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Post-Traumatic Stress Disorder: Neurobiology and Effects of Eye Movement Desensitization and Reprocessing

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ABSTRACT

The aim of this study was to evaluate a new psychotherapy method, eye movement desensitization and reprocessing (EMDR) in the treatment of post-traumatic stress disorder (PTSD) and to study the biological reactions in PTSD during a script-driven symptom provocation.

PTSD is a disorder that may occur after a major psychological trauma. It is characterised by the phenomenon of reliving, bringing the person back to the sensations and reactions that prevailed during the traumatic event. This intrusion is often followed by avoidance of trauma-related reminders, irritability and emotional numbing. The disorder is longstanding to chronic and is a major contributor to psychiatric morbidity.

In this study drivers and other personnel in the Stockholm public transportation system participated. The subjects had experienced a person under train accident or assault at work. Fifty-three subjects, one-third women, participated and were diagnostically evaluated as PTSD or non-PTSD subjects. They were assessed with interview based and self-evaluation symptom scales. In comparison these two groups differed sharply in the scores on psychiatric symptoms, social functioning and well-being. The trauma load was higher in the PTSD group as compared to the non-PTSD group.

The 21 subjects diagnosed with PTSD were randomly assigned to a treatment group and a waiting-list control group. The primary outcome variable was remission of PTSD. The treatment with EMDR followed the standard protocol. The therapy was given in five one-and-a-half hour sessions. When the therapy group was compared with the waiting list group there were significant differences in remission rate (67%, 11%, respectively) and in the interview based scales.

Subsequently, also the waiting-list group received therapy and 20 subjects completed therapy which was assessed immediately after treatment, at eight months and at 35 months. The initial positive results remained and were consolidated (remission rate 65% at 35 months). There was also significant improvement over time in social functioning and work capacity. The effect size comparing scores on the Global Assessment of Functioning (GAF) scale before treatment and at 35 months, was for the total treatment group 1.3 and in the immediate remitters 3.0.

Heart rate and blood pressure increased significantly during the symptom provocation, both in the PTSD and the non-PTSD group and also both before and after therapy, irrespective of outcome. This was evaluated as a reaction to a fear signal which was not identical with the anxiety reaction that characterised the PTSD group.

The total group reacted after the symptom provocation with increased blood flow distribution in the right hemisphere and this was more pronounced in the PTSD subjects and even more in the assaulted subjects. The PTSD group showed higher activity in limbic areas involved in memory and emotion. After therapy there was a trend towards normalisation of tracer distribution with a decrease in limbic and an increase in pre-frontal areas. There was no difference in the size of the hippocampi in the PTSD and the non-PTSD group, but such a difference was observed comparing the remitters with the non-remitters.

Summarising, we found that EMDR was effective in ameliorating PTSD symptoms in this sample and we also found physiological differences in PTSD subjects as compared to non-PTSD subjects regarding regional cerebral blood flow.

LIST OF PUBLICATIONS

The present thesis is based on the following studies, which will be referred to in the text by their Roman numerals.

- I Marco Pagani, Göran Högberg, Dario Salmaso, Berit Tärnell, Alejandro Sanchez-Crespo, Joaquim Soares, Anna Åberg-Wistedt, Hans Jacobsson, Tore Hällström, Stig A. Larsson, Örjan Sundin. Regional cerebral blood flow during auditory recall in 47 subjects exposed to assaultive and non-assaultive trauma and developing or not posttraumatic stress disorder.
European Archives of Psychiatry and Clinical Neuroscience 2005;255:359-365.
- II Göran Högberg, Marco Pagani, Örjan Sundin, Joaquim Soares, Anna Åberg-Wistedt, Berit Tärnell, Tore Hällström. On treatment with eye movement desensitization and reprocessing of chronic post-traumatic stress disorder in public transportation workers – a randomized controlled trial. *Nordic Journal of Psychiatry* 2007;61:54-61.
- III Göran Högberg, Marco Pagani, Örjan Sundin, Joaquim Soares, Anna Åberg-Wistedt, Berit Tärnell, Tore Hällström. Treatment of post-traumatic stress disorder with eye movement desensitization and reprocessing: outcome is stable in 35-month follow-up. *Psychiatry Research*. In press 2008.
- IV Marco Pagani, Göran Högberg, Dario Salmaso, Davide Nardo, Örjan Sundin, Cathrine Jonsson, Joaquim Soares, Anna Åberg-Wistedt, Hans Jacobsson, Stig A. Larsson, Tore Hällström. Effects of EMDR psychotherapy on ^{99m}Tc-HMPAO distribution in occupation-related post-traumatic stress disorder. *Nuclear Medicine Communications* 2007;28:757-765
- V Marco Pagani, Göran Högberg, Yi Zhang, Dario Salmaso, Örjan Sundin, Jeffrey Chee Leong Looi, Alejandro Sanchez-Crespo, Anna Åberg-Wistedt, Tore Hällström, Lars-Olof Wahlund. Brain functional and volumetric analyses in occupational-related post-traumatic stress disorder. *Manuscript*.
- VI Göran Högberg, Marco Pagani, Örjan Sundin, Joaquim Soares, Anna Åberg-Wistedt, Tore Hällström. Heart rate and blood pressure in occupationally related post-traumatic stress disorder and after eye movement desensitization and reprocessing. *Manuscript*.

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LIST OF ABBREVIATIONS

ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BA	Brodmann area
BAI	Beck anxiety inventory
CBT	Cognitive behavioural therapy
CBA	Computerised brain atlas
DBP	Diastolic blood pressure
DLPFC	Dorsolateral prefrontal cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
EMD	Eye movement desensitization
EMDR	Eye movement desensitization and reprocessing
GAF	Global assessment of functioning
HAM-A	Hamilton anxiety scale
HAM-D	Hamilton depression scale
HR	Heart rate
IES	Impact of event scale
MRI	Magnetic resonance imaging
PET	Positron emission tomography
Pixel	Picture element (smallest unit of a 2D digitalised image)
PTSD	Post-traumatic stress disorder
rCBF	Regional cerebral blood flow
ROI	Region of interest
SBP	Systolic blood pressure
SCID	Structured clinical interview for DSM-IV
SDI	Social disability index
SPECT	Single photon emission computerised tomography
SPM	Statistical parametric mapping
SSP	Script driven symptom provocation
SUD	Subjective units of disturbance scale
TAQ	Trauma antecedent questionnaire
^{99m} TcHMPAO	^{99m} Tc- <i>d,l</i> -hexamethylpropylene amine oxime
WHO-10	World Health Organisation (ten) well-being index
Voxel	Volume element (smallest unit of a 3D digitalised image)
VOI	Volume of interest

BACKGROUND

During the five days spent in the village of Rouex, I was continually under our own shell fire and also continually liable to be discovered by the enemy, who was also occupying the village. Each night I attempted to get through his lines without being observed, but failed. On the fourth day my sergeant was killed by a shell. During this time I had nothing to drink or eat, with the exception of about a pint of water. On the fifth day I was rescued by our own troops while I was unconscious. At the present time I am subject to dreams in which I hear these shells bursting and whistling through the air. I continually see my sergeant, both alive and dead, and also my attempts to return are vividly depicted. I sometimes have in my dreams that feeling of intense hunger and thirst which I had in the village. When I awaken I feel as though all the strength had left me and I am in a cold sweat. For a time after awaking I fail to recognize where I am, and the surroundings take on the form of the ruins in which I remained hidden for so long. Sometimes I do not think that I thoroughly awaken, as I seem to doze off, and there are conflicting ideas that I am in the hospital, and again that I am in France. During the day, if I sit doing nothing in particular and find myself dozing, my mind seems to immediately begin to fly back to France.

Frederick Walker Mott (1919), *War Neuroses and Shell Shock*. London: Oxford University Press.

Some historical notes on trauma reactions

Early explanations of the symptoms following industrial or war trauma alternated between physical lesion theories and psychological theories. This bipartite focus has ever since accompanied the trauma study field. In descriptions of post-trauma reactions during the American civil war, symptoms such as increased heart rate and palpitations were observed and the term ‘soldier’s irritable heart’ was coined (Da Costa, 1871).

During the industrial revolution when the railways were rapidly expanding, railway accidents became a common experience. Post railway accident reactions were first studied and described by John Eric Erichsen (1866), who focused on such symptoms as insomnia, nightmares and memory disturbance. He hypothesised that chronic myelomeningitic changes in the spinal cord and the brain caused the symptoms and called the condition railway spine, but was refuted by Page (1885), who suggested a psychological origin to the complaints: “...many errors in diagnosis have been made because fright has not been considered of itself sufficient”.

In the early 19th century, so-called hysterical symptoms were attributed to possession by bad spirits, usually the devil; an interpretation that placed the burden of guilt on the sufferer. Not until the 20th century did there emerge an understanding of external causes of hysterical symptoms, which was first formulated by the physician Robert Carter (Veith, 1965). In 1892, the German neurologist Hermann Oppenheim published a study of 42 patients who had survived severe accidents. His thesis was that the traumas had produced physical micro-lesions in the brain that perpetuated

the symptoms; and in coining the term traumatic neurosis he introduced the word trauma into the understanding of reactions following devastating events. Emil Kraepelin, in his psychiatric textbook (Kraepelin, 1896), called the condition fright neurosis (“*Schreckneurose*”).

In the late 19th century the philosopher and physician Pierre Janet (1889) studied hysteria and related the symptoms to concrete traumatic experiences. In his doctoral thesis based on the study of several hundred psychiatric cases he noted: “I was led to recognize in many subjects the role of one or several events in their past life. The events, which were accompanied by a vehement emotion and a destruction of the psychological system, had left traces.” These traces were partly dissociated from ordinary consciousness in the form of subconscious fixed ideas (“*idées fixes*”) that exerted a strong influence by creating mental and somatic reactions (“*sensations mentales*”, “*sensations physiques*”) that hindered the individual from functional ability to handle novel interactions with the environment. The efforts of the individual to stop the memories and to gain control over the reactions led to considerable loss of energy and passivity. Janet described a wide spectrum of reactions, from dissociative replaying states to deep depression, subsuming the groups of active symptoms under the heading of hysteria, and the passive reactions under the heading of abulia. During World War I, the similarity between Janet’s description of reactions to civilian trauma and reactions to the war was noted by, *e.g.*, C.S. Myers (1915), who wrote about what was then called shell shock in victims of World War I: “The close relation of these cases to those of “hysteria” appears fairly certain.”

During World War II, the term battle neurosis was used and after the Nazi concentration camps, the term KZ-syndrome was coined.

Also hazards in the public transportation service of today may cause adverse reactions. Drivers may be exposed to accidents on the line where they unwittingly cause damage or death. Such so-called person under train (PUT) accidents may result in health sequelae for the drivers (Farmer *et al.*, 1992; Malt *et al.* 1993; Karlehagen *et al.* 1993; Vatshelle & Moen, 1997). In a Swedish study of 40 PUT-exposed subway drivers, from three months to one year after the accident a high rate of sick leave was reported (Theorell *et al.*, 1992).

Current definition of post-traumatic stress disorder (PTSD)

There was thus a lack of coherent diagnostic classification in the field of psychiatric trauma reactions and Kardiner (1969) commented: “It is hard to find a province in psychiatry less disciplined than this one. There is practically no continuity to be found anywhere....the literature can only be characterized as anarchic. Every author has his own frame of reference.” In the diagnostic systems reactions to trauma were described as transient stress reactions. Kardiner’s call was finally answered when the first diagnostic category of long-term psychiatric morbidity following major trauma emerged in the *Diagnostic and Statistical Manual of Mental Disorder* (DSM-III) published by the American Psychiatric Association in 1980. The diagnostic category PTSD was born and became elaborated in the subsequent versions of this manual. The current definition given by DSM-IV (1994) is presented here:

DSM-IV diagnostic criteria for post-traumatic 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 disorganised or agitated behaviour.
- B. The traumatic event is persistently relived 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 re-enactment may occur.
 - (4) intense psychological distress on 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 one month.
- F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

Acute: duration of symptoms is less than 3 months.

Chronic: duration of symptoms is 3 months or more.

Prevalence of PTSD

The National Comorbidity Survey in the United States reported a lifetime prevalence rate of 10.4% in women and 5% in men (Kessler *et al.*, 1995), an Australian national survey found a 12-month prevalence of 1.3% without gender difference (Creamer *et al.*, 2001) and a Swedish survey reported a life-time prevalence of 7.4% in women and 3.6% in men (Frans *et al.* 2005).

PTSD in psychiatric outpatient care.

