Injured body, injured soul? Predicting and preventing posttraumatic stress disorder after injury

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Citation for published version (APA):
CHAPTER 1: Introduction

Chapter adapted from:


1.1 General introduction

*Case of Angela¹, age 18:* It is the first day of Summer and Angela and her friend Nicole are packed and ready to go the beach. The city is buzzing with tourists, making it almost impossible to get through on their scooter. While looking over her shoulder to see the traffic, the car in front of her suddenly stops and Angela crashes into the car at about 15 km/h with no helmet on. She falls to the street and hits her head on the curb. Angela remembers feeling panic, trying to get up to check up on her friend, but being held down by bystanders. She only just notices all the blood when Nicole finally joins her and tries to calm her down. Angela is admitted to hospital for three days with a broken hand, wrist and teeth and contusions to her kidneys, liver and ribs. As Nicole was flung into the brush during the crash, she is lucky to get off with just a fright. In the days after the crash, Angela’s panicky feeling do not seem to go away, she is very emotional and worries a lot about her injuries and about her friend. Even though Nicole was unharmed and visits her often, Angela still feels guilty about the accident.

*Case of Dwayne¹, age 33:* Dwayne has worked as a garbage collector for 7 years now, mostly on the same routes, week in, week out. He knows the neighbourhoods and the people in it. One route even passes by his house. One day, while greeting a neighbour, the garbage truck backs up and his foot gets stuck in between the tire and the curb. He screams, bangs on the side of the truck, thinking he would be run over, and loses consciousness. Luckily, Dwayne is freed almost instantly and suffers no other injuries, but undergoes several surgeries for his foot. Now, after 4 weeks, he is ready to rehabilitate. He suffers from constant pain in his foot and takes as much pain medication as he is allowed. Since the accident, he sees the truck coming towards him almost every time he closes his eyes. His colleagues and friends still pay him daily visits, and sometimes manage to take his mind of the accident or the pain, but only until they leave. Then he is back in between the truck and the curb.
Case of Josine¹, age 45: Just a quick trip to the supermarket, Josine thought. It is near dinner time, snowing and already dark outside. She remembers paying for the groceries and stepping back into the car, but then she wakes up in a hospital bed, surrounded by doctors and nurses and bright lights. A nurse holds her hand and explains that her car collided with another car, flipped on its side and that she was rescued by the fire department. She was lucky, according to the nurse, to only have a concussion and some bruises; it could all have been so much worse. Josine is discharged after a one night stay. At first, not being able to remember what happened makes her feel anxious and insecure. Did she black out in the car before or due to the accident? What if it would happen again, how would she know how to handle it? After a while, with the help from her family and friends, she manages to take her first car ride again. After a few times, driving begins to feel familiar again, although Josine firmly keeps both eyes on the road, just in case.

¹ Cases present accounts of participants in the Trauma TIPS study. Names or other personal or identifiable information has been altered for anonymity purposes.

Accidental injuries may have a major impact on one’s life. Suddenly, that person may be confronted with a serious threat to his or her health or life, may be rushed off to the hospital in an ambulance or trauma helicopter, may undergo extensive medical examination and -often- hospitalisation, causing the immediate and long-term future to be uncertain. In the Netherlands alone, over 7 million injuries are registered yearly, caused by accidents in traffic, at home, at work, or by interpersonal violence (VeiligheidNL, 2014). Half of these require medical treatment and cost up to 2.5 billion euro in medical costs and 3.3 billion euro in costs for labour lost (VeiligheidNL, 2014). Highly specialised level 1 trauma centers, located in eleven hospitals across the Netherlands, provide state of the art medical care for these victims with traumatic injury. Although the (neuro-)psychological and social consequences of traumatic injury have been acknowledged since 1943 (Adler, 1945; Cobb & Lindemann, 1943) and have increasingly been the topic of study in recent years (e.g., see Bryant et al., 2010; O’Donnell, Creamer, Bryant, Schnyder, & Shalev, 2003; Sareen et al., 2013), knowledge is still needed about how many people suffer from mental health problems after injury, how these problems may be predicted, reduced, or even prevented, in order to design ways to better identify...
those at risk for long-lasting psychological problems, and to improve the recovery from their physical and mental injuries.

This thesis focuses on predictors of posttraumatic stress disorder (PTSD) and on prevention of PTSD in the acute phase after traumatic injury. In this introductory chapter, I will first briefly describe the prevalence of trauma and PTSD (paragraph 1.2) and discuss current theories of PTSD (paragraph 1.3). Next, I will focus on biological and psychological predictors for PTSD (paragraph 1.4), strategies for the prevention of PTSD (paragraph 1.5), and the design of the Trauma TIPS study (paragraph 1.6). In the final paragraph (1.7), I present an overview of the aims and chapters in this thesis.

1.2 Prevalence of trauma and Posttraumatic Stress Disorder

Approximately four out of five persons experience a potentially traumatic event, such as an accident, disaster, war or assault, during their lives (Breslau, Peterson, Poisson, Schultz, & Lucia, 2004; de Vries & Olff, 2009; Frans, Rimmo, Aberg, & Fredrikson, 2005; Kawakami, Tsuchiya, Umeda, Koenen, & Kessler, 2014; Kilpatrick et al., 2013; Norris et al., 2003). In the DSM-5 (American Psychiatric Association, 2013), a traumatic event is defined as an event involving actual or threatened death, serious injury or sexual violation. This includes both direct exposure, by experiencing or witnessing the traumatic event in person, and indirect exposure, by learning that a close family member or friend experienced actual or threatened death that was violent or accidental, or by experiencing first-hand repeated or extreme exposure to aversive details of the traumatic event (but not through media, pictures, television or movies unless work-related; American Psychiatric Association, 2013; see Box 1.1).


Criterion A: stressor. The person was exposed to: death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence, as follows: (one required) (1) direct exposure; (2) witnessing, in person; (3) indirectly, by learning that a close relative or close friend was exposed to trauma (if the event involved actual or threatened death, it must have been violent or accidental); (4) repeated or extreme indirect exposure to aversive details of the event(s), usually in the course of professional duties (e.g., first responders, collecting body parts; professionals repeatedly exposed to details of child abuse; not including indirect non-professional exposure through electronic media, television, movies, or pictures).
**Criterion B**: intrusion symptoms. The traumatic event is persistently re-experienced in the following way(s): (one required) (1) recurrent, involuntary, and intrusive memories (Note: Children older than six may express this symptom in repetitive play); (2) traumatic nightmares (Note: Children may have frightening dreams without content related to the trauma(s)); (3) dissociative reactions (e.g., flashbacks) which may occur on a continuum from brief episodes to complete loss of consciousness (Note: Children may reenact the event in play); (4) intense or prolonged distress after exposure to traumatic reminders; (5) marked physiologic reactivity after exposure to trauma-related stimuli.

