to their normal level of anger in the period after deployment. Since symptoms of anger and aggression can seriously hamper the ability to continue

daily life after deployment (Elbogen et al., 2012), this study underlines the importance of monitoring anger and aggression in deployed military personnel.

Neurobiological findings

Chapter 4 describes the startle response in veterans with anger and aggression. The startle response is measured by the eye blink reflex in response to a sudden, intense stimulus, in this case a loud noise. An exaggerated startle reflex can indicate the lowered threshold of perceiving threat, due to the sudden and intense nature of the stimulus that leads to a defensive response. Our study shows an exaggerated startle response in the veterans with anger and aggression. These findings indicate that threat reactivity is increased in anger and aggression problems. These problems are not only caused by an anxious predisposition: the degree of anger also predicts the startle reflex. This points towards heightened vigilance in veterans with anger and aggression problems. This finding supports the hypothesis that impulsive aggression is accompanied by a lowered threshold of perceiving stimuli as threatening (Novaco & Chemtob, 2002) and heightened physiological arousal (Mackintosh et al., 2014). In treatment of anger and aggression difficulties this might clearly be of importance: for example, in reducing this arousal in order to decrease the likelihood of aggressive acts. Training relaxation skills may provide a way to reduce exaggerated arousal (Cuthbert, Kristeller, Simons, Hodes, & Lang, 1981; Parnandi & Gutierrez-Osuna, 2015).

The functional MRI studies show aggression-related differences in attentional systems. In chapter 5 an fMRI study is described in which a virtual predator could attack by increasing in size. Veterans with anger and aggression problems showed enhanced activity within the cuneus and cingulate cortex. The results suggest that anger and aggression problems are related to a generalized sensitivity to proximity rather than preparatory processes related to task-contingent aversive stimuli. No distinction was made between the 'safe' and 'threat' condition in this task; also stimuli close by in the 'safe' condition leaded to enhanced activity. Anger and aggression problems may be related to an overall heightened vigilance. Heightened arousal and vigilance for the environment could lead to increased attention to predictors of potential threat, such as proximity.

In the fMRI study described in chapter 6 it was shown that a patient group with high aggression symptoms showed heightened activity in brain areas such as the supplemental motor area, the cingulum and the parietal cortex during the viewing of potentially emotional stimuli. This heightened neural response to stimuli in general might reflect increased impulsivity in veterans with impulsive aggression, resulting in a tendency towards motor preparation and enhanced attentional focus on potential threats. These results are in line with the effect of deployment on the brain: the neural

coupling between the amygdala and the insula/dorsal anterior cingulate cortex in deployed veterans is mainly influenced by perceived threat rather than by actual threat exposure (Van Wingen, Geuze, Vermetten, & Fernández, 2011).

Chapter 7 concerns a Diffusion Tensor Imaging (DTI) study. White matter integrity was found to be diminished in veterans with anger and aggression problems in the arcuate fasciculus (AF), a white matter tract that connects frontal areas of the brain with parietal areas. The AF has been linked to processes related to understanding, attentional and emotional control. Abnormalities in white matter connectivity related to self-regulation may play an important role in anger and aggression. Furthermore, frontoparietal cortical attention networks are found to be modulated by emotional arousal (Moratti, Keil, & Stolarova, 2004).

The above studies all point towards heightened vigilance and increased attention in aggressive behavior. Processes within the brain related to attention are different between veterans with anger and aggression and control veterans without anger and aggression. Attentional vigilance to emotional stimuli that are possibly threatening is enhanced in anger and aggression. These findings fit well in with the RDoC system. Arousal plays a role in the sensitivity to stimuli. For example, heightened arousal might lead to threat-related vigilance. The domain of arousal within RDoC is an important construct in aggressive behavior, as it regulates the processes within the negative valence system.

