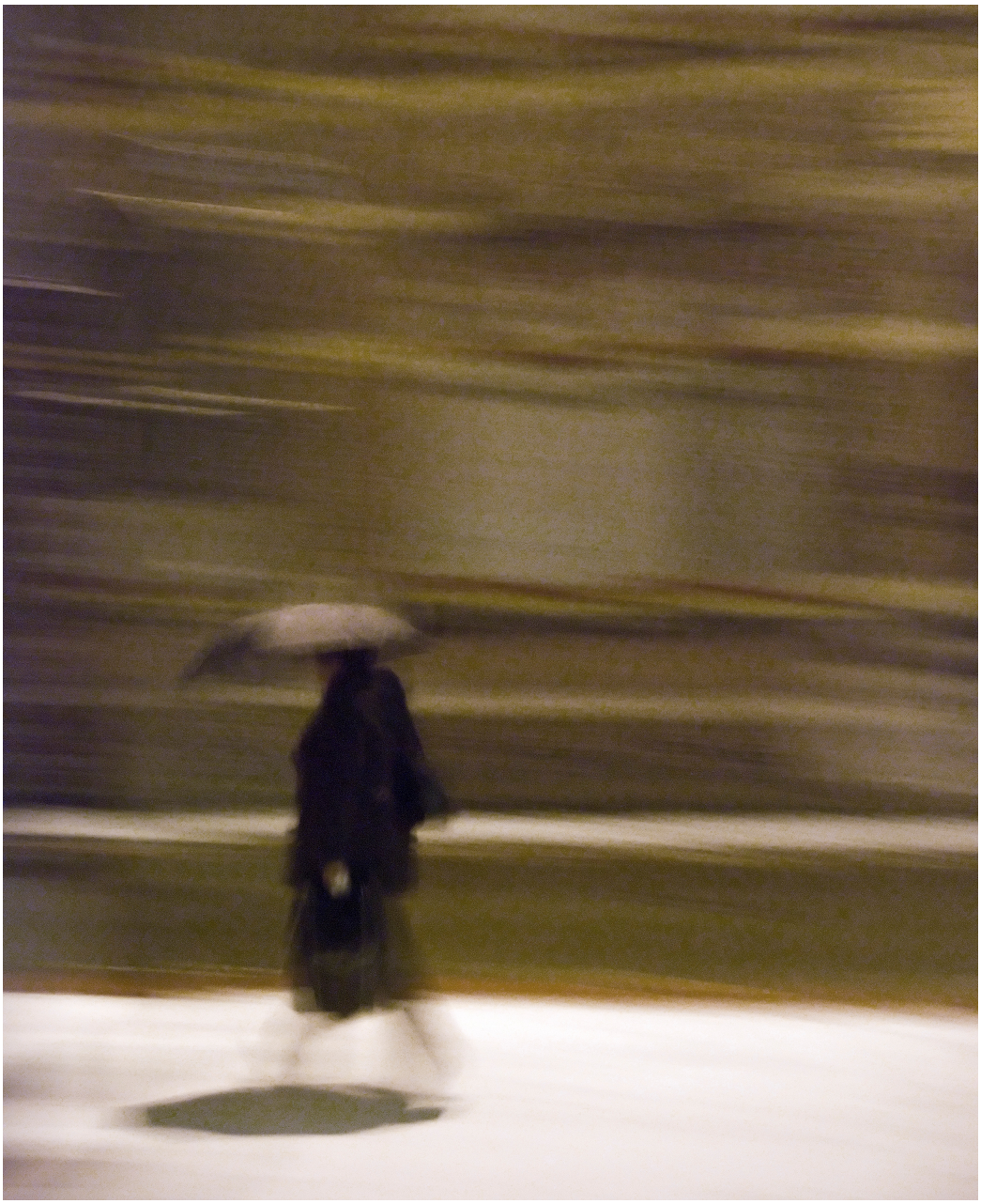
The classification of post-traumatic stress disorder as a disorder of memory based on the current understanding of its pathogenesis



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Preface

Last spring I took a research course in the field of neurosciences. The course, which consisted of 6 weeks of practical laboratory work in the lab of prof. Benno Roozendaal, was my first real introduction to fundamental biomedial research. Although I had been working with some scientific literature in the preceding two and a half years of my bachelor, my stay at the Department of Neuroscience together with a fellow student, gave me an opportunity to learn more in depth about a single subject; memory.

The research I encountered sparked my curiosity and made me want to dive deeper into the neurosciences in general and the field of memory in particular. At the same time I had a gnawing feeling about a question that had come up in my mind as I was reading through some of the literature the professor had provided me with. What does this research imply? What are the practical applications of fundamental research? As I moved on I started to realize that speaking of 'practical applications' and 'fundamental research' in one sentence is a contradiction in terminus. People who are involved in fundamental science take their curiosity as a starting point and not some concrete (medical) problem. Any yield for clinical use should be considered spin-off.

At the same time, the research is performed in a certain social context. Most research requires the use of animal experimentation, which at the end of the day is a political choice. Because of this, researchers are forced to show that their results are expected to have some utility. In the Netherlands 12 percent of the GDP is spent on healthcare. This also creates an economic pressure to find solutions for medical conditions. In my view, it is also a moral obligation of those who study the human body, to consider if their research could be beneficial to people. As a result of the social interdependency and the relation to medical practice of biomedical sciences, almost no research is truly fundamental as is the case with theoretical mathematics for example. In my interpretation, it should instead be placed in an intermediate model of 'from bed to bench and back'.