**Criterion C**: avoidance. Persistent effortful avoidance of distressing trauma-related stimuli after the event: (one required) (1) trauma-related thoughts or feelings; (2) trauma-related external reminders (e.g., people, places, conversations, activities, objects, or situations).

**Criterion D**: negative alterations in cognitions and mood. Negative alterations in cognitions and mood that began or worsened after the traumatic event: (two required) (1) inability to recall key features of the traumatic event (usually dissociative amnesia; not due to head injury, alcohol, or drugs); (2) persistent (and often distorted) negative beliefs and expectations about oneself or the world (e.g., “I am bad,” “The world is completely dangerous”); (3) persistent distorted blame of self or others for causing the traumatic event or for resulting consequences; (4) persistent negative trauma-related emotions (e.g., fear, horror, anger, guilt, or shame); (5) markedly diminished interest in (pre-traumatic) significant activities; (6) feeling alienated from others (e.g., detachment or estrangement); (7) constricted affect: persistent inability to experience positive emotions.

**Criterion E**: alterations in arousal and reactivity. Trauma-related alterations in arousal and reactivity that began or worsened after the traumatic event: (two required) (1) irritable or aggressive behavior; (2) self-destructive or reckless behavior; (3) hypervigilance; (4) exaggerated startle response; (5) problems in concentration; (6) sleep disturbance.

**Criterion F**: duration. Persistence of symptoms (in Criteria B, C, D, and E) for more than one month.

**Criterion G**: functional significance. Significant symptom-related distress or functional impairment (e.g., social, occupational).

**Criterion H**: exclusion. Disturbance is not due to medication, substance use, or other illness.
It is common for trauma survivors to experience an array of acute stress reactions in the first weeks after the event (Bryant et al., 2010), but only in a minority of individuals do these symptoms persist after one month and develop into a posttraumatic stress disorder (PTSD). PTSD is characterized by intrusive recollections of the event (i.e., memories, nightmares, flashbacks), avoidance of trauma-related stimuli (i.e., trauma-related thoughts, feelings or external cues), changes in cognition or affect (i.e., dissociative amnesia, persistent negative trauma-related emotions, constricted affect) and changes in arousal and reactivity (i.e., sleep disturbance, concentration problems, hypervigilance; American Psychiatric Association, 2013; see Box 1.1). Epidemiological studies in the general population have reported lifetime prevalence rates of PTSD ranging from less than 1% (Helzer, Robins, & McEvoy, 1987; Hepp et al., 2006) to 10% (Breslau, Davis, Andreski, & Peterson, 1991; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995), with higher rates of up to 37% in post-conflict regions (de Jong et al., 2001). The overall conditional risk of PTSD after any traumatic event ranges from 1% to 14% (Breslau et al., 1998; de Vries & Off, 2009; Kilpatrick et al., 2013; Olaya et al., 2014), but is strongly dependent on the type of traumatic exposure, as rates of PTSD following intentional trauma (i.e., acts of violence purposefully aimed towards an individual, such as assault, rape, war or terrorist attacks) are higher than following unintentional trauma (i.e., man-made or natural disasters, accidents; Santiago et al., 2013).

Traumatic injuries are one of the most common types of traumatic exposure worldwide, accounting for 9% of global mortality In more than 20 million people every year traumatic injuries are estimated to cause temporary or permanent disability (World Health Organization, 2008). Recently, it was estimated that the burden of disease for injuries would increase by 50% when mental health consequences, such as posttraumatic stress disorder (PTSD), are considered (Haagsma et al., 2012). A recent meta-analysis of studies of injured trauma populations showed PTSD prevalence rates of 8%-45% at 1 month post-trauma that decreased to 7% to 26% at 12 months post-trauma (Heron-Delaney, Kenardy, Charlton, & Matsuoka, 2013). However, the mental health effects of exposure to trauma are considerably more heterogeneous than PTSD. In approximately comparable rates, survivors of traumatic events have been found to suffer from depressive disorders between 6% and 60% (Holbrook, Anderson, Sieber, Browner, & Hoyt, 1999; Mellman, David, Bustamante, Fins, & Esposito, 2001; Schnyder, Moergeli, Klaghofer, & Buddeberg, 2001; Shalev et al., 1998), anxiety disorders, other than PTSD, between 2% and 11% (Brown, Fulton, Wilkeson, & Petty, 2000; O’Donnell et al., 2003; O’Donnell, Creamer, Pattison, & Atkin, 2004) and substance use disorders between 8% and 21% (O’Donnell et al., 2004; Whelan-Goodinson, Ponsford, Johnston, & Grant, 2009) during the first year post-trauma. A diagnosis of acute stress disorder (ASD) has been reported in 6% to 14% of injury populations (Bryant & Harvey, 1998; Fuglsang, Moergeli, Hepp-Beg, & Schnyder, 2002; Harvey & Bryant, 1999a; Harvey & Bryant, 1999b; Mellman et al., 2001). Comorbidity between post-injury mental disorders was found to be as high as 53% between PTSD and depression (Shalev et al., 1998).
1.3 Theories of PTSD: appraising the traumatic event

To explain why some individuals develop PTSD after traumatic exposure and others do not, several theories on PTSD have centred on the construct of cognitive appraisal, defined by Lazarus and Folkman (1984) as “the process of categorizing an encounter, and its various facets, with respect to its significance for well-being – not information processing per se, but more a continuous, evaluative process focused on meaning and significance” (p.31). From a cognitive perspective, it is the interpretation of the traumatic event, rather than the event itself, that causes disruptions in mood and behaviour. Social-cognitive theories focus on how trauma impacts existing mental structures, more specifically cognitions about the self, others and the world, and on ways to deal with the incompatibility of the trauma information with prior beliefs (Brewin & Holmes, 2003; Sherrer, 2011). Information-processing theories focus on memory structures and the encoding, storage and retrieval of trauma-specific and fear-induced information and responses. These memory structures are considered vital to the initial appraisal and subsequent reappraisal of the event (Brewin & Holmes, 2003; Sherrer, 2011). In this paragraph, I focus on three recent theoretical models that have integrated the cumulative scientific evidence about the development and course of PTSD within their theoretical models: emotional processing theory (Foa & Rothbaum, 1998), the cognitive model by Ehlers and Clark (2000), and the traumatic stress-coping model by Olff, Langeland and Gersons (2005).