Clinical relevance and future directions

Psychological treatment protocols are often matched to disorders described in the DSM-5 (American Psychiatric Association, 2013), but in clinical practice therapists also base their treatment method on the concrete symptoms of the patient. These symptoms often cut across disorders. According to the network theory of mental disorders (Borsboom, 2017; Schmittmann et al., 2013), mental disorders are considered to be stable, dysfunctional patterns in interactions between symptoms (Borsboom, 2017). This is similar to NIMH's RDoC system, in which domains are described that underlie mental disorders, involving dysfunctional networks of psychological and neural processes. In future research, it would be interesting to study aggression in depth, in the light of such theoretical frameworks. The studies described in this dissertation are a first step towards this approach. Behavioral assessment methods within the RDoC system have been developed, leading to an empirical basis to measure the constructs within the RDoC system. These methods could help to study disturbances in terms of the different RDoC domains in anger and aggression. This leads to better generalizability of research findings, symptoms of patients also often cut across disorders.

The current studies do give us insight into the underlying mechanisms of anger and aggression, and gives some pointers towards treatment possibilities. However, the nature

of the studies is rather fundamental. Effectiveness of treatment of aggression an anger difficulties, for example, has not been addressed. Furthermore, we included deployed veterans both in the Anger group and the Control group. This leads to the limitation that separate effects of deployment or military training cannot be distinguished. Moreover, problems with anger and aggression are reported in military forces of other countries than the Netherlands as well while other uniformed services, such as the police, are also at risk for the development of these difficulties. However, differences between the Dutch army and for example the US army are great, and also other professions are hard to compare with the current sample, thus the results cannot be generalized without taking these differences into consideration.

Problems with anger and aggression are mainly treated by using cognitive behavioral therapy (Chemtob, Novaco, Hamada, & Gross, 1997; Smeets et al., 2015). Processes in attention have been found to be disturbed in anger and aggression. Brain activation points towards heightened vigilance to potential threat or emotional stimuli. This could be a valuable insight in treatment. For example, it might be helpful for patients with anger and aggression problems to become aware of such tendencies. Attention might also be a target of treatment methods for anger and aggression in psychiatry. For example, cognitive behavioral therapy or cognitive training should target these attentional biases. Non-invasive brain stimulation methods such as transcranial direct current stimulation (tDCS) can reduce aggressive behavior (Dambacher et al., 2015). Treatment studies are necessary to discover whether lowering the heightened vigilance can be trained.

It is important to discover whether the attentional problems are a risk factor or a consequence of developing problems with anger and aggression (cause or consequence). This is relevant, because an answer to this issue gives insight into which individuals are at risk for the development of these difficulties. In this context, it would also be of interest whether these alterations as attentional problems disappear or remain after successful treatment.

Societal relevance

The presence of anger and hostility predicts a higher prevalence of mental disorders. It also deteriorates the possibilities for recovery from these disorders and as such has a negative influence on the prognosis of psychotherapy (McHugh, Forbes, Bates, Hopwood, & Creamer, 2012; Painuly et al., 2005). Due to a high drop-out rate, aggressive behavior is difficult to treat (Chemtob, Novaco, Hamada, Gross, & Smith, 1997). Increasing the number of treatment sessions does not necessarily lead to decreases in aggression (Shin, Rosen, Greenbaum, & Jain, 2012), indicating that these problems are rather persistent.

When we started this research project, we thought that including participants would become difficult due to potential stigma. However, a lot of patients that participated

felt that research into their complaints was a clear form of acknowledgement that their problems were taken seriously. Together with the finding that increases in symptoms take place after a long period of time after deployment and that these symptoms are persistent, this leads to the recommendation to pay attention to anger and aggression in deployed military personnel. Furthermore, it would be helpful to gain insight into the effectiveness of the treatment currently offered by military mental health care and also to discover the effectiveness of other treatment methods as transcranial direct current stimulation (tDCS).

Epilogue

The title of this dissertation, *Attending to anger*, has a twofold interpretation. First, problems with anger and aggression need attention, because these problems arise frequently after deployment. Second, studies into the neurobiology of aggression, as described in this dissertation, point towards stronger attention to potential threat and heightened vigilance. Disproportionate anger and aggression are important problems in the population of military personnel and veterans. It is essential to recognize the impact of these problems and better understand their nature. The research presented in this work provides a theoretical basis for further study and directions for treatment.