As a problem travels from bed to bench, it is split up in many small pieces as fundamental scientists pick it up. Eventually when the pieces of the puzzle are starting to fit into a comprehensive model, the model travels back to the clinic where it finds applications. Although the process is slow, may take decades and involves many dead ends, it does take place.

The course I took made me contemplate my potential (future) role in this cycle. At the time it was uncertain for me if my dream of becoming a doctor would be fulfilled. Nevertheless I was certain about my preference for the more clinical side of medical science. I now know that I will become a physician, which makes this question even more compelling. I am under the impression that researchers and doctors are sometimes troubled in their communication. Researchers may not know enough about clinical reality or doctors possibly do not always understand research. I hope that in the future I could be a link between the bench and the bed by trying to understand a bit of both worlds. Therefore I decided to look for subject for my thesis that was in line with this aspiration.

Introduction

After facing a severely distressing experience or trauma people are said to be 'dealing' or 'coping' with whatever they encountered. Whenever the loss of life involved the term 'mourning' is also frequently used. Regardless of its name, it is considered normal for people who have sustained some form of (psychological) trauma to go through a period of time during which they psychologically recuperate from the trauma and learn to adapt to the changes it has brought to their life. Symptoms like depression, fear, extreme emotion and avoidance of trauma related stimuli are thought to be normal during this period. The result of this 'coping' process is expected to enable the person to let go the trauma and return to normal life. Unfortunately, some people who go through trauma do not recover and are persistently affected by it. In this case they may be diagnosed with Post Traumatic Stress Disorder (PTSD), is a psychiatric disorder that is currently classified as an anxiety disorder.

At this point in time, the knowledge of the mechanism underlying the pathogenesis of PTSD is very extensive in comparison to other psychiatric diseases: "Post Traumatic Stress Disorder (PTSD) promises to be one of the first acquired psychiatric disorders to be characterized, and ultimately treated, rationally; that is, on the basis of an identifiable pathophysiologic mechanism." (Layton & Krikorian, 2002).

The authors that made this statement bring up two main arguments to support it. First they say, "The proximal cause [of PTSD] is specifiable and potentially observable from without". The following argument is that "knowledge regarding the neurobiology of memory has achieved a level that permits increasingly accurate characterisation of the neurophysiological mechanisms induced by extreme aversive emotional stimulation."

The aim of this thesis is to investigate the classification as an anxiety disorder in relation to what is currently known about the etiology of PTSD. Therefore the research question is:

Is the classification of PTSD as an anxiety disorder ratified by what is currently known about its pathogenesis?

Sub questions are:

1. How is PTSD defined and diagnosed?
2. What is the role of fear and anxiety in PTSD?
3. What is the role of memory in PTSD?
4. What is the role of sleep in PTSD?
5. What therapies are currently available and what is their efficacy?

Because the subject is on the interface of psychology, psychiatry and neurosciences, an interdisciplinary approach will be necessary to understand all aspects of the disorder. This thesis is a (non-systematic) literature study to investigate these questions. After providing a definition of PTSD, research from different perspectives is reviewed. These include the role of anxiety, memory and sleep.

The classification of PTSD as an anxiety disorder and the current understanding of its pathogenesis.

Definition and diagnosis

It has long been known that exposure to trauma can cause symptoms of stress and anxiety. The cluster of symptoms occurring in some people who go through trauma was named “Shell shock” during World War I because it was believed to be the result of repeated exposure to heavy artillery. After the world war ended, interest in the syndrome faded until the start of the second world war. As clinicians realized it was the result of extreme combat induced stress, it was variably named traumatic war neurosis, combat fatigue, battle stress and gross stress reaction (Andreasen, 2010). Although most descriptions are of the effect of traumas sustained during wartime, some early reports of post traumatic stress after civilian traumatic events are known. An example is the case study of the Cocoanut Grove fire, the largest nightclub fire in American history, by Adler in 1943. She studied over 500 survivors of the disaster and described symptoms that would now be called PTSD.

The psychiatric diagnosis of post traumatic stress disorder (PTSD) was only first defined as such by the American Psychological Association (APA) in 1980 with the appearance of the third edition of the Diagnostic and Statistical Manual (DSM-III). The establishment of the diagnosis at that time was no coincidence, research on the effect of traumatic stress was boosted during the time of the Vietnam war (1955-1975), when many veterans returned severely traumatized from the battlefield (Andreasen, 2010). While the scientific evidence for the existence of PTSD as a psychiatric disorder resulting from trauma was already quite strong at the time it was first defined, its institutionalization was politically unwanted (Lowe et al, 2006). Acknowledging that combat experience could cause a mental disorder did not fit the tough image of the army and could lead to legal claims.

In the most recent edition of the DSM, the DSM-IV, PTSD is defined as when the memory of a traumatic experience causes great discomfort, is persistently re-experienced, causes avoidance of stimuli associated with the trauma and numbing of general responsiveness and has left the patient with persistent symptoms of increased arousal. (For a full overview of the diagnostic criteria see box 2). It can be severely disabling resulting in the loss of employment, relationships and quality of life and has an estimated lifetime prevalence of 8%. It has a very high co-morbidity with over 50% of patients suffering three or more coexisting psychiatric disorders (DSM-IV, 2000; Kessler et al, 1995). Studies show that exposure to trauma causes PTSD in 25-30% of people, although some specific types of trauma, like rape, are associated with higher rates (Kessler et al, 1995) The question why some people develop PTSD and others do not, could be very important towards a better understanding of the disorder.