Al-Saffar *et al.* (2003) selected 115 patients from a Swedish psychiatric outpatient clinic. Patients from Iran, Turkey and Arab countries of the Middle East along with a Swedish-born group of similar age and gender distribution were studied. Seventy-seven percent were exposed to multiple traumatic events. PTSD symptom criteria were met by about 55% of non-Swedish subjects and by 29% of the Swedish patients. In a study by Howgego *et al.* (2005), 29 patients from the Australian Public Mental Health Service were screened for trauma and PTSD. Seventy-five percent of the patients had been exposed to multiple traumatic events and 34% met diagnostic criteria for PTSD. These findings confirm the conclusion by Davidson that PTSD is one of the most serious and disabling psychiatric disorders (2000).

There is lifetime comorbidity with other disorders such as major depression, generalized anxiety disorder, panic anxiety disorder, phobias, and substance abuse. In a study of female subjects with PTSD such comorbidity occurred in 73% of cases (Breslau *et al.*, 1997). PTSD is one of several possible reactions to an overwhelmingly negative experience, forming part of what can be called the spectrum of trauma related disorders.

PTSD as a disorder of memory

In terms of feelings, PTSD is characterised by: (A) negative valence; (B) high intensity; (C) lack of control, and (D) low spontaneity. Memory could be defined as previous experience that exerts a present influence on the sensations and behaviour of a person. Pitman (1987) proposed: "Reliving instead of remembering in PTSD is most dramatically illustrated in the flashback phenomenon, and the reliving-remembering distinction may be a useful way to conceptualise the disorder." Upon triggers, a reliving reaction without adequate relation to present reality is evoked.

The early researcher of memory, Rickard Semon, proposed in his books *The Mneme* and *Mnemic Psychology* (1904, 1909) that memory could be studied as a phenomenon with distinct aspects; imprinting, storage (engram) and retrieval.

In imprinting, there is a very brief sensory buffer and then by activation of the entorhinal cortex and adjacent parahippocampal gyrus and hippocampus there is a short-term activation of a few minutes. After a period of about eight hours there is memory consolidation into long-term memory. But where is the engram? It seems that memory is not located in a certain area of the brain but is rather a temporal coordination of the re-activation of sensory areas that were activated at the event of imprinting. "This proposal rejects a single anatomical site for the integration of memory and motor

processes and a single store for the meaning of entities of events. Meaning is reached by time-locked multiregional retroactivation of widespread fragment records.” (Damasio, 1989). Memory can be seen as ever waxing and waning associative networks, like the Nordic light, some aspect being in the front, soon to be replaced by another set of combinations. Nadel *et al.* (2007) observed hippocampal activation in retrieval of autobiographical memories and they propose that memory retrieval is a re-encoding, *i.e.* the creation of a new memory trace.

PTSD is related to memory at the levels of imprinting, storage and retrieval. At imprinting there are strong aversive or dangerous situations and increased risk by repeated similar experiences. It seems as if the trauma reliving in PTSD becomes a new aversive memory. At the storage, the engram level, there is instability with difficulties of control and there is the memory quality of a reliving. At the level of memory retrieval there is lack of control, auto-retrieval and trigger-automated retrieval.

The goals of treatment of PTSD

Treatment aims at amelioration of symptoms; and as the key symptom in PTSD is the intrusive reliving type of memory often described as flashbacks, this kind of memory must be either extinguished or neutralised. But as even aversive experiences are important parts of the identity of an individual, the latter option is often preferred in therapy. The valence must not be changed; a bad experience is still a bad experience, but the quality of the memory must change. This means a transformation from reliving to a normal autobiographical memory. In order to achieve this, the intense here-and-now emotional quality must be dismissed, proper temporality restored and control over memory retrieval, *i.e.* both activation and deactivation, must be established. The anxiety reaction associated with trauma-related triggers must be unlearned, and replaced by new no-fear learning. Resulting from this is a larger control of memory and feelings and a more functional interaction with the environment by increased spontaneity and response-flexibility. The subject's social functioning may thus be restored.

How to evaluate psychotherapy?

Can psychotherapeutic interventions be meaningfully evaluated? Such a basic question must be posed as the specific value of such a complex psycho-social intervention as psychotherapy is not easily established. The Dodo-bird verdict “*Everyone* has won and *all* must have prizes” from the adventures of Alice in Wonderland (Carroll, 1946) was proposed by Rosenzweig (1936) and this concept, that there are no discernible differences in therapy outcomes across methods, was confirmed in a study (Stiles *et al.*, 2007) of more than 5000 patients with mainly anxiety and depression as presenting symptoms receiving cognitive-behavioural therapy, person-centered therapy or psychodynamic therapy. All subjects who completed the before and after evaluations averaged marked improvement without regard to type of treatment.

In order to escape this impasse, rigorous work with placebo treatments has been conducted. Systemic de-sensitization is a method within the cognitive-behavioural tradition that combines relaxation exercises followed by a graded trauma exposure. This method has proven to have good effect on anxiety diagnoses in many studies but when this treatment was compared to placebo-treatment that was rated equal in expectancy of positive outcome by the clients, there was no difference in final outcome (Kazdin &

Wilcoxon, 1976). A similar finding was reported by Baskin *et al.* (2003) who compared different psychotherapies with structurally equivalent placebo treatments, *i.e.* treatments with the same input in time, the same format and the same credibility of therapists. By comparison there was no difference between psychotherapy and placebo psychotherapy.

Considering these difficulties in the evaluation of psychotherapy, focus should shift to aspects of: (A) acceptance of treatment and attrition rate during therapy; (B) negative side-effects; (C) ease of therapy delivery; (D) amount of therapy-hours needed to achieve a positive outcome; (E) rapidity of onset of positive outcome; (F) stability of positive outcome at long-term follow-up, and (G) whether previously treatment-resistant groups might benefit from a new therapy.

Notwithstanding the Dodo verdict, there may be important distinctions between therapies when it comes to more defined populations and symptoms.

Pierre Janet and the treatment of post-trauma reactions

Pierre Janet developed in the early 1880s a stage-oriented treatment system for post-trauma reactions, both those dominated by dissociative phenomena and those more dominated by obsessive ruminative tendencies (van der Hart *et al.*, 1989). In the first phase, the treatment concentrated on stabilising the patient through sleep, nourishment, and psychoeducation aimed at establishing a therapeutic relationship and symptom reduction. In the second phase, the work was focused on past traumatic events and modification of their present repercussions. In the third phase, there was a future oriented approach aiming at integration and relapse prevention. The overall principle was to integrate and modify traumatic memories and reactions in the identity of the client. Janet developed the concept of dissociation, which was a way of describing a distorted memory process where the traumatic memory was split away from consciousness and reappeared in dissociated bits and pieces as flashbacks, autonomic reactions and motor activities connected to the original trauma. He was an eclectic psychotherapist utilising many techniques, for instance relaxation and imagery from the hypnotherapy tradition.

Behavioural and cognitive treatment of PTSD

An important starting point is Pavlov's learning theory (1927) aptly described by Kringelbach (2005) as: "...classical conditioning paradigms, in which an arbitrary neutral stimulus is paired with a reward or punishment. After learning, the arbitrary stimulus takes on the predictive value of the specific reward value of the unconditioned stimulus, but it can also code for various aspects of the sensory or general affective properties of the unconditioned stimulus."

The natural course of aversive conditioning is a slow decline in reaction over time. Such decline is associated to concepts such as for instance extinction, de-conditioning, attenuation or counter-conditioning. Hence the focus in treatment on exposure to trauma-related triggers in a safe context, although paradoxically it seems that even only talking about cognitions affected by the trauma had a similar effect of attenuation of the negative emotional reaction (Tarrier *et al.*, 1999). Cognitive-behavioural treatments are influenced by Rotter (1954) who considered psychotherapy to be a learning situation similar to the teacher-student relationship.

Following the operational definition of PTSD in 1980, many studies emerged, broadly arranged under the heading of cognitive behavioural psychotherapy. The practice of cognitive behavioural psychotherapy varies broadly, encompassing different combinations of elements such as getting a treatment rationale, psychoeducation, *in vivo* exposure, imaginal exposure, cognitive restructuring, problem solving, breathing exercises, relaxation exercises, diary-keeping, homework exercises and meditation practice.

The learning aspect of the cognitive behavioural therapy approach is underscored by the present judgement that dysfunctional fear conditioning is not extinguished but can be supplanted by a new competing adaptive learning (Milad *et al.*, 2006; Centonze *et al.*, 2005).

Eye movement desensitization and reprocessing (EMDR)

In 1989, a new treatment approach was proposed by Francine Shapiro called eye movement desensitization (EMD). In her original article she reported a successful treatment response to PTSD after only one session (1989). She described her method in the following way: “The primary component of the EMD procedure is the generation of rhythmic, multi-saccadic eye movements while the client concentrates on the memory to be desensitized. The effect of saccadic eye movements was discovered accidentally by the author when she noticed that recurring, disturbing thoughts were suddenly disappearing and not returning.” The name of the method was changed from EMD to EMD/R in 1991 after the addition to the protocol of a cognitive reprocessing component (Shapiro, 1991). The method was developed further with a more pronounced preparation phase with the self-soothing technique known as safe-place exercise (Wilson, 1995). Shapiro (1996) later expanded the original protocol with alternative bilateral sensory stimulations such as rhythmic tapping of hands or finger-snapping at ears. EMDR is now presented as an eight-phase treatment.

1. Client history, targeting traumatic memories
2. Client preparation. Education about effects of psychological trauma. Presenting a rationale for EMDR. Introduction of relaxation and self-soothing techniques in combination with bilateral alternating sensory stimulation.
3. Focus on the target memory and assessing the concomitant image, negative and wished-for positive thoughts, emotions and physical sensations.
4. Desensitization. The target memory is evoked and combined with 20-30 bilateral stimulations, a so-called set. Emerging associated traumatic memories are also desensitized in the same way. The client may choose not to disclose memories that still can be desensitized.
5. Installation. A positive thought about the client in relation to the traumatic memory is kept in the mind while he is exposed to a set of sensory stimulations.
6. Body scan. At the end of treatment the client is focused on physical sensations in the body while being exposed to sensory stimulation.
7. Closure. Reflection on the treatment session. Instructions on handling sensations in the coming period by, for instance, a log and self-control techniques.
8. Re-evaluation. Client and therapist reflect on treatment outcome and treatment plan and how to keep track of changes over time.

During the desensitization phase there is active thought-stopping. When the set is over the therapist asks the client, “*What comes? What do you experience now?*” or something similar. When the client answers the therapist says, “*Stay with that, go with that*” and continues with a new set of sensory stimulation. In this way the client is not developing talk about the trauma, but is interrupted and over and over entered into imaginal and sensory reliving. In the beginning, at appropriate moments, the subject is asked about the level of present discomfort according to a “subjective units of disturbance scale” (SUD) between 0 and 10. The validity of cognition is a scale introduced by Shapiro to assess how truly the subjects experience a present self-referring positive thought relating to the previous traumatic situation. The desensitization starts with the evocation of the index memory and when there are associations to other traumas or situations they are also exposed to sensory stimulation sets. When several sets, with or without associations are completed, the original trauma-memory is returned to and the present SUD level is assessed. During the desensitization phase also non-disclosed traumas can be exposed to sets. Of note is that also positive images and sensations that arrive during the desensitization are combined with sets in the same way. During a full EMDR-session the number of sets can be substantial, 10-20, and can be considered to be the kernel of the method.

Shapiro calls EMDR a “synclectic” method, including both synthesis and eclecticism. We can note components from many psychotherapy schools in the method, such as presenting a psychoeducation and a treatment rationale, using negative and positive cognitions and trying to change them, using hypnotic techniques such as imaginal exposure, imagined safe-place, eye movements (compare the pendulum) and touching (compare “*passes*”), body-psychotherapy techniques, yoga techniques (eye movements), combination of imaginal trauma exposure with relaxation as in systemic desensitization, and following associative chains as in psychodynamic psychotherapy.

Neuroanatomy: the limbic system

In the search for a biological substrate of feelings the so-called limbic system of the brain is often referred to. Thomas Willis in (1664) named the cortical border encircling the brainstem *cerebri limbus* and in 1878 Paul Broca named the cingulate gyrus, anterior olfactory region and hippocampus the *grand lobe limbique*. This ring of medial cerebrum, he noted, was present in the brains of all mammals and with a strong relation to the olfactory system. Santiago Ramón y Cajal (1900-04) delineated structures associated with the limbic lobe such as the amygdala, parts of the hypothalamus, thalamus and basal ganglia. In MacLean’s definition (1952) of the term limbic system also lateral areas reciprocally connected with the medial ring were included, namely the orbital frontal cortex, temporal lobe and insula. MacLean emphasized the reciprocal connections between the amygdala and the hypothalamus and hippocampus, respectively, and in earlier publications added the sub-title visceral brain.