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Introductie

Het beroep van militair wordt geassocieerd met een sterke fysieke en mentale belasting. Gedurende een uitzending is er een verhoogde blootstelling aan stress en traumatische gebeurtenissen, zoals vijandelijk vuur of het getuige zijn van het gewond raken of sterven van collega's of andere mensen. Na uitzending kan de adaptatie aan het dagelijks leven soms moeizaam verlopen. Schattingen van de prevalentie van psychische klachten in uitgezonden militairen lopen uiteen van 8.9% tot 19.7% (Fear et al., 2010; Reijnen, Rademaker, Vermetten, & Geuze, 2015). Van de Nederlandse militairen die naar Afghanistan uitgezonden zijn geweest, ontwikkelde 6.6% problemen met hostiliteit en boosheid (Reijnen et al., 2015). Zij rapporteerden dat zij gemakkelijk geïrriteerd raakten of frequent woede-uitbarstingen hadden.

Onderzoek naar het ontstaan van boosheid en agressie is daarom van groot belang voor de militaire organisatie. Het biedt de mogelijkheid om inzicht te krijgen in de oorzaken en de ontwikkeling van problemen zoals gerapporteerd door ingezet militair personeel. In geval van een specifieke aandoening, zoals beschreven in DSM-5 (American Psychiatric Association, 2013), zijn behandelingsmethoden duidelijk. Bij meer diffuse klachten is een geschikte methode om het individu te helpen en te ondersteunen, moeilijker te vinden. Inzicht in overeenkomsten en verschillen met andere aandoeningen kan daarom zeer nuttig zijn bij het kiezen van de behandeling.

Vaak wordt een verlaagde drempel voor bedreiging of provocatie beschreven in boosheid en agressie (Berkowitz, 1993; Blair, 2012). Hersengebieden die betrokken zijn bij de verwerking van dreiging spelen een rol in de oorsprong van agressief gedrag (Blair, 2012). Dit systeem is uitgebreid onderzocht in dieren. Uit deze studies blijkt dat dit systeem van de amygdala naar beneden loopt, via de stria terminalis naar de mediale hypothalamus en naar het periaqueductale grijs (Blanchard, Hynd, Minke, Minemoto, & Blanchard, 2001; Blanchard, Blanchard, & Griebel, 2005). Van ditzelfde systeem wordt gedacht dat het bij mensen een rol speelt in defensief gedrag en reactieve agressie (Blanchard, Hynd, Minke, Minemoto, & Blanchard, 2001). Bij mensen is gebleken dat activatie in het periaqueductale grijs toeneemt wanneer de bedreiging van ver weg zich verplaatst naar dichtbij en confrontatie onvermijdelijk wordt (Mobbs et al., 2007).

Het grootste deel van het werk dat in dit proefschrift wordt beschreven, betreft de resultaten van de Military Agressie Regulatie Studie (MARS). In 2012 besloot het ministerie van Defensie de neurobiologische en neuropsychologische achtergrond van woede en agressie in militair personeel te bestuderen. In dit project werden 52 militaire veteranen militairen met woede- en agressieproblemen en 50 controlemilitairen zonder klachten onderzocht. Ze werden geïnterviewd en vulden vragenlijsten in om inzicht

te krijgen in hun problemen met woede en agressie. Verder werden bloedmonsters genomen. Deelnemers ondergingen neuropsychologische taken en namen deel aan een startle-experiment. De helft van de deelnemers werd uitgenodigd voor een tweede afspraak. Tijdens deze afspraak kregen deelnemers een MRI-scan. De MRI-scan bestond uit functionele en structurele scans. Het huidige proefschrift beschrijft deze studies naar de neurobiologische achtergrond van boosheid en agressie bij Nederlands militair personeel.

Resultaten

Hoofdstuk 2 geeft een overzicht van boosheid en agressie, veel voorkomende verschijnselen bij Posttraumatische Stress Stoornis (PTSS). Deze problemen hebben veel negatieve gevolgen als vermindering van de lichamelijke gezondheid en het slechte functioneren binnen de familie. Wanneer PTSS samengaat met boosheid en agressie, is de uitkomst van de behandeling slechter. Boosheid en agressie zelf zijn moeilijke symptomen om te behandelen. Gezien de negatieve gevolgen van woede en agressie is het belangrijk kennis te verwerven over de etiologie van de klachten. De oorspronkelijke focus in wetenschappelijk onderzoek op PTSS als een angststoornis wordt uitgebreid tot problemen met emotieregulatie, waaronder boosheid en agressie. Dat wordt geïllustreerd door de groeiende hoeveelheid onderzoek naar de etiologie van PTSS en de rol van boosheid en agressie bij deze stoornis. Boosheid en agressie lijken te zijn gerelateerd aan de hyperarousal symptomen bij PTSS, waarbij een verlaagde drempelwaarde voor bedreiging een rol speelt. Biologisch kan de nauwe band tussen PTSS, boosheid en agressie worden gevonden in hersenregio's die agressie, hyperarousal en angst regelen.