1.3.1 Emotional processing theory

Building upon previous social-cognitive, conditioning and information-processing theories, emotional processing theory theorizes that PTSD emerges as a consequence of developing a fear structure associated with the traumatic event (Foa & Rothbaum, 1998). This fear structure involves representations of the traumatic event, such as stimuli, responses and their meaning, and serves as a blueprint for escaping or avoiding harm in that type of situation. Any information related to the traumatic event activates the fear structure, causing hyperarousal symptoms, intrusive memories and avoidance behaviour (Rothbaum, Meadows, Resick, & Foy, 2000). For example, in the case of a motor vehicle crash, getting into a car would heighten physiological arousal, trigger memories of the crash, and cause the urge to leave and to consequently avoid that situation. Fear structures are in itself adaptive, when a person is faced with real danger, but become pathological when the associations between stimuli, response and representation do not reflect real danger. Specific to PTSD, the fear structure involves wrongfully interpreting safe stimuli as dangerous (e.g., “Getting into a car is dangerous”), and wrongfully interpreting responses as self-incompetence (e.g., “My symptoms mean that I can’t cope with this”; Rothbaum et al., 2000). These two basic dysfunctional cognitions
about the danger of the world and the incompetence of the self are thought to underlie PTSD.

1.3.2
A cognitive model of PTSD

Another influential PTSD model is the cognitive model of Ehlers and Clark (2000). In their model, they assume that, unlike individuals who recover naturally, individuals with persistent PTSD are unable to see the trauma as a time-limited event that does not have global negative implications for their future. They experience a continuous sense of threat through excessively negative appraisals of the trauma and/or its consequences (Ehlers & Clark, 2000). These negative appraisals include interpretations of one’s initial PTSD symptoms, interpretation of other people’s reactions in the aftermath of the event, and appraisals of the consequences of the trauma on other life domains (e.g., work, physical health, financial situation). Perceiving one’s initial reactions to the trauma, such as intrusive memories, trouble concentrating, sleep difficulties, as inadequate or abnormal, will produce negative emotions (i.e., anger, depression, anxiety) and encourage dysfunctional coping behaviour that ultimately reinforce the traumatic stress symptoms. Otherwise harmless or considerate reactions to the traumatic event of family and friends, such as not confronting the loved one with the event in order to try to minimise distress, can be perceived as careless or blameful.

1.3.3
The traumatic stress-coping model

From a psychobiological perspective, the traumatic stress-coping model of Olff, Langeland and Gersons (2005) proposes that a threat appraisal of the traumatic event is followed by an acute stress response involving emotional, behavioural and biological elements.

When confronted with danger, two neuroendocrine response systems are activated to enable a fight-flight-freeze response: the sympathoadreno-medullar (SAM) axis and the hypothalamus-pituitary-adrenal (HPA) axis. Seconds after danger is assessed, within the SAM axis, the adrenal medulla is activated to release noradrenaline and adrenaline into the blood stream. This sets in motion the central nervous system, increasing heart rate and blood pressure. This enables immediate muscular action in response to the threat. After a few minutes, the HPA axis is activated to prolong the stress response when needed. During acute stress, the hypothalamus secretes corticotrophin-releasing hormone. This in turn stimulates the pituitary gland to release adrenocorticotropic hormone, which leads to the production of glucocorticoids (cortisol) and dehydroepiandrosterone (DHEA) by the adrenal cortex (Vinson, Whitehouse, & Hinson, 2007). Cortisol suppresses metabolic, immuno- and neurodefensive processes to adequately cope with the
stressor, and triggers a negative feedback loop when sufficient circulating levels are reached. When the threat is gone, the negative feedback mechanisms help to restore basal hormone levels.

According to the traumatic stress-coping model, failure to regulate the biological stress response at the time of the trauma sets in motion a cascade of psychobiological alterations that lead to intrusions of the traumatic event, avoidance of reminders of the event and hyperarousal symptoms (Olff, Langeland, & Gersons, 2005). The pathways between the acute psychological and biological responses to the trauma are influenced by background and socio-cultural characteristics (i.e., gender, age, genetic susceptibility to stress, personality, prior trauma, social support), but also by coping strategies. Defensive coping may protect an individual from being overwhelmed and may buffer against their HPA acute stress response, but may, when constituting a general defensive coping style, lead to long term sustained sympathetic arousal. Active coping may help deal with the traumatic stressor and may prevent long term psychophysiological dysregulations and psychopathology (Olff et al., 2005).

1.3.4 Appraisal in PTSD treatment

According to the models described above, altering the appraisal of the traumatic event may result in a decrease in PTSD symptoms. Cognitive-behaviour therapy (CBT) is based on the principles that cognitions influence emotions and behaviour, and behaviour impacts cognitions and emotions (Wright, Ramirez Basco, & Thase, 2006). According to Ehlers and Clark (2000), successful treatment is aimed at identifying cognitive themes or ‘hot spots’, i.e., memories that elicit extreme distress, normalizing the PTSD symptoms, explaining how their usual coping strategies contributed to symptom persistence, and fully processing the trauma, thereby reversing the maintenance factors. According to emotional processing theory, successful treatment of PTSD means correcting the pathological elements of the fear structure by first reactivating the structure and second providing new, incompatible information (Rothbaum et al., 2000). This is the basis of the technique imaginal exposure, in which repeated imaginal reliving is thought to promote habituation and reduce anxiety to trauma-related memories (Rothbaum et al., 2000). Imaginal exposure and cognitive restructuring constitute elements of CBT for PTSD treatment (Ehlers & Clark, 2000; Wright et al., 2006). Other elements of CBT are psychoeducation about the disorder and the treatment, behavioural methods, such as behavioural activation, systematic desensitisation, breathing retraining and stress management exercises (Wright et al., 2006).
1.4 Predictors for PTSD