PTSD is categorised under the anxiety disorders and in the literature several subtypes of PTSD are mentioned. The DSM-IV uses the division between an acute type, a chronic type and a type with delayed onset. Categorization by single- or multi trauma PTSD and combat or civilian PTSD are also common referring to the nature of the trauma underlying the disorder. Amongst others, experiences of combat in the military and different forms of assault or abuse in the civilian world are the main causes of PTSD (box 1).

Causes of PTSD:

- Military combat
- Violent personal assault
- Natural and man-made disasters
- Severe motor vehicle accidents
- Rape
- Incest
- Childhood sexual abuse
- Diagnosis of a life-threatening illness
- Severe physical injury
- Hospitalization in an intensive care unit (ICU)
- Other severely traumatic experiences

Box 1. *Causes of PTSD,* adopted from Ciechanowski et al, 2010

Diagnostic criteria for 309.81 Posttraumatic Stress Disorder

A. The person has been exposed to a traumatic event in which both of the following were present:
    1. the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others
    2. the person's response involved intense fear, helplessness, or horror. **Note:** In children, this may be expressed instead by disorganized or agitated behavior

B. The traumatic event is persistently reexperienced in one (or more) of the following ways:
    1. recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions. **Note:** In young children, repetitive play may occur in which themes or aspects of the trauma are expressed.
    2. recurrent distressing dreams of the event. **Note:** In children, there may be frightening dreams without recognizable content.
    3. acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated). **Note:** In young children, trauma-specific reenactment may occur.
    4. intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event
    5. physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event

C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following:
    1. efforts to avoid thoughts, feelings, or conversations associated with the trauma
    2. efforts to avoid activities, places, or people that arouse recollections of the trauma
    3. inability to recall an important aspect of the trauma
    4. markedly diminished interest or participation in significant activities
    5. feeling of detachment or estrangement from others
    6. restricted range of affect (e.g., unable to have loving feelings)
    7. sense of a foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span)

D. Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following:
    1. difficulty falling or staying asleep
    2. irritability or outbursts of anger
    3. difficulty concentrating
    4. hypervigilance
    5. exaggerated startle response

E. Duration of the disturbance (symptoms in Criteria B, C, and D) is more than 1 month.

F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

Acute: if duration of symptoms is less than 3 months

Chronic: if duration of symptoms is 3 months or more

Specify if:

With Delayed Onset: if onset of symptoms is at least 6 months after the stressor

Box 2. *Diagnostic criteria for PTSD,* source: DSM-IV

Pathogenesis of PTSD

As mentioned before, the DSM-IV classified PTSD under the anxiety disorders. After discussing current views on the etiology of PTSD, I will suggest that this classification may not be in accordance with these views. In order to decide whether or not PTSD is an anxiety disorder, we first need a clear definition of anxiety disorders and of anxiety. In this thesis the term 'anxiety disorder' will be defined as those disorders in which fear or anxiety is the most prominent symptom (Gray, 2007). Although fear and anxiety can be used as synonyms, fear is more used when the feared stimulus or event is specific and present, and anxiety is more often used when the stimulus or event is vague, not identifiable or in the future (Gray, 2007). Fear and anxiety are emotions that can be continuous or transient. So the question is; Is PTSD a disorder in which fear and anxiety are the most prominent symptoms? If anxiety is not the most prominent factor underlying PTSD, then what is?

The role of fear and anxiety in PTSD

Fear conditioning (figure 1) is one of the models that is being used to explain the pathogenesis of PTSD. It is based on the Pavlovian learning theory of classical conditioning. This theory explains how an association can be made between a neutral stimulus and a stimulus that causes arousal. The neutral stimulus is also called the conditioned stimulus (CS) and can be anything like an object, light or a sound. The arousing stimulus is also called the unconditioned stimulus (US), examples are an electrical shock (negative) or getting a food reward (positive). The response of arousal that follows the US is called the unconditioned response (UR). The association is made by repeatedly presenting the CS followed by the US. When the association between the CS and US is established, the presentation of the CS by itself will induce the same arousal. The arousal resulting from the CS only is called the conditioned response (CR). When the CS is presented repeatedly without being followed by a reward or punishment, the conditioned response to the conditioned stimulus will fade and over time no response to the CS will be seen. This fading process, called extinction, is no passive 'forgetting' but actually a form of learning. When the CS is no longer followed by the US, it is learnt that the CS does no longer have predictive value.