Een toename in boosheid en vijandigheid wordt vaak gevonden na militaire uitzending. Het is echter onbekend hoe boosheid en vijandigheid zich ontwikkelen over de tijd en welke veteranen meer risico lopen om deze klachten te ontwikkelen. In hoofdstuk 3 werden gegevens van 745 veteranen een maand voor de uitzending naar Afghanistan en één, zes, twaalf en 24 maanden na de uitzending geanalyseerd in een groeimodel. Dit model onderscheidde vier groepen op basis van hun groei in vijandigheid. De meeste deelnemers behoorden tot een laag-hostiele groep of een mild-hostiele groep die over tijd stabiel bleef. Er werden twee kleinere groepen geïdentificeerd die een stijging van de hostiliteit laten zien na de uitzending. De eerste vertoonde een onmiddellijke toename na uitzending. De tweede liet een vertraagde toename zien tussen twaalf en 24 maanden na uitzending. Opmerkelijk genoeg werden geen groepen geïdentificeerd die een vermindering van de hostiliteitsklachten vertoonden. Multinomiale logistische regressie werd toegepast om groepslidmaatschap te voorspellen volgens leeftijd, opleiding, vroegtijdig trauma, uitzendingsstressoren en persoonlijkheidsfactoren. Deze studie geeft meer inzicht in het verloop van de hostiliteit over tijd en identificeert risicofactoren voor het ontwikkelen van vijandigheid.

Boosheid en agressie zijn veel voorkomende problemen onder uitgezonden militair personeel. Een verlaagde drempel om dreiging waar te nemen en te reageren kan impulsieve agressie veroorzaken. Dit kan worden aangetoond door een verhoogde schrikreactie. In hoofdstuk 4 wordt een studie beschreven waarin 52 veteranen met boosheids- en agressieproblemen en 50 controle veteranen een startle (schrikreactie) experiment ondergingen met 10 startle geluiden en 10 startle geluiden voorafgegaan door een prepulse (minder intens geluid), in willekeurige volgorde en met een willekeurig interval tussen de geluiden. Voorspellers (demografie, dispositieboosheid, toestandsboosheid, mate van leedvermijding en angstsymptomen) voor de schrikreactie binnen de groep met boosheids- en agressieklachten werden getest. Verhoogde EMG-responsen werden gevonden bij de startlegeluiden in de boosheidsgroep in vergelijking met de controlegroep, maar niet voor de geluiden met een prepulse. Bovendien voorspelde de mate van leedvermijding en toestandsboosheid de verhoogde startle-reflex in de Anger-groep, terwijl dispositieboosheid negatief verbonden was met de schrikreactie. Deze bevindingen wijzen erop dat de reactiviteit op bedreiging verhoogd is in woede- en agressieproblemen. Deze problemen worden niet alleen veroorzaakt door een angstige predispositie; de mate van boosheid voorspelt ook de schrikreactie.

Hoofdstuk 5 beschrijft de hersenactivatie in reactie op bedreiging en ontsnapping onder uitgezonden veteranen. Zevenentwintig mannelijke veteranen met boosheids- en agressieproblemen (boosheidsgroep) en 30 controle veteranen voerden tijdens een fMRI-scan een taak uit, waarbij een plaatje kon 'aanvallen' door in te zoomen naar de deelnemer toe. In deze taak werden bedreiging en nabijheid gemanipuleerd. De afstand van het plaatje bepaalt de mate van mogelijkheid tot ontsnapping. Als een plaatje in de dreigingsconditie de deelnemer bereikt zonder dat deze gestopt werd door op een knop te drukken, werd een aversief geluid (een schreeuw van 105 dB) afgespeeld. In de veilige conditie werd het aversieve geluid nooit afgespeeld. In zowel de dreigings- als de veilige conditie leidde de nabijheid van de virtuele predator tot sterkere activatie in de cuneus en de cingulate cortex in de boosheidsgroep ten opzichte van de controlegroep. Dit suggereert dat boosheids- en agressieproblemen gerelateerd zijn aan een algemene gevoeligheid voor nabijheid. Boosheids- en agressieproblemen in natuurlijke, dynamisch veranderende omgevingen kunnen verband houden met een algehele verhoogde waakzaamheid, die niet-adaptief door nabijheid wordt aangedreven.