The understanding of the functions of the limbic system has evolved over the years and relates to the understanding of the environment, internal state of the organism, and regulation of actions on the environment. In mammals, the care of children and forming of social groups demand communication skills and feelings are important in this respect. The limbic system is influenced by modulating neurochemicals such as acetylcholine, dopamine, adrenalin, noradrenalin, vasopressin and oxytocin. Mega *et al.* (1997) propose two functional divisions: “...the orbitofrontal/amygdalar division of the limbic

system, which supports emotional associations and appetitive drives, and the hippocampal/ cingulated limbic division, which supports mnemonic and attentional processes.”

Nauta & Domesick (1982) appreciated the function of the limbic system as more than a reactive system: “The amygdala-cortical connections ... could thus be viewed as limbico-cortical projections reciprocating, partly at least, the flow of multisensory information from the cortex to the limbic system. In the light of these connections, the limbic system could be viewed as a neural mechanism that not only monitors the sensory processes of the cerebral cortex, but can also reach out to intervene in these processes. It could thus be suspected, even on the basis of no more than anatomical data, that the functional set of the limbic system affects not only, as generally acknowledged, the organism’s visceral and endocrine functions and its motivational state, but also the sensory and associative mechanisms involved in its perceptions and ideational processes.”

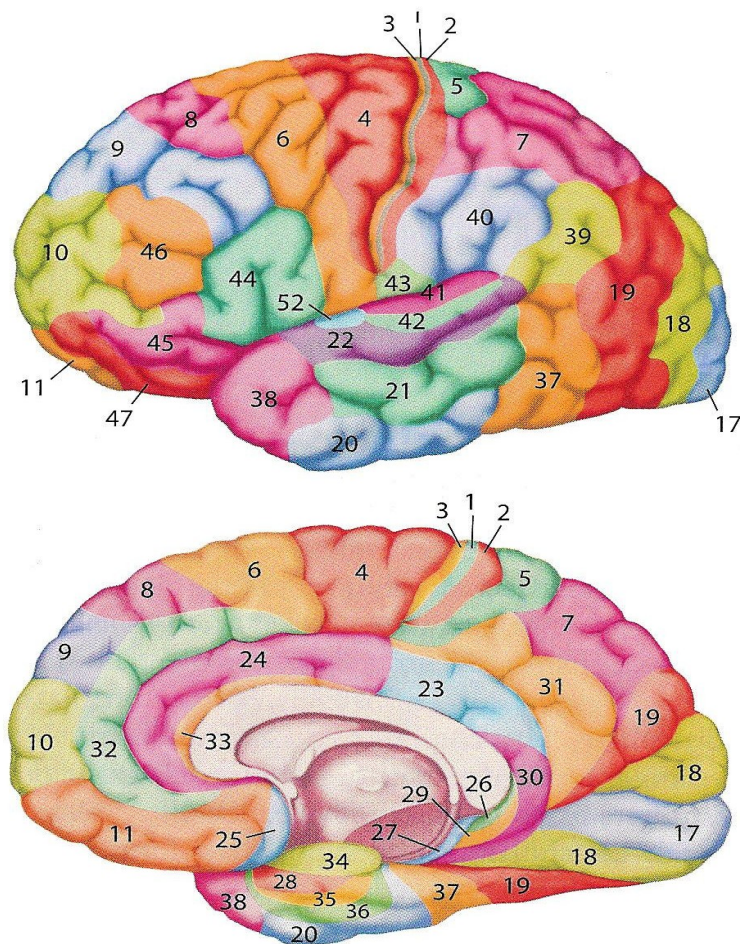


Figure 1. The Brodmann areas, named in the Appendix, shown in the lateral and medial aspect of the brain.

Feelings, emotional imagery and psychophysiology

The science of feelings, emotions, feeling regulation, adaptation to external reality and functionality is an age-old theme in human thinking, as mirrored by the discussion on reason and passion (Solomon, 1976). In the research on feelings there are difficulties in finding coherent descriptions, as feelings are individually experienced and expressed semantically, hence the quest to find physiological correlates. William James (1894) formulated a theory of emotion (the 'James-Lange theory') in which a feeling was suggested to be the subjective counterpart of specific patterns of visceral responses. By contrast, W.B. Cannon (1927) argued that a similar physiological reaction was common in a vast array of emotional states and the factor of importance was the level of activation. Activation or arousal is mediated by the brainstem reticular activating system and is a continuum ranging from low arousal in drowsiness and sleep to high arousal in rage, anxiety and intense joy. The frontal cortex sustains the attention and arousal. The organism is set to act in relation to the environment and feelings can be conceptualised as guiding mental states to implement proper motor programs.

A multidimensional definition of feelings has been proposed and comprises the following: (A) the valence of the feeling; (B) the intensity of the feeling, and, (C) the level of control (Osgood, 1957).

But a further aspect is needed in evaluation of feelings. That is the level of adaptation of the feeling, whether it is appropriate in relation to the present situational demands. Adjacent to this concept is the capability to re-adapt to new situations. This aspect could be called spontaneity according to the definition by J.L. Moreno where he contends that mental health is characterized by a sufficient level of spontaneity, defined as the ability to find new responses in new situations when old responses are inadequate: "Thus the response to a novel situation requires a sense of timing, an imagination for appropriateness, an originality of self-propelling in emergencies, for which a special spontaneity function must be made responsible" (1977). Similar concepts are response flexibility and cognitive flexibility. In PTSD this means that the reliving of an anxiety-laden reaction limits the behavioural options of a person faced with new situations, which leads in the end to a more restricted and self-limiting repertoire of actions.

In order to find physiological correlates to feelings, *i.e.* to study psychophysiology, there must be standardised methods for the evocation of specific feelings. Bower used hypnotic induction to make subjects enter into a feeling state (Bower, 1981). A similar, hypnotic-like, but more formalised method of emotion evocation was created by the Lang group (1983). They asked subjects about the event related to the desired feeling. The interview focused on sensory impressions and autonomic reactions in order to be able to create a personalised emotion-producing script as suggestive as possible. This individual script was then re-read in present tense and second person to the subject and often the reader afterwards coached the subject into the feeling state produced by the script. Lang also developed a theory pertaining to the emotional picture where he described the emotional image as an action sequence: "It is both stimulus and response, organized into a processing unit which is as much a behavioural set as an internal percept." (Lang, 1977). The emotional image according to this theory is supposed to connect a distributed neural network in which stimulation of one part of the network activates other parts.

Two feelings are of special importance in PTSD, fear and anxiety. It is not always clear what is fear and what is anxiety, but fear can be seen as closer to the spectrum of adaptive reactions to a concrete situation, whereas anxiety is both another feeling quality when the reaction is very intense as well as when it is implicated in the expectation of pain and danger. By constructing an individualised trauma script such feelings can be evoked. In a classical article by Pitman *et al.* (1987) the method of script-driven symptom provocation was brought into the study of psychophysiology in PTSD when he found convergent arousal of heart rate, skin conductance and electromyogram in combat related PTSD upon exposure to a personalised trauma script.

Physiological variables to study in relation to emotions are for example, heart rate, systolic blood pressure, diastolic blood pressure, skin conductance, the startle reflex, facial electromyography and electroencephalogram recordings. There is a wide variability of physiological contexts relating to the psychophysiological measurements so different aspects of reactions can be studied. Summarising fifty-eight resting baseline psychophysiological studies of PTSD subjects, Pole (2007) reported that only heart rate differed significantly between PTSD and non-PTSD subjects. Analysing the studies with script-driven symptom provocation (n=22), he found significant elevations of heart rate and facial electromyography. These findings lend support to the notion of Hermann Oppenheim (1889) who commented: "The abnormal excitability of the cardiac nervous system is an almost constant symptom of traumatic neurosis, only in few instances is there serious cardiac disease." Kardiner, who treated psychiatric casualties in World War II, even named the reaction "physioneurosis" (1941).

The fear reaction

The fear reaction is adapted to the situational demands of a dangerous situation and is characterised by preparation to use large muscle groups in order to manage the threat by fighting, fleeing or hiding. The senses are sharpened and there are changes in subjective experience, in behaviour and in the internal milieu regulating central, autonomic and endocrine response systems (Lang 1995). The emotion is activated by an evaluation of an internal or external stimulus. The fear reaction catches on rapidly and declines rapidly but leaves a minor arousal lingering past the dangerous situation. The aspects of temporality and magnitude are thus important aspects of the fear reaction, *i.e.* turning on, keeping activated and turning off. When there is a serious event, the time for recuperation may be about four weeks. This is the time during which the individual is sensitised to fear reactions and still is suffering from acute stress reaction.

In the autonomic nervous system the sympathetic system is engaged in energy mobilisation and gross motor activity and the parasympathetic system is associated with restorative and vegetative functions. These two branches are in constant dynamic interaction. It is suggested that the default reaction is the sympathetic activation to novel stimuli, thus favouring safety activity such as the fight or flight response. The parasympathetic system is disinhibited in the fear reaction. The tonic inhibition is restored afterwards (Thayer & Brosschot, 2005). Such inhibition is dependent on the prefrontal cortex, thus forming a top-down regulation. Heinzel *et al.* (2005) had normal subjects watch emotional pictures during functional magnetic resonance imaging and found a decreased signal in the orbitomedial prefrontal cortex. This suggests a decrease of the frontal tonic inhibition in visually elicited fear reactions.

The brainstem/midbrain is implicated in the regulation of autonomic response by brainstem nuclei such as the reticular system and the nucleus coeruleus (noradrenaline). The amygdala, which evaluates the valence, positive or negative, of external and internal stimuli, activates the fear system upon perceived danger. The hippocampus as well as the amygdala by associative learning attaches the fear reaction to new situations reminding of the original danger (Büchel *et al.* 1999). As Mayberg (1997) commented: "There are reciprocal pathways linking midline limbic structures (cingulated, hypothalamus, hippocampus, and amygdala) with widely distributed brainstem, striatal, paralimbic, and neocortical sites."

The hypophysis, pituitary, and adrenal systems are also involved in regulation of the stress response. This system does not, except perhaps for subpopulations, seem to be dysregulated in PTSD (Breslau *et al.*, 2006; Meewisse *et al.*, 2007).

The PTSD reaction

Situations involving personal threat and risk for physical damage can result in psychological trauma and may cause strong aversive reactions. Also experiences of serious threat to, damage to or the death of others may cause such affect. When the normal fear reaction does not subside post-trauma there is a risk for the development of a disabling psychological state, especially if there is repeated exposure to a dangerous situation. Emotional memory is always experienced with a distorted temporality, *i.e.*, old feelings are relived although somewhat changed. When the natural fear reaction is complicated by pathological anxiety it can be described as a severely disturbed temporality of the trauma memory. This means that the emotional experience during the trauma is relived in sensory, autonomic and muscular modalities, both during the day-time as sensory and autonomic flashbacks and at night in anxiety-laden trauma-associated nightmares. This reliving character of the emotional memory is also caught in the flashback phenomenon, as has been noted during electrical brain-stimulation during brain surgery (Penfield, 1959; Gloor *et al.*, 1982).

In cases of severe trauma and severe reactions this disturbed temporality dominates the personality, as in cases of dissociative psychosis (van der Hart, 1994) where the person lives almost constantly in a trauma replay. In PTSD the person can, albeit sub-optimally, function in daily life but lives in a constant contingency-preparation with ordinary life being intersected by temporality shifts to the trauma experience. This temporal shift can occur through external or internal triggers and even be auto-activated when the person is resting or sleeping. The subject experiences loss of control and predictability concerning the temporal shifts. Perhaps the anticipatory aspects of repeating trauma reliving are of importance in forming the anxiety response. Ensuing from this are the concomitant symptoms of PTSD such as avoidance of trauma related triggers, emotional numbing and irritability.

In this pathological anxiety reaction, the tonic inhibition of basal brain catecholamine systems by cholinergic output and prefrontal activation is dysfunctional. Kosten *et al.* (1987) found increased 24-hour urine excretion of adrenaline and even more pronounced increase of noradrenaline in nine Vietnam War veterans. Night-secretion of catecholamines were reported elevated in PTSD-subjects (Mellman *et al.*, 1995) and Breslau *et al.* (2006) reported from an epidemiological sample that catecholamines (noradrenaline, adrenaline and dopamine) were elevated in PTSD-subjects as compared to controls without PTSD. However, Murburg *et al.* (1995) found

that basal sympathetic nervous system functioning was not increased in PTSD patients and suggested that the increases of catecholamines found indicated increased sympathetic reactivity. Thus PTSD might be defined as an anxiety disorder with a dys-regulated balance of the inhibitory and excitatory impulses at trauma-trigger related exposure (O'Donnell, 2004).