1.4.1 Biological PTSD predictors

Cortisol
As mentioned in the previous paragraph, an inability to attain homeostasis after HPA axis activation is considered a risk factor for developing PTSD (Olff et al., 2005; Yehuda, 2002). As a result, studies have focused on the role of the acute cortisol response in the development of PTSD. So far, findings have been inconsistent. Some studies found no direct relationship between initial cortisol and subsequent PTSD (Bonne et al., 2003; Resnick, Yehuda, Pitman, & Foy, 1995; Shalev et al., 2008). Others found that acute low cortisol levels predicted PTSD (Delahanty, Raimonde, & Spoonster, 2000; McFarlane, Atchison, & Yehuda, 1997) or PTSD symptoms (Aardal-Eriksson, Eriksson, & Thorell, 2001; Ehring, Ehlers, Cleare, & Glucksman, 2008; McFarlane, Barton, Yehuda, & Wittert, 2011), although in some the association disappeared when controlling for possible confounding variables, such as injury severity and history of PTSD (Delahanty et al., 2000), and time of the accident or blood sampling (McFarlane et al., 1997). Variations in methodology, for example, when (i.e., immediately post-trauma up to several days after the event) or how (i.e., saliva, urine or plasma) cortisol was measured, might explain these differences. Lack of power due to a small sample size has been referred to by some studies as a possibility for not finding a significant association (Delahanty et al., 2000; Ehring et al., 2008). Therefore, it has been argued that the predictive effect of cortisol should be replicated in large, consecutively recruited samples, taking into account the important confounders.

DHEA(S)

During the acute stress response, DHEA is secreted alongside cortisol by the adrenal cortex (Vinson et al., 2007). Animal studies have found DHEA and its sulfate form DHEAS to possess anabolic, neuroprotective and antiglucocorticoid effects (Kaminska, Harris, Gijsbers, & Dubrovsky, 2000; Karishma & Herbert, 2002; Kimonides, Khatibi, Svendsen, Sofroniew, & Herbert, 1998; Kimonides, Spillantini, Sofroniew, Fawcett, & Herbert, 1999). These effects may lead to an upregulation of HPA-axis responses and mitigate possible adverse effects of high cortisol levels on the brain in PTSD (Rasmusson, Vythilingam, & Morgan, III, 2003). As such, dysregulations in the HPA-axis associated with PTSD may also be evident in an abnormal DHEA-response. DHEAS is much more abundant than DHEA, because DHEAS has longer half-life and lower clearance (Lennartsson, Kushnir, Bergquist, & Jonsdottir, 2012). Studies on long term effects of stress have often reported on DHEAS levels, as they are more stable and show no diurnal variation (Kroboth, Salek, Pittenger, Fabian, & Frye, 1999). Studies on acute stress, on the other hand, have
often focused on DHEA, since DHEAS serves as a reservoir for DHEA biosynthesis and DHEA rather than DHEAS is expected to respond to acute psychosocial stress (Izawa et al., 2008; Morgan, III et al., 2004; Oberbeck et al., 1998; Pico-Alfonso, Garcia-Linares, Celda-Navarro, Herbert, & Martinez, 2004; Shirotoku et al., 2009). However, in a recent study, although the response of DHEA was more pronounced, both DHEA and DHEAS were found to increase in response to acute psychosocial stress (Lennartsson et al., 2012). In addition, DHEAS was found to increase in response to low, but not high, intensity military stress exposure (Morgan, III et al., 2004; Taylor et al., 2007). As of yet, DHEA or DHEAS have not been prospectively studied in the prediction of PTSD.

**Cortisol-to-DHEA(S) ratio**

Cortisol and DHEA(S) are often addressed as a ratio, representing the balance between anabolic and catabolic hormones (Maninger, Wolkowitz, Reus, Epel, & Mellon, 2009). A high ratio of cortisol-to-DHEA(S), or conversely a low DHEA(S)-to-cortisol ratio, represents a catabolic balance. A low cortisol-to-DHEA(S) ratio, or a high DHEA(S)-to-cortisol ratio, reflects an anabolic balance. A higher cortisol-to-DHEA ratio has been linked to a chronic stress response in depressed adolescents and adults (Goodyer, Herbert, & Altham, 1998; Young, Gallagher, & Porter, 2002), as well as more resilient functioning in both maltreated and non-maltreated children (Cicchetti & Rogosch, 2007), whereas a higher DHEAS-to-cortisol ratio was positively correlated with fewer dissociative symptoms after prolonged and extreme training stress (Morgan, III et al., 2004; Taylor et al., 2007). Thus, previous findings are inconclusive with respect to the role of the cortisol-to-DHEA(S) ratio in the onset of psychiatric disorders such as PTSD.

**Heart rate**

As a parameter for increased psychophysiological arousal following trauma, studies have examined the initial basal heart rate (HR) in injured trauma survivors, assessed at the emergency department, in association with PTSD symptoms (Blanchard, Hickling, Galovski, & Veazey, 2002; Bryant, 2006; Bryant, Creamer, O’Donnell, Silove, & McFarlane, 2008; Buckley et al., 2004; Coronas et al., 2011; Kassam-Adams, Garcia-Espana, Fein, & Winston, 2005; Kraemer, Moergeli, Roth, Hepp, & Schnyder, 2008; Kuhn, Blanchard, Fuse, Hickling, & Broderick, 2006; Zatzick et al., 2005). Some studies reported a positive association between initial HR and later PTSD (Bryant et al., 2008; Kassam-Adams et al., 2005; Shaikh al et al., 2012; Zatzick et al., 2005), others found no significant association between HR and PTSD (Buckley, Holohan, Greif, Bedard, & Suvak, 2004; Kuhn et al., 2006), and one study found a lower HR to be correlated with chronic PTSD (Blanchard et al., 2002). One study found that only HR measured at the scene of the traffic accident and not HR assessed at hospital admission was predictive of later PTSD (Coronas et al., 2011).
1.4.2 Psychological PTSD predictors

Appraisal

Psychological factors related to the appraisal of the traumatic event or the immediate emotional response to the event have consistently shown to predict PTSD. One of these is perceived life threat, which is often used as a measure of the subjective severity of the traumatic exposure (Ozer, Best, Lipsey, & Weiss, 2003; Sijbrandij et al., 2013). Perceived life threat during a road traffic accident was found to be one of the largest predictors for PTSD after a road traffic accident in a recent systematic review and meta-analysis (Heron-Delaney et al., 2013).