Boosheid en agressie zijn gerelateerd aan verschillen in sociaal-emotionele verwerking. Tijdens het bekijken van boze gezichten is een verhoogde amygdala-activiteit gevonden bij patiënten met impulsieve agressie. Het is echter onbekend of algemene negatieve emotionele afbeeldingen ook een sterkere amygdala-respons oproepen bij patiënten met woede- en agressieproblemen. In hoofdstuk 6 wordt een studie beschreven waarin 28 militairen met woede- en agressieproblemen en 28 veteranen zonder psychiatrische

diagnose (allen mannen) hebben deelgenomen. Tijdens een fMRI scan werden 32 negatieve, 32 positieve en 32 neutrale foto's voor twee seconden gepresenteerd. Daarna beoordeelden de deelnemers de foto's door op een knop te drukken. Tijdens de presentatie van de foto's, gemeten over alle categorieën, tonen de deelnemers in de agressiegroep een verhoogde activiteit in verschillende hersengebieden, zoals de supplemental motor area, het cingulum en de pariëtale cortex. Er werden geen significante verschillen gevonden tussen de agressie- en de controlegroep op amygdala-activatie. Amygdala-reactiviteit op algemene emotionele stimuli bij veteranen met impulsieve agressie lijkt niet abnormaal te zijn. De verhoogde neurale respons op stimuli in het algemeen zou kunnen leiden tot een verhoogde impulsiviteit bij veteranen met boosheids- en agressieklachten, die resulteert in een neiging tot motorische voorbereiding en aandacht.

In Hoofdstuk 7 werd diffusion tensor imaging (DTI) tractografie van twee witte-stof banen uitgevoerd. Integriteit van de Uncinate Fasciculus (UF) en de Arcuate Fasciculus (AF) werden onderzocht. Verschillen in de integriteit van de witte stof werden gevonden in de AF. De AF verbindt de frontale gebieden van de hersenen met pariëtale gebieden en is gekoppeld aan processen die verband houden met begrip, aandacht en emotionele controle. De huidige resultaten geven meer inzicht in woede en agressie bij militaire veteranen. Afwijkingen in witte stof die verband houden met zelfregulering kunnen in deze problemen een belangrijke rol spelen.

Discussie

Problemen met agressief gedrag komen veel voor bij psychische aandoeningen: ze treden op bij depressie (Painuly, Sharan, & Mattoo, 2005), angststoornissen (Makin-Byrd, Bonn-Miller, Drescher, & Timko, 2012) en schizofrenie (Bulgari et al., 2016). Daarom zijn deze klachten zeer geschikt om binnen het RDoC-framework (Research Domain Criteria) te onderzoeken. RDoC is een recent ontwikkeld kader voor onderzoek naar de mechanismen die onderliggend zijn aan psychische aandoeningen en is gebaseerd op dimensies van neurobiologie en waarneembaar gedrag. Deze dimensies doorkruisen de huidige heterogene stoorniscategorieën (Cuthbert, 2014; Insel et al., 2010). In het RDoC-kader passen boosheid en agressief gedrag in verschillende domeinen: het *negative valencesystem* (verhoogde reacties op bedreiging en potentieel leed), het *cognitive system* (aandacht, cognitieve controle) en *arousal* (gevoeligheid voor stimuli).

De studies beschreven in dit proefschrift wijzen op verhoogde waakzaamheid en verhoogde aandacht in boosheid en agressie. Processen in de hersenen gerelateerd aan aandacht zijn verschillend tussen veteranen met boosheid en agressie en controleveteranen zonder boosheid en agressie. Waakzaamheid en aandacht voor emotionele stimuli die mogelijk bedreigend zijn, zijn verhoogd in woede en agressie. Deze bevindingen zijn goed te verklaren vanuit het RDoC-systeem. Arousal speelt een rol in de gevoeligheid voor

stimuli. Verhoogde opwinding kan bijvoorbeeld leiden tot aan bedreiging gerelateerde waakzaamheid. Het domein van arousal binnen RDoC is een belangrijk construct in agressief gedrag, omdat het de processen in het *negative valence system* regelt.