The increase of adrenaline/noradrenaline affects the frontal cortex following the curve of an inverse U. At first an increase stimulates activity but at higher levels there is a decrease of activity in frontal cortex (Arnsten, 1997). In moderate stress there is an increase in cerebral blood flow (CBF) whereas in severe anxiety there is a general decrease of global CBF, suggested to indicate a cerebral vasoconstrictive factor associated with severe anxiety (Mathew & Wilson, 1990). Thus the intensity of anxiety is one important factor to consider during emotive brain imaging. Results from neuroimaging are equivocal but a present hypothesis is promulgated by Nutt & Malizia (2004): "...functional imaging studies that have used script-driven imagery and other methods of provoking re-experiencing symptoms of PTSD as well as studies using cognitive activation models have, for the most part, demonstrated a pattern of hyper-responsive amygdalae operating in the context of attenuated negative feedback from the medial prefrontal cortex and the anterior cingulate gyrus."

Brain imaging

In the last 30 years functional brain imaging has been increasingly applied to psychiatric disorders. In the field of neurodegenerative disorders, single photon emission computerized tomography (SPECT) and positron emission tomography (PET) allow today for the identification of diseases with a sensitivity and specificity approaching 80-90%. Such high accuracy has not been realized for psychiatric disorders such as dementias, schizophrenia, PTSD or depressions in which the links between the findings of functional brain imaging studies and the neural substrates of such disorders have not been clearly established yet.

Optimised nuclear medicine techniques and algorithms for functional brain imaging can now be implemented in research on psychiatric patients for finer discrimination of mild CBF or metabolic changes. Such changes have for a long time been neglected due to the fact that the quality of both functional images and image analysis was not sufficient to identify the sometimes small functional regional variations occurring in psychiatric diseases.

SPECT is a widespread imaging technique detecting the gamma rays emitted by various radioisotopes. The use of ^{99m}Tc -d,l-hexamethyl-propylene amine oxim (^{99m}Tc - HMPAO) is generally considered to reflect CBF and neuronal activity. ^{99m}Tc -HMPAO has been in recent years the most commonly used tracer at SPECT investigations regarding CBF.

Table 1. SPECT investigation in PTSD studies at resting state, symptom provocation and before/ after treatment.

Author, year	Statistics	Trauma type, PTSD group	N	Condition during SPECT	Controls	N	Relative increase of rCBF	Relative decrease of rCBF
Lucey <i>et al.</i> 1997	Region of interest	Mixed	16	Resting state	Healthy controls	15		Right caudate nucleus, bilateral superior frontal cortex
Levin <i>et al.</i> 1999	Not reported	civilian	1	Trauma script vs neutral	Before and after treatment		Anterior cingulate, left frontal lobe	
Liberzon <i>et al.</i> 1999	Region of interest	War veterans	14	Combat sounds	Non-PTSD War veterans /normal subjects	14/11	Amygdaloid region	Right retrosplenial region
Zubieta <i>et al.</i> 1999	Region of interest	War veterans	12	Combat sounds	Non-PTSD War veterans /normal subjects	11/12	Medial prefrontal cortex	
Sachinvala <i>et al.</i> 2000	Region of Interest	War veterans	17	Resting state	Healthy volunteers	8	Limbic areas and the right and parietal cortex	
Mirzaei <i>et al.</i> 2001	Region of interest	Torture victims	8	Resting state	Healthy volunteers	8	Left parietal and temporal cortex	
Bonne <i>et al.</i> 2003	SPM	Mixed	11	Resting state	Healthy volunteers	11	cerebellum	
Pavic <i>et al.</i> 2003	Region of interest	War veterans	25	Angry reaction in group therapy	No controls	25	Left projection area of ventral basal ganglia (nucleus accumbens)	
Lindauer <i>et al.</i> 2004	SPM	Police-men PTSD	15	Trauma scripts	Police-men without PTSD	15	Right cuneus	Medial frontal gyrus
Lansing <i>et al.</i> 2005	SPM	Police-men PTSD	6	Concentration task	Before and after therapy	6	Left inferior frontal gyrus	Occipital lobes, left parietal lobe, right precentral frontal lobe
Chung <i>et al.</i> 2006	SPM	Mixed trauma	23	Resting state	Healthy volunteers	64	Limbic regions	Superior frontal gyrus, parietal and temporal regions
Kim <i>et al.</i> 2007	SPM	Survivors of fire	19	Resting state	Healthy volunteers	19	Right superior parietal lobe	Right thalamus
Peres <i>et al.</i> 2007	Region of interest and SPM	Mixed, subclinical PTSD	16	Trauma scripts	Waiting-list group, mixed subclinical PTSD	11	Parietal lobes, left hippocampus, thalamus, left pre-frontal cortex	

SPECT studies of PTSD

Previous studies by SPECT of PTSD are shown in Table 1. There are studies in resting state, in symptom provocation by combat sounds as well as by personalised trauma scripts. There are also studies of treatment effects. SPECT shows activations or de-activations in comparison with controls in all studies and implies areas involved in memory, emotion and motor activity, such as are needed in an active response-preparation related to an external danger. This field of study is in its inception and the differences in the findings might be attributed to factors such as trauma type, comorbidity, medication, substance abuse, gender, type of statistical analysis, type of symptom provocation, intensity of reaction, reaction-type to trauma cues, laterality of emotional reactions, etc. There is a growing accumulation of findings that might in the future provide substance for conclusive patterns.

Brain morphology in PTSD.

The hippocampal formation is vital in acquisition of new information, in retrieval of autobiographical memory and in regulation of emotional response (Eichenbaum, 1999; Eldridge *et al.*, 2000). Animal research has suggested hippocampal damage to occur from stress. Monkeys who died spontaneously after sustained social stress showed hippocampal degeneration (Uno, 1989). In humans with Cushing's syndrome, hippocampal volume varied inversely with plasma cortisol in one study (Starkman *et al.*, 1992).

These findings have instigated researchers to formulate a hypothesis that there might be stress-induced gluco-corticoid toxicity (Sapolsky, 1996; Bremner, 1999) that would explain an association between decreased hippocampal volume and PTSD. Two meta-analyses summarise the findings of imaging studies in the field (Kitayama *et al.* 2005; Smith, 2005) and conclude that the findings were consistent with smaller hippocampal volume in adult subjects with chronic PTSD. However the field is complicated by the finding that gluco-corticoids often were lowered in persons with PTSD (Yehuda, 2001). In an epidemiological study there were no differences between normal and PTSD subjects in cortisol excretion (Breslau *et al.*, 2006) The Gilbertson *et al.* (2002) twin study showed that in mono-zygotic twins discordant for Vietnam War combat experience also the non-exposed twins had smaller hippocampi, suggesting pre-existing hippocampal volume as a risk factor for the development of PTSD. In a critical note Jellic & Merckelbach (2004) commented: "As it stands, the glucocorticoid toxicity hypothesis is just what it is: an interesting hypothesis that is in need of further empirical testing. Currently, it cannot be considered a validated part of clinical neuroscience."

GENERAL PURPOSE

The prevalence of chronic PTSD is of such a magnitude that this disorder can be regarded as a public health problem. A high proportion of PTSD cases have unmet needs of treatment as is the case for most non-psychotic disorders. The outcome of the established treatment – cognitive behavioural therapy – has been reported to be good

end-state functioning in 32-66% of the cases (Schnyder, 2005). EMDR has been shown to have a good short-term efficacy but the long-term effects have hitherto not been studied. As stated by Schnyder: “Further research into the devastating consequences of traumatic events, and, even more urgent, into the development of more effective therapeutic interventions aimed at ameliorating trauma-related psychiatric disorders, is of utmost importance”. The general purpose of this thesis is to attract attention to PTSD and its neurobiological background as well as to the novel EMDR therapy for this disorder.

SPECIFIC AIMS

- **Paper I** aimed to analyse rCBF in conjunction with trauma-script provocation in traumatised subjects diagnosed or not with PTSD and to record possible differences in rCBF between the groups. A further aim was to deepen understanding of neural activity in PTSD.
- In **Paper II** the aim was to compare treatment with EMDR and waiting-list status in a randomized controlled trial, and to identify possible group differences between treated and untreated subjects regarding PTSD diagnostic status as pre-defined primary effect variable as well as in self-evaluated and assessor-rated psychometric scale scores.
- In **Paper III** the plan was to assess all the EMDR-treated subjects before treatment, immediately after treatment, at eight and at 35 months; and to record changes over time in diagnostic status, psychiatric symptoms, social functioning and well-being.
- In **Paper IV** the idea was to compare the rCBF in the EMDR-treated group of subjects in order to identify possible changes in rCBF from pre- to post-treatment. An ultimate aim of this study was to increase understanding of the pathological brain activity in PTSD.
- In **Paper V** the aim was to describe differences between traumatised subjects with and without PTSD regarding hippocampus and temporal lobe volumes along with the rCBF in the same subjects. The intention was both to explore whether there were any correlations between rCBF and brain volumes and whether there were any differences in brain volumes between subjects with and without PTSD.
- In **Paper VI** we studied the reactions in heart rate and blood pressure during script-driven symptom provocation. These measures represent peripheral sympathetic activity. The first aim was to identify differences in reaction between the PTSD-group and the non-PTSD group at baseline. The second aim was to evaluate possible differences in the physiological reactions before and after treatment with EMDR. The ultimate aim of this study was to demonstrate the possible utility of such physiological variables in diagnosis and therapy evaluation.

SUBJECTS AND METHODS

Methodological considerations

EMDR was chosen as treatment method because it was promising, brief, manualised, and trauma-focused. At the start of this study we found only a few others dealing with short-term efficacy. The waiting-list control group design was chosen because it gives an evaluation of the impact of the therapy research procedure proper. A structurally equivalent placebo must entail the same number of sessions, same length of sessions, same format, the possibility to address the presenting complaint, an individualised treatment (Baskin *et al.*, 2003), and a similar extent of credibility and expectancy (Kazdin & Wilcoxon, 1976). We estimated that we did not have resources enough for such an endeavour although it would have ensured an improved quality of the study.

The choice of study population was made with an eye to the advantages of working with a previously healthy group with documented and well-defined occupational traumas. The choice of diagnostic remission as the primary outcome variable was motivated by the prevailing opinion on depression research, which focuses on the need to have remission and restoration of function as the primary outcome variable (Nierenburg, 1999). Assessment of psychiatric symptoms, social functioning, and well-being were based on interviews or on self-rating. We used instruments commonly employed in therapy studies with generally good or acceptable psychometric properties. In the choice of physiological variables we were guided by previous studies reporting cardio-vascular effects of PTSD. The choice of SPECT to study brain physiology was motivated by the experimental versatility of the SPECT method, in which the tracer infusion is given in a natural setting and not in the scanning machine. This is an advantage (Peres, 2007) in subjects with anxiety, who can be in a quiet and safe environment and move freely because the infusion of the $^{99m}\text{TcHMPAO}$ occurs 20 minutes before the subject is brought to the camera, and thus the subject does not have to be immobilised during the symptom provocation.

Subjects

This study recruited workers from Stockholm Public Transport and Swedish Rail. With start in 1999, all personnel who had been exposed to a person-under-train accident (PUT) during the previous five years but not within the last three months were invited to participate in the study. One hundred and sixty invitations were sent to the PUT accident population of whom 59 accepted the invitation. Six were excluded because the trauma was too old, one was excluded because of major depression, which was an exclusion criterion, and 13 dropped out. The remaining 39 took part in the study. After 2001 also workers exposed to threats or violence (assault) while at work in the public transportation system were invited to join the study. One hundred and seventy letters were sent to those who had experienced assault and of these, 24 accepted the invitation. Two were excluded because the trauma was more than six years old and eight dropped out. The remaining 14 entered the study. The total number of subjects ($n=53$) were after the initial diagnostic interview divided into a PTSD ($n=24$) and a non-PTSD group ($n=29$).

The study populations in this thesis (**Papers I – VI**) are presented below.

Table 2. The study populations in **Papers I-VI**.