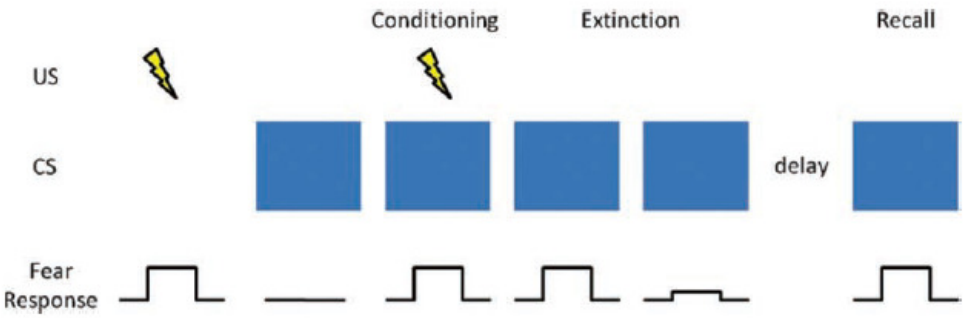


Figure 1. *Fear conditioning, adopted from Koenigs & Grafman, 2009.*

In the case of fear conditioning, a fear inducing event (US) is coupled to neutral stimuli like locations, sounds, objects, etcetera (CS). The fear conditioning model is widely used in animals for research on anxiety disorders, including PTSD. If we apply this model to the etiology of PTSD, some symptoms of the disorder can be explained. The avoidance of stimuli related to the trauma fits the model very well. This is also seen in other disorders like phobias, where fear conditioning is believed to be important. The model is also applicable for the increased arousal caused by the memory of the trauma or trauma related stimuli (conditioned response). The amygdala is considered to play a central role in emotion (le Doux, 2003). The prefrontal cortex is seen as the area for reason, planning and higher order regulation of emotion. It has a strong inhibitory influence on fear (Amat et al, 2005). The

activity of the basolateral nucleus of the amygdala (BLA) is regulated by the medial prefrontal cortex (mPFC) (Milad et al, 2006). The mPFC is primarily involved in higher-order cognitive functions such as thought, decision-making and working memory (de Quervain et al, 2009; Ramnani et al, 2004). Koenigs and Grafman hypothesized in 2009 that the amygdala and the mPFC mutually inhibit each other balancing out in the healthy condition. In PTSD, they argue, the mPFC is less active and does not inhibit the amygdala as much, which in turn might become hyperactive. This hyperactivity would cause PTSD symptoms, as well as further mPFC inhibition, maintaining the disorder. They try to support this hypothesis in various ways, of which one is particularly interesting. Using data from the Vietnam Head Injury Study (VHIS) they selected veterans that suffered either an amygdala lesion, a mPFC lesion, a lesion not in the mPFC/amygdala or with no brain damage. They found that the incidence of PTSD among veterans with amygdala lesions was 0%. This shows that the area is crucially involved in the development of PTSD and could support their theory. However, the mPFC group showed a decrease in the incidence compared to no brain damage. This make the hypothesis of mutual inhibition misbalance as a cause of PTSD rather unlikely because if it were true, mPFC lesions would cause PTSD incidence to increase. Instead, the data suggests that mPFC hypoactivity is a result of PTSD rather than a cause. This would be in line with the observation from fMRI studies that the mPFC is hypoactive in PTSD patients but lesioning of the mPFC does not cause PTSD. At least the results make clear that one should caution to interpret associations found with fMRI as causality.

Fear conditioning has some limitations in explaining PTSD. First of all, many patients suffering from PTSD experience ‘flashbacks’, dreams or other intrusive memories of the trauma. This unwanted mental exposure that causes great distress is not explained by fear conditioning. Also, the persistent state of arousal, even in the absence of trauma related stimuli, cannot be explained by this theory. Finally, impairment of memory for events directly preceding or following the event and the dissociation of the memory is widely found as a symptom of PTSD. (Marshal et al, 1999; van der Kolk et al, 1995) These alterations in the episodic memory cannot be explained by fear conditioning (Layton & Krikorian, 2002). It is also notable that fear conditioning is a form of learning. So if the model would be the essential mechanism of PTSD, it is not only anxiety that plays a role (like in a panic disorder) but memory is also involved.

The role of Memory in PTSD

Hence, in the view of several different authors, PTSD is more a disorder of memory than one of anxiety (de Quervain et al, 2009; Layton et al, 2002; Elzinga et al, 2002). It is well recognized that emotionally arousing experiences are remembered better than neutral events (Roozendaal et al, 2009). Experiencing a stressfull event initiates a physiological stress response (figure 2). In this response the hypothalamus stimulates the adrenal cortex through a cascade of signals to secrete cortisol (corticosterone in rodents) and adrenalin. This is called the hypothalamic-pituitary-adrenal (HPA) axis. Also the sympathetic branch of the autonomous nervous system is activated. Cortisol in turn binds to the glucocorticoid receptor that is present in many areas of the brain. Because cortisol is a lipid hormone it can easily cross the blood-brain barrier and enter the brain. Glucocorticoids enhance learning, but also extinction (Yang et al, 2006). They however inhibit the retrieval of memories (de Quervain, 2009). This was concluded from the observation that a post-training injection of glucocorticoids in rodents enhanced performance in subsequent testing whereas pre-testing injection impairs performance. Adrenalin causes the release of noradrenalin through stimulation of the vagus nerve.

The amygdala plays an important role in the effect of glucocorticoid enhancement of memory consolidation of emotionally arousing experiences (de Quervain et al, 2009). Studies in animals have shown that lesions of the BLA block the memory enhancing effect of systemic glucocorticoid injections (Roozendaal et al, 1996). In addition, there is evidence that

glucocorticoids require noradrenergic activation within the BLA to influence memory (de Quervain et al, 2009). A blockade of the β-adrenoreceptor in the BLA blocks the memory enhancing effects of systemically administered glucocorticoids (Roozendaal, 2006). For an overview see figure 3.