Peritraumatic reactions

Other psychological predictors for the onset of PTSD are peritraumatic dissociation and distress. Peritraumatic dissociation refers to disturbed awareness, impaired memory, or altered perceptions during and immediately after a traumatic experience (Cardena & Spiegel, 1993). These reactions may include emotional numbing, reduction in awareness of one’s surroundings, depersonalization, and amnesia. Peritraumatic distress refers to the broader emotional response during and immediately after trauma exposure, that could lead to dissociative responses (Brunet et al., 2001). Symptoms of peritraumatic distress include sadness, grief, anger, helplessness, and disgust. Meta-analytic evidence indicates both peritraumatic dissociation and distress are predictors of PTSD (Ozer et al., 2003). Recently, however, the role of peritraumatic dissociation in the prediction of PTSD has been criticized (Briere, Scott, & Weathers, 2005; Wittmann, Moergeli, & Schnyder, 2006), since it is associated with acute PTSD (i.e., PTSD diagnosed within 3 months after traumatic exposure), but is not a predictor for chronic PTSD (i.e., PTSD diagnosed at 3 months or more after traumatic exposure; cf. DSM-IV; see American Psychiatric Association, 2000), after symptoms of acute PTSD are controlled for (van der Velden & Wittmann, 2008).

1.4.3 Trauma-related characteristics

Important trauma-related characteristics in the prediction of PTSD are: type of traumatic event, physical injury, and injury-related aspects, such as type of injury, consciousness during the event and pain.
Type of event

As mentioned briefly in paragraph 1.1, the type of traumatic event greatly impacts the prevalence of PTSD. A general distinction may be made between intentional trauma (i.e., acts of violence purposefully aimed towards an individual, such as assault, abuse, war or terrorist attacks) and unintentional trauma (i.e., man-made or natural disasters, accidents). A recent systematic review showed that whereas prevalence rates decrease during the first year following unintentional trauma (1-month median=30.1, 95% CI [16.7-35.1], 12-month median=14.0, 95% CI [2.2-28.3]), the prevalence of PTSD increases in the year after intentional trauma (1-month median=11.8, 95% CI [3.1-87.5], 12-month median=23.3, 95% CI [2.6-43.8]; Santiago et al., 2013).

Physical injury

Physical injury during a traumatic event is embedded in the A-criterion of the PTSD diagnosis in DSM-5 (American Psychiatric Association, 2013; see Box 1.1). So far, the results of studies on the association between injury severity and PTSD have been inconsistent. Some showed a positive relationship between the severity of injury and symptoms of PTSD (Blanchard, Hickling, Taylor, & Loos, 1995; Frommberger et al., 1998; Hamanaka et al., 2006; Koren, Norman, Cohen, Berman, & Klein, 2005; Michaels et al., 1998). Two studies found a negative association between injury severity and PTSD (Delahanty, Raimonde, Spoonster, & Cullado, 2003; Dougall, Ursano, Posluszny, Fullerton, & Baum, 2001), and others failed to confirm either (Bryant & Harvey, 1995; Curran et al., 1990; Ehlers, Mayou, & Bryant, 1998; Feinstein & Dolan, 1991; Gabert-Quillen, Fallon, & Delahanty, 2011; Holbrook, Hoyt, Stein, & Sieber, 2001; Joy, Probert, Bisson, & Shephered, 2000; Perry, Difede, Musngi, Frances, & Jacobsberg, 1992; Zatzick, Jurkovich, Gentilello, Wisner, & Rivara, 2002). To understand the discrepancies in findings, it is important to account for the timing of the PTSD assessment. In the immediate days and weeks following the injury, patients are likely to be occupied with their physical recovery and the psychological processing of the event probably occurs later (O’Donnell, Elliott, Lau, & Creamer, 2007). Moreover, most injury survivors, while in the hospital, may not be exposed to trauma reminders that may cause PTSD symptoms at a later stage. Furthermore, not all studies took important confounding or moderating factors into account, such as gender (Olff, Langeland, Draijer, & Gersons, 2007), threat to life (Olff et al., 2005), type of traumatic event (Breslau et al., 1998), stress hormone levels (Delahanty et al., 2003), or peritraumatic dissociation (Sijbrandij et al., 2012).
**Traumatic brain injury (TBI)**

TBI is defined as trauma to the head that results in an alteration or loss of consciousness or posttraumatic amnesia (American Congress of Rehabilitation Medicine, 1995). In a study of injury burden in six European countries, the incidence of skull-brain injury was on average 25 persons per 1000 inhabitants, whereas overall incidence of (any) injury ranged between 36 persons (for Ireland) and 116 persons (England) per 1,000 inhabitants (Polinder, Meerding, Mulder, Petridou, & van, 2007). A recent review indicated 14% PTSD in TBI patients, 5.8 times the relative risk of PTSD observed in the general community population (Carlson et al., 2011). The severity of TBI is often classified with the Glasgow Coma Scale (GCS), a neurological scale to record level of consciousness. In general, brain injury is classified as: Severe (GCS ≤ 8), Moderate (GCS 9-12) and Mild (GCS 13-15; Teasdale & Jennett, 1974). In civilian populations, mild TBI is the most frequent type of TBI. Most individuals with mild TBI recover fully within 90 days after the injury (Karr, Areshenkoff, & Garcia-Barrera, 2013). However, a minority of individuals continues to suffer from post-concussive somatic, cognitive, and/or behavioural symptoms that lead to long-term functional limitations. Persistent postconcussive symptoms are often non-specific and can be identical to symptoms of chronic stress or other mental health disorders, further complicating differential diagnosis (Larrabee & Rohling, 2013).