Study	Study population	Name of article
I	47 subjects, 20 with PTSD and 27 without	Regional cerebral blood flow during auditory recall in 47 subjects exposed to assaultive and non-assaultive trauma and developing or not posttraumatic stress disorder
II	21 subjects with PTSD	On treatment with eye movement desensitization and reprocessing of chronic post-traumatic stress disorder in public transportation workers – A randomized controlled trial
III	20 subjects who completed EMDR therapy	Treatment of post-traumatic stress disorder with eye movement desensitization and reprocessing: Outcome is stable in 35-month follow-up
IV	15 subjects who underwent EMDR therapy and completed SPECT before and after	Effects of EMDR psychotherapy on ^{99m} Tc-HMPAO distribution in occupation-related post-traumatic stress disorder
V	36 subjects, 17 with PTSD, and 19 without, who had undergone both MR before treatment as well as SPECT before and after treatment	Brain functional and volumetric analyses in occupational-related post-traumatic stress disorder
VI	47 subjects, 21 with PTSD, and 26 without PTSD, who underwent physiological testing of heart rate and blood pressure. Subsequently, the EMDR-treated group was also studied	Heart rate and blood pressure in occupationally related post-traumatic stress disorder and after eye movement desensitization and reprocessing

Ethical considerations

The subjects were given an oral and written description of the study and written informed consent was obtained. The study was approved by the Local Ethics and Radiation Safety Committees. The study was conducted in close co-operation with the transportation companies, the occupational health services and the trade unions, with whom regular meetings were held before, during and after the project, to inform on the progress of the study and report on the results at group level.

Study procedure

Initially, the study population underwent diagnostic and psychometric assessments. Thereafter, sessions were held with a research psychologist who interviewed the subjects about the trauma and then constructed for each a personal trauma script. After this came the script-driven symptom provocation. This was done in connection with SPECT, and the bio-chemical and physiological measurements.

The PTSD subjects thereafter underwent a randomized controlled trial with a treatment group and a waiting-list group for a period of about ten weeks, after which there was a new diagnostic evaluation and a new symptom provocation, SPECT, bio-chemical and physiological measurements. The subjects were randomized by picking

sealed ballots in the presence of a research nurse. In the randomized controlled trial, the waiting-list group received the same amount of research project procedures and attention as the treatment group with the exception of EMDR therapy.

After the randomized controlled trial, a treatment period for the waiting-list group was instigated followed by a new assessment, symptom provocation, SPECT, biochemical and physiological measurements. Finally, all treated subjects were assessed by interviews and questionnaires at eight and at 35 months after the end of therapy.

EMDR treatment

A description of the content of EMDR treatment was given in the introduction. EMDR therapy was delivered in five sessions of 90 minutes duration. The interval was not exactly fixed, one or two weeks might pass between sessions. The therapy was given at the occupational health agency engaged by the transportation company or in a private therapy office. Participants were randomly allotted to one of two therapists, both experienced in the method. Sessions were recorded on a mini-disc which was later analysed for fidelity to the treatment protocol by an EMDR-experienced psychologist not otherwise engaged in the project.

Interviews

Participant characteristics were obtained through an interview carried out by a research nurse. The diagnostic interviews were performed according to SCID-1 (First *et al.*, 1997) by a psychiatrist not otherwise engaged in the study and blind to the experimental condition of the participants. Cohen's kappa values between 0.7 and 1.0 are reported for this interview (First *et al.*, 1999). Psychiatric diagnoses, including PTSD, were established according to the DSM-IV criteria. Full PTSD diagnosis was pre-defined as the primary outcome variable. The first diagnostic interview was performed when the participants were recruited into the study. A second diagnostic interview was conducted during the first two weeks after treatment/waiting-list completion (mean 10 days SD ± 5). Diagnostic interviews were also carried out at eight and 35 months post-treatment.

The interview-based ratings of symptoms and functional assessment were carried out by the same person who performed the diagnostic interviews using the following three scales.

The Global Assessment of Functioning (GAF) (American Psychiatric Association, 1994). This is a scale from 1 to 100 with intervals of 10 with descriptions of symptoms, social and vocational capacity in each interval. When the scale was used by trained raters an intraclass correlation coefficient of 0.86 was reported (Hilsenroth *et al.*, 2000).

The Hamilton Anxiety Scale (HAM-A) (Hamilton, 1959) is a scale of 14 items. This scale encompasses both somatic and mental complaints and was intended for patients with the diagnosis of anxiety neurosis. This scale is today being replaced by more precise diagnoses. An internal reliability of 0.93 and test-retest reliability of 0.97 was reported.

The Hamilton Rating Scale for Depression (HAM-D) in the 21-item version targets anxiety, depressed mood and somatic complaints (Hamilton, 1960). This scale has shown internal reliability ranging from 0.46 to 0.97 and test-retest reliability ranging from 0.82 to 0.98 (Bagby *et al.*, 2004)). In our study the internal reliability was 0.83.

In connection with the diagnostic interview subjects were also asked about previous occupational traumas. Working capacity as judged by sick leave was also estimated.

Self-rating scales

Self-rating scales were administered immediately before all diagnostic interviews. The assessments were performed on a computer with the research nurse present in the room. The self-assessment outcome scales used were:

- The Impact of Event Scale (IES) (Horowitz *et al.*, 1979) is a 15-item scale focusing on intrusion and avoidance. In the original study Cronbach's alpha was 0.79 for intrusion and 0.82 for avoidance, and test-retest reliability was 0.87 for intrusion and 0.79 for avoidance. In our study Cronbach's alpha was 0.93.
- The Beck Anxiety Inventory (BAI) (Beck *et al.*, 1988) is a 21-item anxiety scale asking about anxiety symptoms during the preceding week. The internal consistency was 0.92 and the test-retest reliability 0.75 when the scale was presented. In our study Cronbach's alpha was 0.91.
- The WHO (Ten) Well-Being Index (WHO-10) (Bech *et al.*, 1966; Janca *et al.*, 1996). This is a scale with ten items focusing on well-being and coping during the preceding week. A Cronbach's alpha value of 0.85 was reported as well as evidence for concurrent and discriminant validity.
- The Social Disability Index (SDI) (Ormel *et al.*, 1999) is the role functioning part of the Brief Disability Questionnaire which has reported a Cronbach's alpha of 0.88 (VonKorff *et al.* 1996).

In order to assess the load of previous traumatic experiences the Trauma Antecedent Questionnaire (TAQ) was used (Herman *et al.*, 1989). The TAQ entails a lifespan history of trauma and neglect (TAQ-negative) as well as resilience factors (TAQ-positive). This is an anamnestic, not a diagnostic, tool.

Script-driven symptom provocation and psychophysiological recording

In order to study the reactivity of the subjects upon exposure to a trigger, a symptom provocation was introduced according to the method described by Lang *et al.* (1983). For each participant an individualised trauma script was obtained with focus both on perceptions and reactions. This script of circa 1.5 minutes was read by a research assistant into a tape-recorder. It was presented in the present tense and second person, with focus on details and physiological responses in order to evoke the traumatic memory as effectively as possible. At the examination the script was replayed to the participant and immediately after the replay the research psychologist asked the subject to enter the feeling state. Heart rate, systolic and diastolic blood pressure were measured before, during and after the symptom provocation and recorded with a semi-automatic Dinamap monitor. In the resting period preceding the script reading the intervals were about 1.5 minutes. In the period following the script these measures were registered every 20-40 seconds.

After the script replay and the memory evocation the psychologist asked questions about the subjective disturbance and noted it on a visual analogue scale (VAS) 1-5, forming a score of subjective disturbance (SUD). The SUD consists of three subscales with three questions on the vividness of the memory, five questions on the negative

emotions and 13 questions on the perceived autonomous bodily reactions. Visual analogue scales have been shown to correlate well with established anxiety scales (Bond *et al.* 1995).

SPECT

Most SPECT systems today are based upon rotating gamma cameras. A gamma camera is a position-sensitive device that allows visualization of the distribution of gamma emitting radiotracers. It is built up of a collimator, a scintillation detector, light detecting photomultiplier tubes (PM-tubes), and electronics for signal processing. Due to the complex brain anatomy, tomographic examination is a pre-requisite for tracer distribution studies by SPECT in order to better identify anatomo-functional structures.

Visible light flashes are emitted from the local site to the scintillation detector where the photon is absorbed. For each event, the signals are weighed together to give the two-dimensional (2-D) position coordinates. The image quality of a gamma camera system is generally characterized in terms of spatial resolution (approximately 8-11 mm in the three-headed scanners), system sensitivity and energy resolution. The sensitivity (*i.e.*, the number of detected photons per unit of activity) of a SPECT system is generally very low and in the order of 10^{-4} detected events per emitted photon. Modern SPECT cameras are often designed with more than one camera head to improve sensitivity. We used a three-head system (TRIAD XLT 20, Trionix Research Laboratory Inc., Twinsburg, OH, USA) which gave a three-fold sensitivity increase compared with a single-head camera.

Normalization of the measured tracer uptake is necessary in the semi-quantification of SPECT data. The normalization procedure rates each pixel or voxel (the smallest units of a 2-D picture or a 3-D volume, respectively) as a proportion of the average of those pixels or voxels that are chosen as reference.

Digital analyses of SPECT data may be performed with different manual, semi-automatic or automatic methods for outlining 2-D regions of interest (ROIs) and 3-D volumes of interest (VOIs), and comparing them with corresponding ROIs or VOIs from a second scan or other subjects. Standardization software with 3-D coordinates and processing of ^{99m}Tc -HMPAO SPECT data were applied in the papers included in this thesis; *e.g.*, Statistical Parametric Mapping (SPM) and Computerized Brain Atlas (CBA).

^{99m}Tc -HMPAO properties

Intracellular trapping of lipophilic d,l - ^{99m}Tc -HMPAO and its conversion to hydrophilic form has been considered to be the basis of retention of the tracer (Neirinckx *et al.*, 1988; Jacquier-Sarlin *et al.*, 1996)). ^{99m}Tc is a nuclear isomer that when attached to the organic molecule HMPAO can be taken up by brain tissue in a manner proportional to brain blood flow.

The computerised brain atlas (CBA)

The Computerised Brain Atlas is a software tool originally developed by Greitz *et al.* (1991) and applicable to any brain imaging modality. It is based on data from one cryosectioned brain and contains 3D surface descriptions (VOIs) of approximately 400

brain structures including the brain surface, the ventricular system, the cortical gyri and sulci, and the cortical cytoarchitectonic areas (Brodmann areas). The major basal ganglia and the brain stem nuclei are also included.

All image sets are spatially normalized into the stereotactic space of the atlas by using the global polynomial transformation (Thurfjell *et al.*, 1995). This consists of translations, rotations and linear scaling along and around each of the three image axes. It also contains 18 non-linear shape-deforming parameters, which makes it possible to adapt the shape of the brain to a reference scan. A major advantage of the technique is that it creates an almost fully automatic tool able to decrease the analysis time and to standardize patient's brain shapes providing additional anatomic information.

Statistical parametric mapping (SPM)

In brain imaging, univariate analysis is typically performed by SPM (Friston *et al.*, 1995). SPM is the pre-dominantly used worldwide voxel-based standardization software in brain imaging for between- and within-subject rCBF comparisons. Images are spatially standardized into a common space and smoothed. Hypotheses expressed in terms of the model parameters are assessed at each voxel with univariate statistics. This results in an image whose voxel values are statistics, producing t-statistical maps of significant changes in distribution and basing the output on the analyses of voxel clusters. Such analysis should take into account the statistical threshold as well as the size of the cluster in relation to the implemented methodology, the higher the spatial resolution of the camera the smaller the size of the voxel cluster for statistical significance.

Comparisons between CBA and SPM

The analyses performed by CBA and SPM show some similarities and several conceptual differences. Both softwares use roughly the same spatial standardisation procedure, minimising the 3D differences with a reference template and reducing the inter-individual anatomical differences by smoothing the images. They also both make possible the inter-individual comparisons of the radiopharmaceutical distribution by normalising the intensity uptake to the average intensity of the whole brain. The constitution of different groups for within- or between-subject comparisons is also a common feature.

However, the two softwares approach statistical analysis from different points of view. SPM implements univariate analysis, creating t-statistic based maps, CBA utilises the data from regions or volumes of interest to feed mostly multivariate analysis, mainly ANOVAs and ANCOVAs, enabling investigations of more general statistical effects. The implications of such different approaches are several. First of all the SPM analysis is conducted at voxel cluster level while the CBA is conducted at VOI level. This means that SPM cannot analyse regions defined *a priori*, or identify diffuse changes not clustering in a number of voxels exceeding the determined threshold. Conversely, CBA cannot analyse voxel clusters smaller than the pre-defined VOIs, often missing fine regional changes.

It is therefore not surprising that the two methods often in the same analysis highlight different topographical changes. They can be seen as complementary in identifying either global (CBA) or local (SPM) functional changes.