Glucocorticoids have effects on memory in many brain regions. The hippocampus is crucially involved in memory. An exceptional number of experiments have been done that show that the hippocampus is required for spatial- and episodic memory formation, storage and retrieval (Corkin, 2002; Sacchetti et al, 1999; Morris et al, 1982; Moser et al, 1992). Glucocorticoids also affect the hippocampus. The injection of a glucorticoid receptor (GR) agonist in the hippocampus enhances memory for spatial learning tasks. This effect is not seen in animals with BLA lesions (Roozendaal et al, 2006). These results suggest that the BLA is not the site of storage for memory but rather has a modulatory effect on other areas implicated in memory.

The medial prefrontal cortex (mPFC) is also implicated in the regulation of memory. The mPFC is known to have a strong fear reducing influence on behaviour (de Quervain et al, 2009; Amat et al, 2005) through inhibition of the amygdala. This inhibitory effect is known to be reduced by stress (Lyons et al, 2000). The injection of a GR agonist in the mPFC after training in an inhibitory avoidance paradigm raised levels of phosphorylated Extracellular Signal-Regulated Kinase (pERK) in the BLA (de Quervain et al, 2009). pERK is associated with memory formation (Kobayashi et al, 2009) so these findings suggest that GR activation within the mPFC may enhance memory consolidation via a loss of inhibitory control over the BLA (de Quervain et al, 2009)

All in all it can be said that glucocorticoids enhance memory formation but impair memory retrieval (de Quervain et al, 2009).

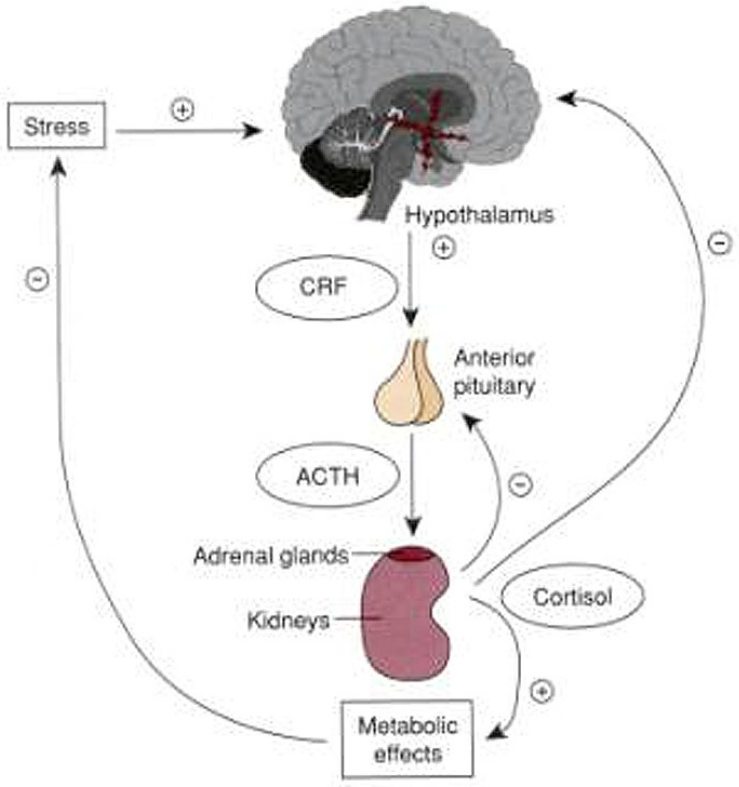


Figure 2. *Stress response, the release of cortisol*

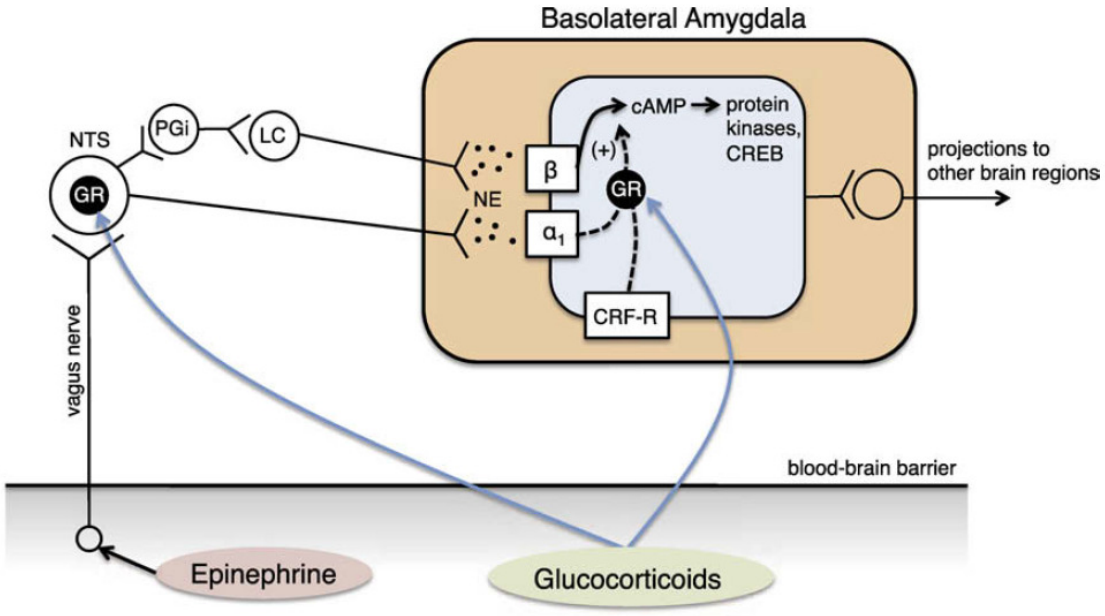


Figure 3. Adopted from de Quervain et al, 2009.