**Pain**

Acute pain in the context of physical injury has been linked to the development of acute stress reactions (Fuglsang et al., 2002; Saxe et al., 2005), PTSD (Asmundson, Coons, Taylor, & Katz, 2002; Kuch, Cox, & Evans, 1996; Norman et al., 2011; Norman, Stein, Dimsdale, & Hoyt, 2008) and other post-trauma psychopathology, such as depression and substance use (Cairns, Adkins, & Scott, 1996; Tate, Forchheimer, Krause, Meade, & Bombardier, 2004). A mutual maintenance model for pain and PTSD is suggested in which pain may serve as trauma reminder, triggering flashbacks (Asmundson et al., 2002). Conversely, PTSD symptoms, such as sleep deficiency, may maintain or worsen pain (Smith, Egert, Winkel, & Jacobson, 2002).
1.5 Strategies for PTSD prevention

1.5.1 Early PTSD risk screening

Early identification of trauma survivors at risk for PTSD through risk screening may facilitate adequate monitoring of symptoms, thorough follow-up diagnostics and early treatment if needed. Studies have shown that psychological treatment of acute PTSD symptoms as early as two weeks after trauma is effective in treating acute PTSD or ASD (Roberts, Kitchiner, Kenardy, & Bisson, 2009; Sijbrandij et al., 2007). To properly assess the diagnostic accuracy of a screening tool, sensitivity (i.e., the probability that someone with PTSD has a positive test result) and specificity (i.e., the probability that someone without PTSD has a negative result) are important. The higher the sensitivity, the lower the specificity, and vice versa. Based on the trade-off between sensitivity and specificity, an optimal cut-off point is usually chosen in diagnostic accuracy studies (Smits, Smit, Cuijpers, & de Graaf, 2007).

Related to sensitivity and specificity, but more important for clinical practice, are the positive predictive value (PPV) and the negative predictive value (NPV) of a screening instrument. The PPV refers to the proportion of people scoring positive on the screening instrument who indeed develop PTSD, whereas the NPV refers to the proportion of people scoring negative on the screener who do not develop PTSD. PPV and NPV are both dependent on the population prevalence of a disorder. Typically, when the prevalence of a disorder in the population is low, there is a smaller chance of an individual scoring positive on the test to actually develop the disorder, causing PPV to be low and NPV to be high. Overall, screening for concurrent (existing) PTSD shows good diagnostic accuracy (Brewin, 2005; O’Donnell, Bryant, Creamer, & Carty, 2008).

As put forward by Brewin (2005), screening instruments for PTSD may be based on any measure that predicts a PTSD diagnosis. Most instruments consist of self-report scales of acute symptoms of PTSD (Brewin et al., 2002; Meltzer-Brody, Churchill, & Davidson, 1999). Brewin (2005) systematically reviewed the diagnostic accuracy of 13 screening instruments for concurrent PTSD that did not exceed 30 items, and concluded that those with fewer items, simpler response scales and simpler scoring methods showed equal diagnostic accuracy to longer and more complex scales. Screening to predict future PTSD, i.e., assessing prognostic accuracy, has generally shown less favourable results compared to screening for a concurrent PTSD diagnosis, with lower specificity values and PPVs (O’Donnell et al., 2008). Generally, prognostic screening instruments show high NPVs, making them particularly useful in filtering out individuals who will not develop PTSD. In other studies, demographic, premorbid, injury- and recovery-related factors were used in addition to acute psychological symptoms (O’Donnell et al., 2008; Ward-Begnoche et al., 2006). Overall, these instruments showed high sensitivity, but
moderate specificity, indicating a good accuracy in identifying those with possible future PTSD, but a diminished capacity for ruling out those without future PTSD. Current literature still lacks evidence on the comparability of screening instruments for future PTSD.

1.5.2
Early psychological interventions

Until recently, the most common prevention strategy in the immediate aftermath of traumatic events has been Critical Incident Stress Debriefing or, more generally named, “psychological debriefing” (Mitchell & Everly, 2001). Key elements of psychological debriefing are an emphasis on ventilating emotions, and psychoeducation about common psychological reactions and adequate coping strategies (Mitchell & Everly, 2001). Research has shown that psychological debriefing is not effective in preventing symptoms of PTSD, anxiety, or depression and may even increase the risk of PTSD (Rose, Bisson, & Wessely, 2003). It has been suggested that the emphasis on expressing emotions related to the trauma may exacerbate and sustain arousal, causing PTSD symptoms to escalate rather than diminish (Sijbrandij, Olff, Reitsma, Carlier, & Gersons, 2006). Routine use of such trauma-focused early interventions for everyone involved in the traumatic event is currently advised against (Impact, 2007; National Institute for Clinical Excellence (NICE), 2005).

Other prevention strategies have been examined, such as written psychoeducation, but no preventative effects have been found both in non-selected trauma patients and highly symptomatic trauma patients (Ehlers et al., 2003; Scholes, Turpin, & Mason, 2007; Turpin, Downs, & Mason, 2005). The authors suggested that the unguided provision of information about acute stress symptoms could have sensitized patients, thereby disrupting the natural recovery process (Scholes et al., 2007; Turpin et al., 2005).

Psychological first aid complies with the current guidelines for early interventions based on expert consensus and scientific evidence (National Child Traumatic Stress Network and National Center for PTSD, 2005), stating that stringent attempts to make victims express their emotions and relive their experiences are to be withheld. Psychological first aid consists of supportive, empathic listening, and helping victims with practical assistance, such as ensuring safety and facilitating contact with organizations and resources that may help them to meet more basic needs (National Child Traumatic Stress Network and National Center for PTSD, 2005). The efficacy of psychological first aid awaits to be studied (Pekevski, 2013).

Other research evaluating strategies to prevent PTSD focused on offering interventions to selected individuals at high risk for developing PTSD. Zatzick et al. (2004) randomized injury patients with high initial PTSD and/or depressive symptoms to a trauma support specialist, who monitored medical and psychological
symptoms and acted as case manager during 1 year following injury (collaborative care condition), or to a usual care control condition in which patients received a list of community referrals for mental health services. Collaborative care patients did not show any change in PTSD symptoms during the follow-up year, whereas symptoms worsened in usual care patients (Zatzick et al., 2004).

The Internet is increasingly used for the administration and dissemination of mental health interventions. Curative and (guided) self-help interventions for depression and anxiety, including PTSD, have been found effective, with comparable effect sizes to face-to-face treatment (Spek et al., 2007; van’t Hof, Cuijpers, & Stein, 2009). Few initiatives have yet been undertaken using the Internet as a medium for the prevention of PTSD (Cox, Kenardy, & Hendrikz, 2010; Ruggiero et al., 2006; Ruggiero et al., 2012). One web-based program for post-disaster mental health, among which PTSD, was found feasible (Ruggiero et al., 2006), but efficacy results remain to be published (Ruggiero et al., 2012). Preliminary evidence from one other study on the efficacy of a self-guided Internet-based psychoeducational program for injured children and their parents showed greater anxiety reductions in children who had completed the program compared to those who had not (Cox et al., 2010). Another internet-based intervention for injured children, an interactive game designed to provide practical information and teach children adaptive coping strategies, with the aim of preventing or reducing PTSD symptoms after acute pediatric medical events is currently being tested (Marsac et al., 2013).