Problemen met woede en agressie worden vooral behandeld door gebruik te maken van cognitieve gedragstherapie (Chemtob, Novaco, Hamada, & Gross, 1997; Smeets et al., 2015). De huidige studies geven ons inzicht in de onderliggende mechanismen van boosheid en agressie, en verschaffen een aantal aanwijzingen voor behandelingsmogelijkheden. Aandachtsprocessen blijken een rol te spelen in boosheid en agressie. Hersenactivatie wijst op verhoogde waakzaamheid naar potentiële dreiging of emotionele stimuli. Dit kan een waardevol inzicht voor de behandeling zijn. Het kan bijvoorbeeld nuttig zijn voor patiënten met boosheids- en agressieproblemen om bewust te zijn van dergelijke tendensen. Aandacht kan ook een doel zijn van behandelingsmethoden voor boosheid en agressie in de klinische psychologie en psychiatrie. Bijvoorbeeld, cognitieve gedragstherapie of cognitieve training zou zich kunnen richten op deze verhoogde aandacht. Niet-invasieve hersenstimulatiemethoden zoals *transcranial direct current stimulation* (tDCS) kan agressief gedrag verminderen (Dambacher et al., 2015). Behandelingsstudies zijn nodig om te onderzoeken of het verlagen van de verhoogde waakzaamheid en aandacht kan worden getraind.

Het is belangrijk om te onderzoeken of de gevonden aandachtsproblemen een risicofactor zijn of het gevolg van problemen met boosheid en agressie. Dit is relevant, omdat een antwoord op dit probleem inzicht geeft in wie risico loopt op het ontwikkelen van deze klachten. In dit verband zou het ook van belang zijn om te onderzoeken of deze veranderingen als aandachtsproblemen verdwijnen of aanwezig blijven na een succesvolle behandeling.

Het huidige proefschrift richt zich op Nederlandse uitgezonden militairen. Echter, problemen met boosheid en agressie worden ook gerapporteerd in krijgsmachten van andere landen. Daarnaast lopen andere geüniformeerde beroepen, zoals de politie, ook risico voor het ontwikkelen van deze klachten. Ondanks de verschillen tussen het Nederlandse leger en bijvoorbeeld het Amerikaanse leger en andere beroepen, zijn de huidige studies relevant voor vele andere groepen.

Epiloog

De titel van dit proefschrift, *'Aandacht voor agressie'*, heeft een dubbele interpretatie. Ten eerste, aandacht voor problemen met boosheid en agressie is belangrijk, omdat deze problemen vaak ontstaan na een militaire uitzending. Ten tweede, studies naar de neurobiologie van agressie, zoals in dit proefschrift beschreven, wijzen op verhoogde aandacht voor potentiële dreiging en verhoogde waakzaamheid. Bovenmatige boosheid en agressie zijn belangrijke problemen onder militair personeel en veteranen. Het

is essentieel om de weerslag van deze problemen te herkennen en hun aard beter te begrijpen. De studies in dit proefschrift bieden een psychobiologische basis voor verder onderzoek en aanwijzingen voor de behandeling.

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About the author

Lieke Heesink was born on September 15th 1987 in Tubbergen, the Netherlands. She graduated high school in 2005 at the St. Canisius in Almelo. Thereafter, she moved to Amsterdam to start het Bachelor in Psychology, at the VU University in Amsterdam. She graduated in 2008. Subsequently, she started the Master Clinical Neuropsychology at the VU University. After obtaining her degree, she enrolled in the Research Master Cognitive Neuropsychology at the VU University. In 2012, she started her PhD program, for which she set up a study to investigate the neurobiological background of anger and aggression in deployed military personnel. The study was conducted at the Research Center of the Military Mental Health Care, under supervision of Prof.dr. Rolf Kleber, Prof.dr. Jack van Honk and Dr. Elbert Geuze. This research resulted in the dissertation Attending to Anger, which she will defend July 7th, 2017.