Supposing that PTSD is in fact a memory disorder, the idea that PTSD is a condition in which the effect of stress on memory turns pathological is quickly raised. Especially considering the evidence for the role of stress in memory brought up in the previous section. What is the evidence for this proposition?

First of all, Memory consolidation and peritraumatic amnesia are not maladaptive mechanisms. Enhancing the detail and episodic 'contrast' of arousing experiences help an organism learn from the experience. Nevertheless, prolonged stress is known to cause damage to the hippocampus and is associated with reduced hippocampal volume (Bremner, 1999). Although several studies make this observation, critics have pointed out that memory impairments could be a result of acute cortisol levels at the time of testing rather than a chronic effect. Moreover, it is also questioned whether cortisol really affects hippocampal volume (Coluccia et al, 2008). The incidence of alzheimer's disease is elevated among war veterans suffering from PTSD (Yaffe et al, 2010). Whether this is specific for PTSD or a result of general hippocampal damage remains unclear.

de Quervain et al (2009) present a model for the role of glucocorticoids in the pathogenesis of PTSD (figure 4). Their argumentation, based on extensive experimental research, is as follows. Glucocorticoids are known to enhance memory consolidation but impair retrieval. It is assumed that traumatic experiences lead to acutely elevated cortisol levels, contributing to enhanced consolidation of the traumatic memory. This hypothesis brings up the suggestion to block the glucocorticoid receptor directly after trauma is sustained as a preventive treatment. However, apart from practical difficulties, there is evidence that reduced cortisol levels after trauma are actually associated with increased development of PTSD (Yehuda et al, 1998). As a traumatic memory is continuously re-experienced, it's reactivation causes further consolidation through long term potentiation, lowering the threshold for retrieval. This creates a vicious cycle. According to the authors, glucocorticoids may enhance the initial consolidation of the memory, but the reduction of cortisol in a later stage allows the disinhibition of memory retrieval. This suggest that glucocorticoids could actually interrupt the vicious cycle of re-experiencing through their impairing effect on retrieval. Whereas some authors report the observation of depressed cortisol levels in PTSD patients as an anomaly (Nemeroff et al, 2006), it is in accordance with this model. First tests with low-dose cortisol administration to PTSD patients have even found a positive effect outlasting treatment duration (Aerni et al, 2004).