1.5.3 Early CBT for PTSD

Early interventions based on CBT have consistently shown effective in preventing chronic PTSD in a selection of highly symptomatic survivors of traumatic injury, (see for a review, Roberts, Kitchiner, Kenardy, & Bisson, 2010). Several trials were conducted studying the efficacy of early CBT in a selection of highly symptomatic survivors of traumatic injury, such as patients with a diagnosis of ASD (Bryant & Harvey, 1998; Bryant, Moulds, Guthrie, & Nixon, 2005; Bryant, Moulds, & Nixon, 2003) or patients with increased acute distress or symptoms of anxiety or PTSD (Bisson, Shepherd, Joy, Probert, & Newcombe, 2004; Sijbrandij et al., 2007). All studies showed fewer cases of PTSD at post-treatment in the CBT condition versus the control conditions. Ehlers and colleagues (2003) also demonstrated the effectiveness of 12 sessions of cognitive therapy in the prevention of chronic PTSD. Although interventions based on CBT are mostly offered in the form of individual face-to-face psychotherapy of at least 4 sessions, a recent randomized controlled trial found evidence for the effectiveness of 3 sessions of prolonged (imaginal) exposure, starting within 12 hours of the traumatic event, in counteracting later symptoms of PTSD and depression (Rothbaum et al., 2008). It is yet unclear whether CBT-techniques administered as a single session early intervention are effective in preventing PTSD.
1.5.4 Early pharmacological interventions

To intervene in the early development of PTSD symptoms, a number of pharmacological substances have been tested as a secondary prevention strategy for PTSD, such as beta-adrenergic antagonists, hydrocortisone, and benzodiazepines.

Beta-adrenergic antagonists, such as propranolol, interfere with the binding to the receptor of epinephrine and other stress hormones. A pilot RCT showed that propranolol decreased psychophysiological responding to personalize trauma scripts relative to placebo at 3 months post-trauma in trauma survivors with elevated heart rate at the Emergency Department (Pitman et al., 2002). This has been replicated in a non-randomized controlled study (Vaiva et al., 2003). Subsequent RCTs (Nugent et al., 2010; Stein, Kerridge, Dimsdale, & Hoyt, 2007) and a case-control study (McGhee et al., 2009), however, failed to find significant effects of propranolol in preventing PTSD.

Hydrocortisone is another pharmacological intervention that has been proposed as a strategy to prevent PTSD (Aardal-Eriksson et al., 2001; Delahanty et al., 2000; Ehring et al., 2008; McFarlane et al., 1997; McFarlane et al., 2011; Resnick, Yehuda, & Acieno, 1997; Yehuda, Resnick, Schmeidler, Yang, & Pitman, 1998). Lower levels of circulating cortisol have been found to predict PTSD (Aardal-Eriksson et al., 2001; Delahanty et al., 2000; Ehring et al., 2008; McFarlane et al., 1997; McFarlane et al., 2011), although some studies did not confirm this association (Bonne et al., 2003; Resnick et al., 1995; Shalev et al., 2008). Cortisol is assumed to terminate the adrenergic response. As such, low levels of cortisol may lead to prolongation of the acute stress response and strengthening of the consolidation of the fear memory (Yehuda, 2002). In addition, cortisol administration has also been related to impaired memory retrieval (see for an overview, Rimmlele, Besedovsky, Lange, & Born, 2013). Thus, it has been suggested that early administration of glucocorticoids following trauma may counteract and impair memory consolidation and recall. Non-randomized (Schelling et al., 1999) and randomized (Delahanty et al., 2013; Schelling et al., 2001; Schelling et al., 2004; Zohar, Yahalom et al., 2011) controlled trials have demonstrated that hydrocortisone administration after trauma attenuated acute or posttraumatic stress symptoms (Schelling et al., 2004; Zohar, Yahalom et al., 2011) and, in some studies, reduced the incidence of PTSD (Delahanty et al., 2013; Schelling et al., 2001).

Benzodiazepines are frequently prescribed sedatives or anxiolytics during hospitalization (Zatzick & Roy-Byrne, 2006). They act on the neurotransmitter GABA at the GABAA receptor with sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant, and muscle relaxant effects (Page, Curtis, & Walker, 2005). Benzodiazepines are also known for enhancing emotional memory and increasing the risk for PTSD (for a review, see Zohar et al., 2011), and thus far the use of benzodiazepines early after trauma is recommended against (World
Health Organization, 2013). Pre-clinical evidence suggests that acute post-stressor alprazolam administration negatively affects behavioural outcomes to subsequent stress exposure (Matar, Zohar, Kaplan, & Cohen, 2009). Acute benzodiazepine administration was positively associated with PTSD in two small trials of injury victims (Gelpin, Bonne, Peri, Brandes, & Shalev, 1996; Mellman, Byers, & Augenstein, 1998). However, retrospective studies of combat injury patients (Holbrook, Galarneau, Dye, Quinn, & Dougherty, 2010; Schofield, Johnston, & de Mello, 2010) and a prospective study in children with burns (Saxe et al., 2001) did not find significant associations between benzodiazepines during acute trauma care or hospital stay and PTSD outcomes.

Other approaches to pharmacological PTSD prevention have also been explored. Findings from preclinical and clinical studies suggest that early use of opiate analgesics after trauma might prevent or impair traumatic memory consolidation by attenuating noradrenergic activity and dampening fear conditioning by containing the HPA response (Good & Westbrook, 1995; McNally & Westbrook, 2003; Pitman, 1989). Support for this protective effect was found in post-hoc examinations in prospective studies of trauma survivors. Studies in children with burns (Saxe et al., 2001; Stoddard, Jr. et al., 2009) and traumatic injury (Nixon et al., 2010) found positive associations between morphine dosage during hospitalization and greater decline in PTSD symptoms in the first 6 months post-trauma. In addition, a prospective study of 155 adult injury patients reported that morphine dose within the first 48 hrs, but not within the first week, was associated with fewer PTSD symptoms at 3 months (Bryant, Creamer, O'Donnell, Silove, & McFarlane, 2009). A retrospective study of combat injury victims found that morphine during acute trauma care was associated with a reduced risk for a PTSD diagnosis within 24 months following injury (Holbrook et al., 2010).