Magnetic Resonance Imaging (MRI)

This technique was originally named Nuclear Magnetic Resonance Imaging. It is based on the properties of excited hydrogen nuclei in different distributions and environments. When a strong magnetic field is applied to the tissue the spins of some of the atomic nuclei align parallel or anti-parallel to the magnetic field. The tissue is then exposed to brief electromagnetic pulses and some of the magnetically aligned hydrogen nuclei temporarily assume a high-energy state. When these nuclei relax they emit energy at rates that can be recorded and give information about the tissue. In our study, the MRI was performed on two GE Sigma 1.5 T Scanners (GE, Milwaukee, WI, USA) at MR Centrum, Karolinska University Hospital, Solna.

Statistical methods

Non-parametric data were analysed with the Mann-Whitney U-Test for differences between groups, and the Wilcoxon Matched-pairs Test for differences within subjects. Differences in parametric characteristics were calculated with Student's t-Test or ANOVA and differences in categorical outcome rates with Fisher's Exact Test. Discriminant analysis was used to test the ability of SPECT to correctly assign the subjects to the clinical group. SPECT was analysed by both CBA and SPM software (for details see **Papers I, IV and V**). Level of significance was set at $p < 0.05$.

RESULTS

The study sample

Here, participants with PTSD will be compared with those without PTSD regarding psycho-social characteristics, psychiatric symptoms, social functioning, well-being, physiological response, subjective disturbance during symptom provocation, rCBF, and brain volumetrics.

Psycho-social characteristics (Paper II)

There were no demographic differences in characteristics between the participants with PTSD and those without except for exposure to trauma (Table 3). Most PTSD subjects had experienced two or more occupational traumas, which also were reflected in the higher load of TAQ-reported adult trauma.

Psychiatric symptoms, social functioning, well-being and subjective disturbance (SUD) during symptom provocation (Paper VI)

There were distinct differences between the PTSD-subjects and the non-PTSD subjects in terms of scores on psychiatric symptoms, social functioning and well-being at the first diagnostic assessment (Table 4). SUD is a process-oriented measure giving an estimate of the subjective negative experience during the symptom provocation. There was no difference between PTSD subjects and those without PTSD regarding vividness of the memory whereas regarding negative feelings and autonomic arousal during the

memory retrieval there were significant differences between PTSD and non-PTSD subjects.

Table 3. The psycho-social characteristics of subjects with and without PTSD and the levels of significance for differences between the groups.

Variable	PTSD group n=24	Non-PTSD group n=29	
	Mean(S.D.)	Mean (SD)	p
Age	43 (9)	43 (10)	ns
Months since trauma	39(19)	34(17)	ns
TAQ-pos	47(11)	50(9)	ns
TAQ-neg	65(29)	45(32)	<0.01
TAQ-neg adult	26(10)	17(9)	<0.01
BMI	27 (5)	26 (5)	ns
	Proportion	Proportion	
Female/male	7/17	7/22	ns
Swedish born/foreign born	11/13	20/9	ns
Co-habiting/single	14/10	20/9	ns
Single trauma/several traumas	2/22	18/11	<0.05
Trauma-type PUT/assault	17/7	22/7	ns
Smoker/non-smoker	11/13	12/17	ns
Previous psychiatric/psychol. care yes/no	3/21	0/29	ns
Present psychotropic medication yes/no	2/22	1/28	ns

Table 4. The mean (SD) scores in psychiatric symptoms, well-being, social functioning as well as subjective experience during the symptom provocation (SUD).

Variable	PTSD group Mean(SD) n=24	Non -PTSD group Mean(SD) n=29	P
GAF	64(5)	87(6)	<0.01
HAM-A	17(6)	5.5(4.3)	<0.01
HAM-D	8.8(3.4)	1.9(2.1)	<0.01
IES	37(14)	7.5(8.9)	<0.01
BAI	15(10)	2.9(4.0)	<0.01
WHO -10	11(5)	19(5)	<0.01
SDI	5.4(3.3)	2.0(2.2)	<0.01
SUD-vividness	3.7(1)	3.5(0.8)	ns
SUD-negative feelings	2.7(0.9)	1.7(0.8)	<0.01
SUD-bodily reactions	2.2(0.9)	1.6(0.7)	<0.01

Therapy

The randomized controlled trial of EMDR therapy

In **Paper II** the randomized controlled trial is described. The pre-defined primary effect variable was remission of PTSD. The fidelity check validated that the given therapy was in accordance with the EMDR protocol. There were no drop-outs during therapy. Eight of 12 subjects (67%) remitted during therapy in the treatment group compared with one of nine in the waiting-list group ($p<0.05$).

In Table 5 the levels of psychiatric symptoms, social functioning and well-being before and after treatment/waiting-list periods are shown. There were after treatment/waiting-list significant differences between the treatment group and the waiting-list group in psychiatric symptoms as measured by the HAM-D and HAM-A, and in global functioning as measured by the GAF scale.

The levels of psychiatric symptoms and well-being in the treatment group were all changed significantly in the direction to normality (Table 5). Only the Social Disability Index remained unchanged immediately after EMDR. There was no significant change in scores on psychiatric symptoms, well-being or social functioning in the waiting-list group.

According to the Helsinki Declaration, in a randomised trial all subjects must be offered the best treatment found in the study. In this case the waiting-list subjects were also offered EMDR treatment.

Table 5. The psychometric and SUD scores (mean SD) for the treatment and waiting-list groups before and after EMDR/WL and the significant change between and within groups.

Variable	Before EMDR/WL						After EMDR/WL					
	EMDR			WL			EMDR			WL		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
GAF	12	64	3.6	9	65	3.9	12	79*†	13	9	67	6
HAM- A	12	16	6.5	9	18.2	6.6	12	9.8*†	7.2	9	16.1	5.1
HAM- D	12	8.7	3.7	9	9	3.2	12	5.4*†	4.9	9	9.7	4.3
IES	12	39	17	8	39	13	12	23†	17	9	34	16
BAI	12	16.7	10	8	13.1	9.3	12	9.5†	14	8	11.4	4.9
WHO-10	12	10.3	6.4	9	11.9	5.3	12	14.8†	8.2	9	12.7	4.8
SDI	12	4.5	2.3	8	5.9	4.5	12	4.2	3.3	9	5.4	3.4

Note. *= $p<0.05$ between groups difference.

†= $p<0.05$ within group difference.

Changes during the 35-month follow-up after EMDR therapy in the total treatment sample (Paper III)

After the waiting-list period those subjects who were on the list were also offered EMDR treatment, which was accepted by all. Including the first therapy group, altogether 20 subjects completed treatment without drop-outs during therapy. This group was followed for 35 months after the end of therapy.

Immediately after treatment, 12 subjects (60%) were no longer diagnosed as having PTSD. One subject was lost to follow-up before the eight months assessment and two more subjects before the 35 months assessment. Their last diagnostic status was carried forward. With this intent-to-treat analysis 14 subjects (70%) had lost the diagnosis at eight months as had 13 (65%) at 35 months. There was not any significant difference in treatment outcome between men and women either immediately after therapy or at 35 months.

In the group of 17 study completers (per protocol analysis) 13 subjects (76%) were no longer diagnosed as having PTSD at the 35 months follow-up. One subject who had lost the diagnosis immediately after treatment and at eight months became diagnostic again at 35 months after a severe illness. Two subjects who immediately after treatment were still diagnosed as having PTSD lost the diagnosis at eight and 35 months, respectively. One subject retained the PTSD diagnosis immediately after treatment, lost it at 8 months but regained it at 35 months.

Only two subjects had received additional psychiatric treatment, consisting of psychotropic medication, in the follow-up period between eight and 35 months, one initial remitter and one non-remitter.

Psychiatric symptoms, social functioning and well-being

Scores on psychiatric symptoms, social functioning and well-being in the total treatment group are presented in Table 6 (last observations carried forward, *i.e.* intent-to-treat analyses). All scores except the WHO (Ten) and SDI changed significantly immediately after treatment and this change remained during the follow-up. At the eight months assessment the WHO-10 score was significantly increased from before treatment and remained so at the 35 months assessment.

The changes regarding psychiatric symptoms, social functioning and well-being in the two categories of initial remitters and non-remitters are shown in Table 7 (intent to treat analysis). As can be seen, in the group of initial remitters, the initially significant changes after therapy compared with scores before treatment remained during the follow-up period. The only exception to this was that the scores on the SDI changed significantly in the direction of normality, compared with scores before treatment, not until the 35 months assessment.

In the group of initial non-remitters, a significant difference developed between IES scores before treatment and at the 35 months assessments. In other respects, this group neither improved nor deteriorated significantly during the 35-month observation period. The effect sizes (Cohen's *d*) pre-treatment/post-treatment and pre-treatment/35 months were calculated for the group of all treated subjects, the initial remitters as well as the non-remitters (Table 8). As can be seen, effect sizes were good or excellent for nearly all secondary outcome measures both immediately after therapy and at 35 months.

Table 6. Pre-, post-, and follow-up scores, mean(SD), in psychiatric function, well-being and social disability for all subjects (n=20).

	Before treatment	Directly after treatment	8 months	35 months
GAF	64(4)	76(12)**	77(11)**	76(13)**
HAM-A	17(6)	11(7)*	10(7)**	10(7)**
HAM-D	9(4)	6(4)**	5(5)**	6(5)*
IES	26(8)	15(11)**	15(12)**	15(10)**
BAI	16(10)	9(12)*	10(12)*	11(12)*
WHO-10	11(6)	14(7)	15(8)*	13(7)*
SDI	5.3(3.3)	4.8(3.6)	5.2(4.5)	3.9(4.0)

Note. Significant within subject difference: * = ($p < 0.05$); ** =($p < 0.01$).

Table 7. Pre-, post-, and follow-up scores, mean(SD), in psychiatric function, well-being and social disability in remitters (R), n=12), and non-remitters, n=8, (NR), respectively.

	Before treatment		Directly after treatment		8 months		35 months	
	R	NR	R	NR	R	NR	R	NR
GAF	64(3)	65(4)	84(8)†††*	65(16)	85(7)†††*	67(8)	84(9)†††*	64(8)
HAM-A	17(8)	17(5)	7(5)†††*	17(5)	6(5)††*	14(6)	7(5)††*	18(5)
HAM-D	8(4)	10(2)	3(3)†††*	10(3)	3(3)†††*	9(4)	4(3)†*	10(4)
IES	39(18)	43(10)	14(15)††*	34(14)	18(8)††	26(22)	16(15)††	27(18)†
BAI	14(9)	18(11)	5(4)††*	16(17)	5(5)††*	13(10)	6(4)††*	18(16)
WHO-10	12(6)	10(6)	17(6)†*	8(4)	17(6)†*	12(9)	18(6)†*	8(5)
SDI	4.7(2.5)	6(4.1)	3.8(3.3)	6.3(3.9)	3.6(4.0)*	6.7(4.8)	2(2)†*	6.8(4.6)

Note. † = significant difference ($p < 0.05$), or †† ($p < 0.01$) for R and NR groups, respectively, compared to baseline values. * = significant between group difference ($p < 0.05$), or ** ($p < 0.01$).

Table 8. The effect size (Cohen's *d*) in all subjects, the initial remitters and the non-remitters (NR).

	Pre-treatment/post-treatment			Pre-treatment/35 months		
	All	Remitters	Non-remitters	All	Remitters	Non-remitters
GAF	1.3	3.3	0	1.3	3.0	-0.2
HAM-A	0.9	1.5	0	1.1	1.5	-0.4
HAM-D	0.8	1.4	0	0.7	1.1	0
IES	1.4	1.5	0.7	1.2	1.7	1.1
BAI	0.6	1.3	0.1	0.5	1.2	0
WHO-10	0.5	0.8	-0.4	0.3	1.0	-0.4
SDI	0.1	0.3	-0.1	0.4	1.2	-0.2

Working capacity

Working capacity before EMDR and at follow-up is an important indicator of real life changes. Four of 20 (20%) had full working capacity before therapy but 12 of 20 (60%) at 35 months after end of therapy ($p<0.05$). Of the initial remitters, three of 12 (25%) had full working capacity before treatment, but 10 of 12 (83%) at 35 months ($p<0.05$). One of eight (13%) of the non-remitters worked before treatment, and two of eight (25%) at 35 months.

Heart rate and blood pressure (Paper VI)

Heart rate and blood pressure (Paper VI) in the PTSD and the non-PTSD group

One subject displayed extreme changes in physiology during the symptom provocation. This subject was excluded from all analyses. However, this did not affect the statistical outcomes. There were no significant differences between the PTSD group and the non-PTSD group in terms of resting heart rate and blood pressure. In both groups, heart rate, systolic and diastolic blood pressure increased significantly after symptom provocation. These results are presented in Table 9.

Table 9. The mean (SD) values in heart rate, systolic and diastolic blood pressure before and after symptom provocation.