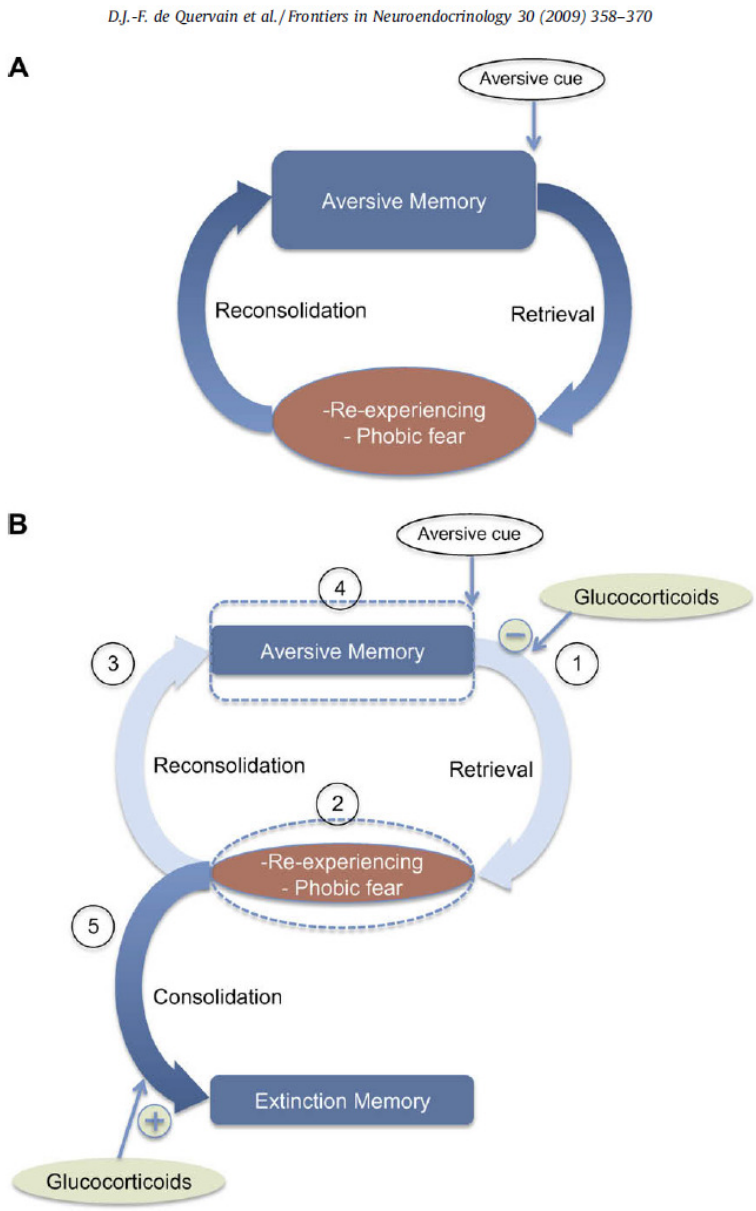


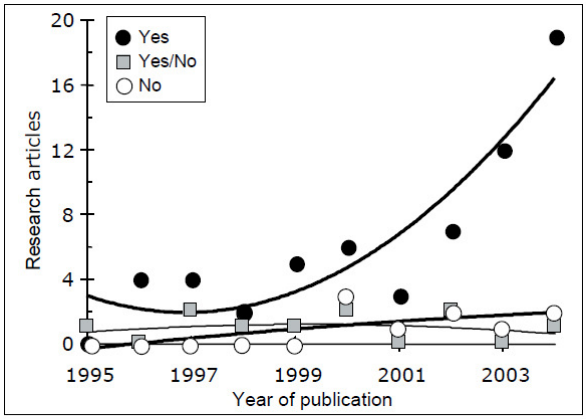
Figure 4. *Model for the role of glucocorticoids in PTSD.* Adopted from de Quervain et al, 2009.

The role of sleep in PTSD

Sleep disturbances are a frequent symptom in PTSD (Otte et al, 2005). Also the observation that the development of PTSD is associated with a more fragmented REM sleep (Mellman et al, 2002) suggests a role for sleep in the disorder. It has been suggested that HPA alterations are a cause of impaired sleep. Cortisol levels were found to have an inverse relation with delta sleep duration in PTSD patients (Otte et al, 2005). It has also been hypothesized that disrupted sleep in PTSD prevents proper processing of the traumatic memory preventing its integration with older, related memories (Paller et al, 2004). A paper published in 2002 by Rober Stickgold presents a putative mechanism of action of Eye-movement desensitization and reprogramming (EMDR) therapy. The proposition of the paper is that the integration of traumatic memories into long-term memory in PTSD fails. The migration from short-term to long-term memory, he claims, takes place during REM sleep. The bilateral stimulation in EMDR would induce a REM-like state facilitating the failing integration. Francine, inventor of the therapeutic technique, also believes there is a relation between her therapy and sleep (Shapiro, 1989; Shapiro, 1996). Although EMDR should be taken seriously for it is effective (Seidler, 2006), there is a total lack of experimental evidence to support such a theory.

Considering the evidence for PTSD as a disorder of memory, a better understanding of the role of sleep in memory could lead to a better understanding of the disorder. Two articles illustrate the heated debate on this topic. In 2000, Vertes and Eastman published a review paper arguing that sleep has no role in memory whatsoever. The reaction of Stickgold and others in 2005, in which they directly address mister Vertes, is slightly fanatic. One of the figures included in this reaction nevertheless is rather convincing in supporting a role for sleep in memory (figure 5). However, a paper by Siegel of 2001 points out that sleep deprivation methods for investigating the role of sleep in memory are highly stressful, so the effects of stress and sleep become inseparable for the observer. This is very important considering the role of stress in memory formation (Roozendaal et al, 2009) as discussed before.
While sleep deprivation is a contested method for research on sleep and memory, there is a paper that uses a different approach. In 2007, Rasch and others showed that re-exposing human subjects to a rose scent during slow wave sleep that was contextually present during a learning task, improved memory consolidation. Concurring with these findings, functional magnetic resonance imaging revealed significant hippocampal activation in response to odor re-exposure during SWS (Rasch et al, 2007).
This observation is a proof of concept that processing of memories during sleep can be improved by reactivating memories through external cues and it may be of interest for therapeutic use in PTSD (Stickgold, 2007; Rasch et al, 2007).

There are several authorities that consider the relation between sleep and memory convincing (Kopasz et al, 2010; Walker et al, 2004). However, almost nothing is known about the underlying mechanism. As correlations between certain qualities of sleep (e.g. REM sleep) tell us nothing about causality, at this point it is not possible to fit sleep into existing models for memory and/or PTSD. Also, it must be noted that sleep could also play a role in PTSD but not in memory.



—Research articles on sleep and memory. The number of papers cited in PubMed1 for each year from 1995 to 2004 that contained both "sleep" and either "memory" or "learning" in their titles, whose abstracts indicated support for (filled circles), no support for (open circles), or ambiguous support (gray squares) for sleep-dependent memory consolidation. Solid lines are second order polynomial fits to each curve.

Figure 5. *Articles dealing with sleep and memory,* adopted from Stickgold et al, 2005.

Available therapies for PTSD and their efficacy

For the treatment of PTSD several options are available of which psychotherapy in different forms is believed to be the most effective. (Cukor et al, 2010)

Cognitive Behavioral Therapy (CBT) has the strongest evidence base as is illustrated by several large meta-analyses and reviews. These studies underline the conclusion that the symptoms of patients receiving CBT significantly improve compared to patients who are on a waitlist. This shows that CBT works better than doing nothing. It is however not superior to other effective PTSD treatments. (Bisson et al, 2007a; Bradley et al, 2005, Robertson et al, 2004; Bisson et al, 2007b; Cukor et al 2010) Two types of CBT are most often used, prolonged exposure therapy (PE) uses repeated (imaginal-) exposure to the trauma and is based on the learning model. According to this model, repeated exposure to a conditioned stimulus without the presence of the unconditioned stimulus should induce extinction of the association between the two stimuli. Another variant of CBT is cognitive processing therapy (CPT). CPT focuses on the cognitions a patient has about the traumatic event en tries to restore the balance between emotions and cognitions and between positive and negative cognitions. (Cukor et al, 2010).