Recently, one clinical study found that salbutamol, a beta2-adrenergic blocker used to treat acute asthma attacks and respiratory failure or insufficiency after injury, was associated with fewer 6 PTSD symptoms at 6 weeks in 23 MVA victims compared to 232 patients without salbutamol (Kobayashi et al., 2011).

1.6 Design of Trauma TIPS

This thesis describes the results from a large scale multicenter, prospective, longitudinal trial of consecutive traumatic injury patients, called Trauma TIPS. Trauma TIPS stands for The Incidence, Prediction and Prevention of Post-trauma Psychopathology Study, and consisted of the projects Incidence & Prediction and Prevention.
1.6.1  
Project I: Incidence & Prediction

The overall aim of this project was to investigate the incidence of posttraumatic psychopathology, such as PTSD, depressive disorders, anxiety disorders and substance use disorders, in a prospective cohort of adult injury victims, and to identify predictors for the development of posttraumatic psychopathology in the year following injury. From September 2005 to March 2009, all adult patients transported by ambulance or trauma helicopter to the Trauma Units of the Academic Medical Center (AMC) and the VU University medical center (VUmc)² were approached to participate in a prospective longitudinal study. Patients were included if they were 18 years of age or older, if their injuries were sustained in a traumatic event cf. the A1-criterion for PTSD in the DSM-IV (American Psychiatric Association, 2000), and if they had sufficient understanding of the Dutch language. Patients with injuries due to deliberate self-harm, with an organic brain condition, current psychotic symptoms or disorder, bipolar disorder or depression with psychotic features, with moderate to severe traumatic brain injury (according to the Glasgow Coma Scale score of less than 13; Teasdale & Jennett, 1974), or who permanently resided outside the Netherlands were excluded from participation.

Upon arrival at the Trauma Unit (T0; see Figure 1.1), hospital staff collected blood samples for stress hormone assessment. Research assistants selected eligible patients from the hospitals’ registrations, and contacted them within 72 hours of the injury in-hospital or by telephone for further eligibility assessment. Participants provided oral and written informed consent prior to data collection. A baseline clinical assessment (T1) of medical and psychiatric history and current psychological symptoms occurred at approximately 1 week post-injury. At 4-6 weeks (T2), 3 months (T3), 6 months (T4), and 12 months (T5) post-injury, follow-up clinical and self-report assessments of current psychopathology were performed. Assessments took place at the AMC’s Centre for Anxiety Disorders, at bedside or at the private home of the patient by trained master’s- and doctoral level assessors. Figure 1.1 presents an overview of the study procedures. Results from Project Incidence & Prediction are presented in Chapters 2, 3 and 7. Table 1.1 shows the incidence of PTSD, depressive disorders and anxiety disorders during one year following injury in the entire sample.

² Inclusion in VUmc started in September 2007.
Table 1.1. Frequencies (%) of Diagnoses of Psychopathology in Adult Injury Patients ($N = 852$)

<table>
<thead>
<tr>
<th>Diagnoses of psychopathology</th>
<th>1-Month Follow-Up</th>
<th>3-Month Follow-Up</th>
<th>6-Month Follow-Up</th>
<th>12-Month Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTSD</td>
<td>74 (11.9)</td>
<td>25 (8.9)</td>
<td>39 (8.4)</td>
<td>32 (7.9)</td>
</tr>
<tr>
<td>Depressive disorder</td>
<td>59 (9.6)</td>
<td>14 (5.0)</td>
<td>44 (9.6)</td>
<td>33 (8.2)</td>
</tr>
<tr>
<td>Anxiety disorder†</td>
<td>49 (8.0)</td>
<td>19 (6.8)</td>
<td>46 (10.0)</td>
<td>29 (7.2)</td>
</tr>
<tr>
<td>Any PTSD, depressive or anxiety disorder</td>
<td>125 (19.8)</td>
<td>45 (16.0)</td>
<td>90 (19.4)</td>
<td>63 (15.6)</td>
</tr>
</tbody>
</table>

PTSD: Posttraumatic Stress Disorder.

† Includes: Panic disorder w/out agoraphobia, Generalized Anxiety Disorder, specific phobias, Obsessive Compulsive Disorder, social phobia, adjustment disorder.
The 3-Month Follow-Up was added to the study design at the start of project II to expand the assessments of short term effects of the internet-based intervention. As a consequence, clinical data at this time point is present for a proportion of participants.
Participants

**Project 1: Incidence & Prediction**

- **T1**: appr. 1-7 days
- **T2**: 1 - Month
- **T3**: 3 - Months
- **T4**: 6 - Months
- **T5**: 12 - Months

**Baseline Clinical Assessment of Psychopathology**

- **151**: Intervention
- **149**: Control

**Project 2: Prevention**

- **778**: Clinical Assessment of Psychopathology
- **304**: Clinical Assessment of Psychopathology
- **607**: Clinical Assessment of Psychopathology
- **448**: Clinical Assessment of Psychopathology
1.6.2
Project II: Prevention

From September 2007 to March 2009, a RCT was carried out with the aim of testing the effectiveness of a web-based prevention programme for PTSD. A personal log-in code provided access to the intervention website for intervention group patients who were instructed to perform the intervention whenever they wanted within the first month of their injury. Patients in the control condition were not offered any intervention, but had access to usual care, as had intervention group patients. Baseline and follow-up clinical assessments of current psychopathology were similar to those in Project I (see Figure 1.1). Details of the Trauma TIPS internet intervention and results from the RCT on the effectiveness of the program for the prevention of PTSD are described in Chapters 4, 5 and 6.

1.7 Research questions and outline of thesis

The focus of this thesis is on the prediction and prevention of psychological symptoms, especially PTSD symptoms, as a consequence of traumatic injury. The aims of the studies described in this thesis are:

1. to investigate the predictive role of acute post-injury cortisol and DHEAS for acute and chronic PTSD (Chapter 2);

2. to examine the diagnostic accuracy of three early screening instruments for 6-month PTSD (Chapter 3);

3. to develop and test the effectiveness of a web-based early psychological intervention to prevent PTSD in injured trauma survivors (Chapters 4, 5, and 6);

4. to investigate the association between early pharmacotherapy within the initial 48 hours of injury and PTSD at 6 weeks and within the first year after trauma (Chapter 7).

In Chapter 8 (Discussion), I summarize and discuss the results of the studies, the clinical implications and directions for future research.