Variable	PTSD group n=21	Non PTSD group n=26
HR-Before	62(8)	63(10)
HR-After	75(18)*	70(12)*
SBP-Before	120(14)	118(14)
SBP-After	139(28)*	131(18)*
DBP-Before	83(35)	79(13)
DBP-After	87(12)*	83(11)*

Note. *= difference before and after symptom provocation $p<0.01$.

Heart rate and blood pressure before and after therapy (Paper VI)

As is described in **Paper VI** and with values shown in Table 10, during the script-driven symptom provocation, heart rate and blood pressure increased significantly ($p<0.01$) for both the initial remitters and the non-remitters. This result was produced both before and after treatment. By contrast, the change in SUD scores towards normality was significant ($p<0.01$) only for the initial remitters but not for the non-remitters.

Table 10. Heart rate, blood-pressure and SUD, mean (SD), during the script before and after EDMR in remitters (R) (n=12) and non-remitters (NR) (n=6-7).

Variable	Group	Before treatment		After treatment	
		<i>Before script</i>	<i>After script</i>	<i>Before script</i>	<i>After script</i>
Heart rate	R	61(9)	71(13)	61(10)	68(13)
	NR	65(6)	76(11)	63(5)	70(7)
Systolic BP	R	127(14)	147(27)	113(11)	123(15)
	NR	127(14)	147(27)	127(18)	141(29)
Diast BP	R	73(5)	84(11)	73(6)	79(7)
	NR	81(8)	89(10)	81(7)	90(10)
SUD	R	2.2(0.8)		1.4(0.4)*	
	NR	2.4(1.1)		2.2(1.0)	

Note. *= difference between values before and after treatment, $p < 0.01$

Cerebral blood flow (**Papers I, IV and V**)

Cerebral blood flow in the PTSD and the non-PTSD group

Forty-seven of the 53 subjects underwent a SPECT in order to explore the rCBF. In the total sample, the right hemisphere had a higher relative rCBF distribution than the left hemisphere. There was a relatively higher CBF distribution in the subjects with PTSD compared with subjects without PTSD in the analysed VOIs. (**Paper I**). This was a general response not restricted to specific VOIs. However, the highest CBF distribution was found in the right hemisphere in the group of assaulted subjects, irrespective of PTSD diagnosis.

Discriminant analysis performed to explore the ability of SPECT data (all analysed VOIs) to differentiate between the PTSD group and the non-PTSD group was consistent with clinical diagnosis in 66% of cases with a sensitivity of 75% and a specificity of 59%. When the type of traumatic stressor was taken into account (person under train accident or assault) the discriminant analysis correctly classified 72% of cases, identifying 86% of the assaulted subjects, and 67% of persons having experienced a person under train accident.

SPECT data were cross-checked with MRI in 36 of the 47 trauma exposed subjects (**Paper V**). Temporal lobes and hippocampi were segmented for statistical analysis. VOI analysis for all subjects showed a lower rCBF distribution in the left hemisphere of the two investigated regions (**Paper V**). There was a higher rCBF distribution in 17 PTSD-subjects versus 19 non-PTSD subjects and this difference was significant in the left temporal lobe.

In a non-published investigation of the 47 subjects from **Paper I** we restricted the analysis to the temporal lobes, regions that at the time of publication were not analysed specifically. We then found a higher CBF distribution in both the left ($p<0.01$) and the right ($p<0.05$) temporal lobes in PTSD-subjects as compared with non-PTSD subjects. The finding of a higher CBF distribution in the right temporal lobe in all the 47 subjects taken as a whole was also confirmed.

Using voxel-based analysis (SPM) of smaller areas, the analysis of differences between subjects with PTSD and the non-PTSD group before treatment manifested significant increase of tracer uptake in the left temporal pole (BA38), the left parahippocampal gyrus (BA36) and the orbito-frontal cortex (BA11).

Changes in rCBF after treatment (Paper IV)

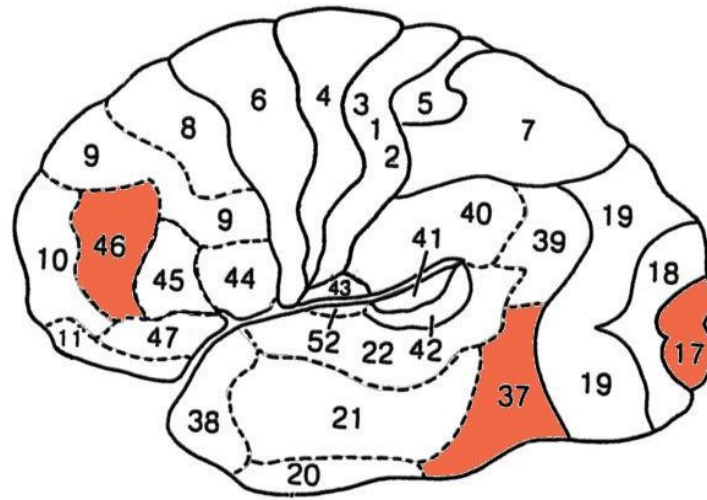
There was a significant difference in global tracer uptake in VOI analysis in the PTSD-group ($n=15$) before treatment compared with the non-PTSD ($n=27$) group. This difference remained after treatment. When we restricted the analysis to the 11 immediate remitters we found a within-subjects trend towards normalisation and there was no longer a significant difference in tracer uptake between the remitters and the controls. However, there was no significant within-subject difference before and after therapy.

Comparing the 11 remitters with the four non-remitters there was no difference before treatment but a significant difference after treatment. This difference was due to significantly increased rCBF in the dorso-lateral prefrontal cortex (DLPFC) (BA 46) and significantly decreased rCBF in the primary visual cortex (BA17), the occipito-temporal multimodal association cortex (BA 37) and in the hippocampi (**Paper IV**). These results are shown in Figure 2.

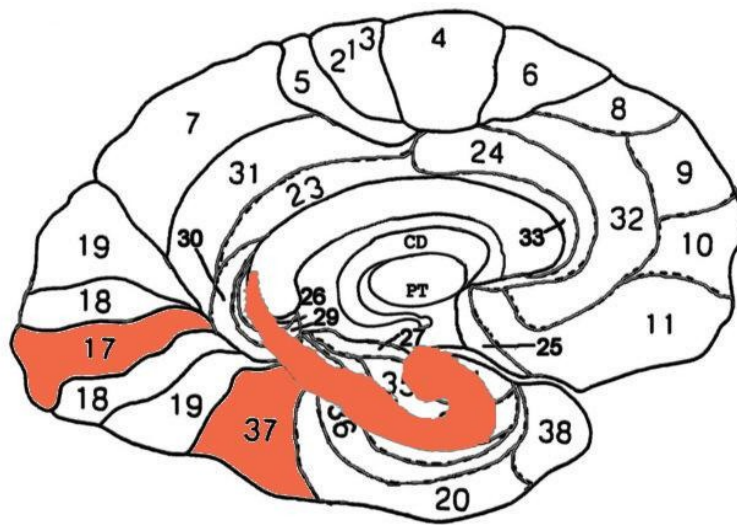
Using voxel-based analysis (SPM) of smaller areas the significant increase found before treatment in comparison with controls in the temporal pole (BA 38) and the orbito-frontal cortex (BA 11) remained after treatment. By contrast there was after EMDR treatment an increase of rCBF activity in the lateral temporal cortex (BA 21) and the hypothalamus, and a normalisation of rCBF activity in the parahippocampal gyrus (BA 36).

Brain volumetrics (Paper V)

Considering all 36 subjects on whom MRI was performed we found a significant decrease in the size of the left temporal lobe compared with the right one. There were no such hemispheric differences in the size of the hippocampi. No correlation was found between the volumetric data and the rCBF. The hippocampi of remitters on both sides were, before EMDR, significantly larger than the ones of non-remitters ($p<0.05$) (unpublished data).



LATERAL



MEDIAL

Figure 2. The areas with significant difference between remitters and non-remitters are highlighted. Areas shown are the visual cortex (BA17), the occipito-temporal cortex (BA37), the hippocampus and the dorsolateral prefrontal cortex (DLPFC) (BA46).

DISCUSSION

The study sample

General aspects

The total study sample was characterised by the lack of comorbidity, low previous psychiatric care and sparse present psychotropic medication. All participants had been exposed to one of two defined trauma types and they had similar working situations. This might lower the impact of confounding factors. None of the subjects were lost during therapy and there were only very few drop-outs during the 35 month follow-up. This is suited to give credibility to the findings.

Psychiatric symptoms, social functioning and well-being

As expected, the PTSD subjects as compared to the non-PTSD group had much higher mean scores on psychiatric symptoms and lower scores on well-being and social functioning (Table 3). The only psycho-social characteristics of the participants that were different between subjects with and without PTSD was the number of traumas and also the trauma load as measured by the TAQ-scale, indicating that repeated trauma exposure increases the risk for developing PTSD. This finding supports the notion that classical Pavlovian conditioning plays an important role in the development of PTSD (Coupland, 2000). Such increased PTSD-symptomatology in train drivers with two or more previous accidents was also reported by Karlehagen *et al.* (1993). Al Saffar *et al.* (2003) also found a relationship between number of traumas and risk for PTSD among psychiatric outpatients.

Therapy

The randomized controlled trial of EMDR therapy (Paper II)

Notable is that all subjects completed the treatment. This implies that the EMDR therapy was well accepted. The treatment was given in up to five sessions of one and a half hours which in psychotherapy is considered a brief treatment. One important question is what effect the research procedure proper had upon symptoms. In one study (Kolk *et al.*, 2007) an initial pill placebo effect as high as the EMDR treatment effect was found. This was attributed to the effects of the research procedure. In our randomised controlled trial, the waiting-list group was exposed to five research interventions of about four hours duration each that in every instance included an amount of exposure to trauma-related cues as well as the undivided attention of the research staff. These procedures might in themselves make up a treatment. But in the waiting-list group only one subject lost the PTSD diagnosis so this research-condition effect was not a major one. The advantage of the waiting-list design is that the procedural effects can be thus evaluated. The negative aspect of the waiting-list design is that the placebo effect of EMDR cannot be established. In order to evaluate what outcome is due to credibility, expectancy and self-hypnosis and what is caused by treatment-specific factors there must be a structurally equivalent placebo treatment (Baskin *et al.* 2003). We can safely state that there was a substantial initial curative effect of EMDR that might be a placebo or a combination of a placebo and a treatment-specific effect.

Table 12. Randomised controlled trials of EMDR in PTSD (only the EMDR treatment arm). Author, year, number of subjects, type of trauma, mean age of subjects, mean years since trauma, gender proportion and percent of remitters defined by PTSD diagnosis or clinically significant change (two standard deviations) or falling within normative data scores post-treatment.

Author, year	Subjects N	Trauma type	Age years	Years since trauma	Men/ women	Remission rate %
Shapiro 1989	22	Rape, Vietnam War combat	53	23	5/17	64
Boudewyns <i>et al.</i> 1993	9 (20)	Vietnam War combat	—	> 20	17/0	—
Jensen 1994	25	Vietnam War combat	43	>20	25/0	0
Renfrey & Spates 1999	8(23)	Mixed	—	—	5/18	—
Vaughan <i>et al.</i> 1994	12 (36)	Mixed	32	6.6	13/23	60
Silver <i>et al.</i> 1995	13 (100)	Vietnam War combat	46	> 22	100/0	—
Wilson <i>et al.</i> 1995	80	Mixed	39	14	40/40	—
Pitman <i>et al.</i> 1996	17	Vietnam War combat	44	>21	17/0	—
Rothbaum 1997	10 (21)	Rape	31	5	0/10	90
Marcus <i>et al.</i> 1997	33 (67)	Mixed	43	—	14/53	77
Deville <i>et al.</i> 1998	19 (51)	Vietnam War combat	50	22	51/0	67
Scheck <i>et al.</i> 1998	30 (67)	Childhood trauma, 50% sexual	22	—	0/60	100
Carlsson <i>et al.</i> 1998	10 (35)	Vietnam War combat	52	>22	10/0	78
Deville & Spence 1999	17 (32)	Mixed	40	9	8/15	73
Cusack & Spates 1999	13 (27)	Mixed	35	—	4/23	—
Rogers <i>et al.</i> 1999	6 (12)	Vietnam War combat	50	>26	6/0	—
Ironson <i>et al.</i> 2002	10 (22)	Mixed	30	—	5/17	90
Lee <i>et al.</i> 2002	12 (24)	Mixed	35	Recent	13/11	83
Power <i>et al.</i> 2002	34 (105)	Mixed	39	3.4	15/12	60
Taylor <i>et al.</i> 2003	19 (60)	Mixed	37	9	15/45	40
Rothbaum <i>et al.</i> 2005	25 (72)	Rape	34	12	0/72	60
van der Kolk <i>et al.</i> 2007	29 (88)	Mixed	39	12.2	7/22	76
All studies	EMDR 453					65

Note. — = not reported

Table 13. Randomised controlled trials of EMDR in PTSD, or near PTSD, (Only the EMDR treatment arm). Author, year, comorbidity, psychotropic medication, previous therapy and delivered treatment.