EMDR has been found to be equally effective as CBT (Seidler, 2006). The evidence base however is narrower than that of CBT and a satisfactory model for its efficacy is yet to be found. Because it is a relatively new treatment and much is still unclear about it's mechanism some consider it controversial (Perkins & Rouanzoin, 2002). Nevertheless it is widely used by clinicians around the world in the treatment of PTSD (Bisson et al, 2007).

In the United states as well as in the Netherlands only two drugs are registered for the psychopharmacological treatment of PTSD. Sertraline and paroxetine, both selective serotonin re-uptake inhibitors (SSRI's), are registered with the Food and Drug Administration (FDA) and the Dutch 'College van Zorgverzekeringen' (CVZ) for PTSD. The effect of these drugs on PTSD symptoms is limited and reverses when the medication is stopped. (Davidson et al, 2001; Berger et al, 2009) but see (Marshall et al, 2001; Vermetten et al, 2003). All in all no satisfactory drug treatment for PTSD is available at this time.

Other therapies that have been investigated for their efficacy with PTSD have been found to be ineffective. Examples are supportive therapy, non-directive counseling, psychodynamic therapy and hypnotherapy (Bisson et al, 2007a; Robertson et al, 2004). The advice to do sports in order to decrease arousal can be found in many non-scientific sources. After extensive searching, I have been able to fiend one review on this issue. Lawrence et al found 5 studies on the effects of sports on PTSD, however, none of them met their inclusion criteria. It can be concluded from this that the claim that doing sports helps PTSD patients is scientifically unsupported. Nevertheless, the US Army is running a special program, named 'Warrior Adventure Quest', that aims to help PTSD veterans by doing sports (Channel one News, 2011).

Conclusion and discussion

The present thesis reviewed papers from studies in both animals and humans to investigate if the current understanding of the etiology of PTSD supports the current classification of PTSD as an anxiety disorder.
In the past, a fear-conditioning model was used to explain the syndrome seen in PTSD. However, progress made in the field of memory research has changed this view. It is now believed that the mechanism underlying PTSD is a problem of memory. There is an important role for cortisol and adrenalin, both substrates of the physiological stress response, in the consolidation and retrieval of memory. It has been suggested that sleep may play a role in this process. However, no evidence was found to support this hypothesis. Cognitive behavioural therapy and eye-movement desensitization and reprogramming are moderately effective treatments, but lack a rational explanation for their mode of action. The conclusion is that, with the current understanding of its pathogenesis, PTSD is not an anxiety disorder. Moreover, because fear or anxiety is not the most prominent symptom it also doesn't fit the definition of anxiety disorders as derived from psychology. Based on the literature reviewed by this thesis, it would better to define PTSD as a memory disorder.

Although much is already known about the etiology of PTSD, the suggestion of Layton and Krikorian that it is close to being fully understood is false. Very much still remains unknown. There are several limitations to PTSD research in humans as well in animals. Although it is now possible to look 'inside' the human brain using fMRI, opening the black box, it will never be possible to randomly assign people to the condition for ethical reasons. While PTSD may be a single cause acquired psychiatric disorder, susceptibility and resilience is highly variable among the general population, studies may easily be confounded by such factors (Yehuda, 2006). Because the problem is so multifactorial, it can never be solved from one standpoint (e.g. neuroanatomy, epigenetics, psychology) alone.

There are two major problems with animal studies. Firstly, there is currently no good animal model for the simulation of PTSD. Because of that, researchers rely on the generalization of observations from models like fear conditioning to work on a theoretical model for PTSD. Secondly, because animals live under strictly controlled conditions, it is questionable whether any model could approach the complex social and cultural context that patients live in. While today witnessing murder could well cause PTSD, the Romans took their children to see gladiator fights for entertainment and no PTSD was reported. This shows that there are all kinds of emotional and contextual qualities to aversive experience that are hard to simulate.

Generally speaking, the focus of most neurobehavioral research is on relating specific areas or substances to specific types of behavior. While this could potentially lead to great treatments like deep brain stimulation, knowing the locus is not the same as knowing the process. In other words, knowing that something happens in the hippocampus, does not tell you how it happens. These two things should not be confused.

For future research I would make the following recommendations. Firstly, PTSD research is limited by the available techniques. To get ahead, it is essential to find improved (animal) models for research on PTSD. Although difficult since animal studies cannot inform us about the impact of trauma on verbal, declarative memory and the meaning and consequences of trauma (Elzinga & Bremner, 2002), work is already being done on this issue (Cohen & Yehuda, 2011; McFarlane et al, 2002). Secondly, having a more interdisciplinary approach could help. If scientists from the fields of psychiatry, psychology, neurosciences and artificial intelligence were to work together, this could lead to a more complete understanding of all aspects of PTSD. It would for example be interesting to look why available therapies are effective. Experience of psychologists could also help in the development of an animal model.

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Figures

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Figure 2: http://www.montana.edu/wwwai/imsd/alcohol/Vanessa/vwhpa_files/image003.jpg