Study	Co-morbidity (%)	Psychotropic medication (%)	Previous therapy and psychiatric care	Treatment. EMDR if not otherwise stated
Shapiro 1989	—	—	100%, mean 6 years	One session of EMD
Boudewyns <i>et al.</i> 1993	—	—	—	Two 90-min sessions of EMD
Jensen 1994	40	—	—	Three sessions
Renfrey & Spates 1999	—	—	—	Up to six sessions of EMD
Vaughan <i>et al.</i> 1994	17-55	Up to 31	Up to 31%	Four 50 min sessions
Silver <i>et al.</i> 1995	—	—	—	One to three sessions
Wilson <i>et al.</i> 1995	—	—	64%	Three 90 min sessions
Pitman <i>et al.</i> 1996	100	—	—	About ten including placebo treatment
Rothbaum 1997	—	—	30% concurrent	Four sessions
Devilly <i>et al.</i> 1998	—	—	—	Two 90-min sessions
Scheck <i>et al.</i> 1998	—	—	—	Two 90-min sessions
Carlsson <i>et al.</i> 1998	—	—	80%	Twelve 60-75 min sessions
Devilly & Spence 1999	—	43	About 50%	Up to eight 90 min sessions
Cusack & Spates 1999	—	—	—	Three 90-min sessions
Rogers <i>et al.</i> 1999	—	83	100%	One 60-90 min sessions
Ironson <i>et al.</i> 2002	—	—	—	Three to six sessions
Lee <i>et al.</i> 2002	—	42	33%	Nine 90-min sessions
Power <i>et al.</i> 2002	—	70	37%	Up to ten 90 min sessions
Taylor <i>et al.</i> 2003	12-42	48	—	Eight 90-min sessions
Rothbaum <i>et al.</i> 2005	65	—	—	Nine 90 min sessions
van der Kolk <i>et al.</i> 2007	Mean no. of diagnoses 3.1	0	—	Six 90 min sessions

Note. — = not reported

Tables 12 and 13 outline the characteristics of the EMDR-treated groups in previous randomized controlled trials in PTSD. The studies focused on different populations such as war veterans (eight studies), adult and childhood sexual trauma (four studies) and mixed civilian trauma (eleven studies). Comorbidity from 12% to 100% was reported in five studies. Previous psychiatric therapy, including psychotherapy, was reported in nine studies, ranging from 30% to 100% of the samples. Ongoing psychotropic

medication was reported in six studies with a range from 31% to 83%. These factors might have been of importance for the reported outcomes. Our study population was previous-treatment and present-medication naïve and without comorbidity, which might increase the probability that our treatment results were related to the study intervention.

The duration of the symptoms was another factor that differed between studies. In studies with Vietnam War veterans, 20-30 years had elapsed since the index trauma, as also is the case in studies of childhood sexual assault. With such a long duration of PTSD, factors such as substance abuse and other negative life-style variables might have worsened the disorder, which might also have grown to be a more established part of the subjects' identity. In our study we chose a five-year trauma interval, where our subjects were still associated with the employer and the prospect of vocational rehabilitation.

EMDR seemed to work equally well in our study with women as with men, which is in line with the positive results both in studies of male-only Vietnam War veterans and of women-only sexually abused subjects. In our study there were about 30% women and with respect to this and to trauma types our study is best compared to studies on mixed civilian trauma.

The number of given EMDR-sessions varied across studies; was not fixed in six studies and fixed in 15. In previous studies, the number of given sessions varied from one to 12 (mean five). In our study we chose to have a fixed number of five sessions. However, a fixed number of sessions is not ecologically sound and a flexible number of sessions could have improved our results.

In previous studies, remission as defined by diagnostic status or clinically significant change occurred after EMDR in 65% of cases. In the mixed trauma studies, this proportion was 67% as compared to 67% remitters post-treatment in our study.

The SUD was presented in nine studies. This measure follows the reaction to a trauma-trigger and was in most studies a process factor in the EMDR treatment (Shapiro, 1989; Jensen, 1994; Marcus *et al.*, 1997; Rogers *et al.*, 1999; Cusack & Spates, 1999; Devilly & Spence, 1999; Ironsson *et al.*, 2002). In some studies there was a SUD rating on a provocation both at a fixed time and during treatment (Devilley *et al.*, 1998; Devilly & Spence, 1999) independent of the treatment situation. The introduction of this measure in PTSD research comes from the field of psychophysiology and its relevance for outcome is not clear. The unique quality of the SUD is that it monitors the actual level of anxiety during some part of the treatment session. In our study, the SUD was only recorded in the context of a script-driven symptom provocation and there was a significant pre- and post-treatment difference ($p < 0.01$).

IES was recorded in eight studies (Marcus *et al.*, 1997; Rothbaum, 1997; Scheck *et al.*, 1998; Carlsson *et al.*, 1998; Rogers *et al.*, 1999; Devilly & Spence, 1999; Lee *et al.*, 2002 and Power *et al.*, 2002). This self-evaluation scale records intrusion and numbing related to the trauma during the past week. The pre-treatment mean score across previous studies was 46 and in our study 39. For the post-treatment scores the figures were 24 and 23, respectively. The GAF-scale, which is an assessor rated global function evaluation, was used in one other study (Marcus *et al.*, 1997), where the pre-treatment mean score of 63 and post-treatment score of 78 are very close to our figures of 64 and 79, respectively. The HAM-A was used in one previous study (Power *et al.*, 2002) where the mean scores pre- and post-treatment were 26 and 16 as compared to 16 and 10 in our study. The HAM-D was used in one other study (Vaughan *et al.*, 1994). Here the mean scores were 14 and 10 pre- and post-therapy compared with 9 and 6 in our

study. The HAM-D is a multi-functional scale with ratings of mood, sleep, anxiety, somatic status, work situation and comorbidity. In our study the only subject with major depressive disorder was not allowed to enter the study according to the inclusion criteria. Actually, Hamilton originally stated that the use of the HAM-D could only be justified in patients who had already received a diagnosis of depression (Hamilton, 1960). Only our study used the BAI, and the WHO-10. The BAI showed a prompt and robust immediate change post-treatment indicating the effect of EMDR on anxiety symptomatology. Finally, the WHO-10 followed the results of the other psychometric scales that showed improvement at post-treatment, indicating that this scale can be used in assessment of quality of life in PTSD. An advantage of this scale that it can be used across psychiatric and somatic conditions.

Changes during the 35-month follow-up after EMDR-therapy in the total treatment population (Paper III)

Altogether, the treatment arm of the randomized controlled trial and the waiting-list group who later were offered treatment comprised 20 subjects. All completed treatment without any drop-out which indicates that the treatment was well tolerated. Immediately after treatment 12 (60%) subjects remitted, 14 (70%) at 8 months and 13 (65%) at the 35 months follow-up. This is a new – and promising – finding, as no previous studies on the effect of EMDR have had such a long follow-up period. There was little diagnostic crossover; one initial remitter had relapsed at 35 months after severe somatic illness whereas two initial non-remitters had remitted at 8 and 35 months, respectively. This stability in initial treatment results over time favours a notion of a true treatment effect as the placebo effect is considered to be of shorter duration. There was no significant difference in outcome between the sexes at 35 months.

In order to be able to evaluate real life changes after psychotherapy it is important to evaluate social functioning. One study of EMDR reported immediate positive change in social functioning after EMDR (Power *et al.* 2002) whereas in our study there was no significant improvement in SDI and working capacity until at 35 months.

In order to evaluate the results in a long-term view it is important to understand the natural course of the disorder. The subjects in this study had a mean time passed of 3.2 years since the index trauma. The mean of 17 studies (Table 8) is about 15 years but this includes all the studies of Vietnam War veterans in which the time elapsed is approximated. If those studies are deleted and only those ten studies that gave a precise time since index trauma are included, the mean number of years amounts to about nine. All our subjects suffered from chronic PTSD and the natural course of the disorder indicates stability but it can be worsened as is shown by Bremner *et al.* (1996). In a community epidemiologic survey by Breslau *et al.* (1998) it was shown that after the initial 12-18 months there is a very slow remission tapering off. The conclusion is that the natural course of the disorder probably did not affect the long-term results to a large extent as chronic PTSD lasts longer than our study period.

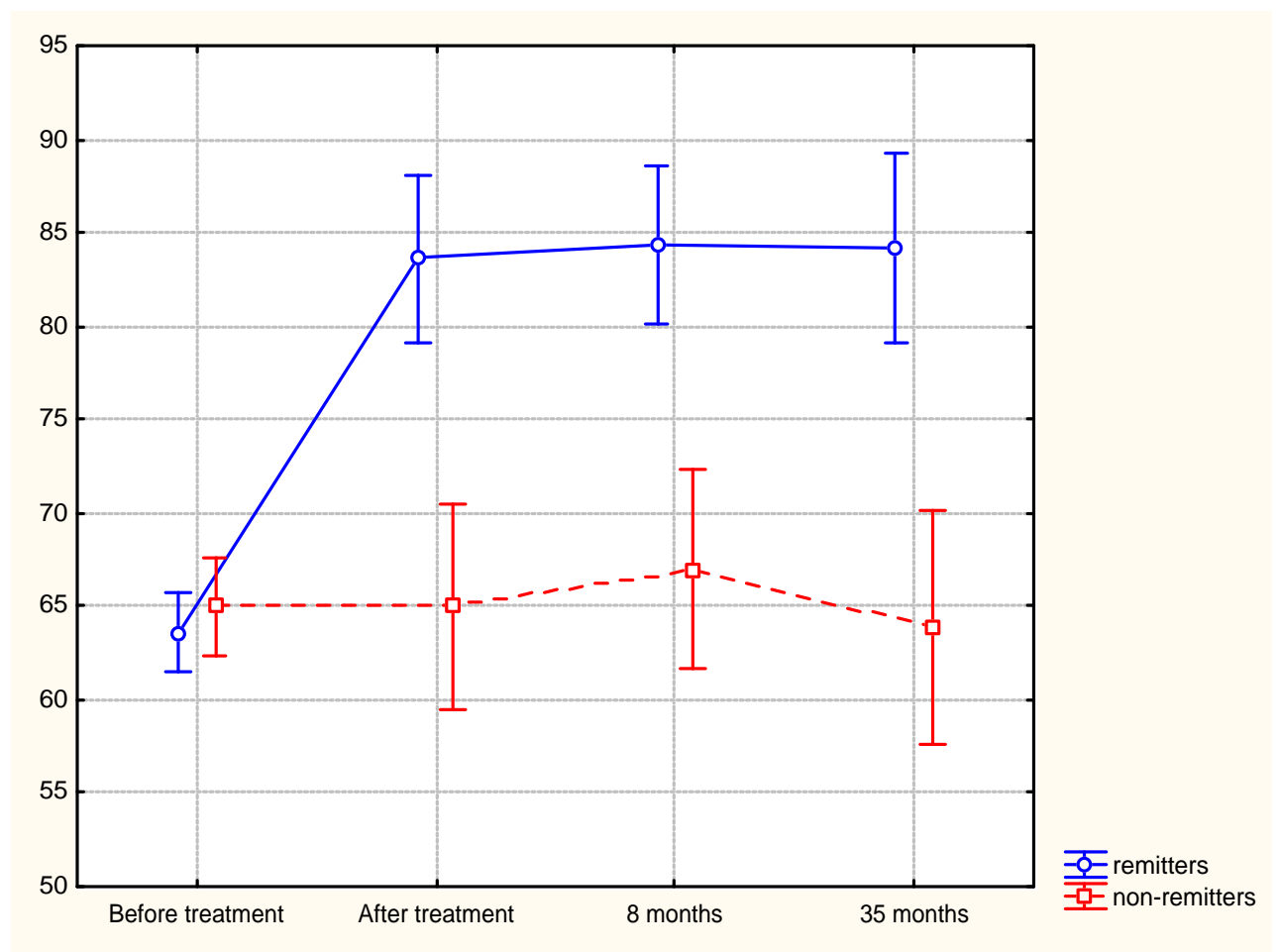
Psychiatric symptoms, social functioning and well-being

The general pattern was that an immediate positive response after therapy was maintained during the long-term follow-up. In Figure 2 this general trend is exemplified by the GAF scores before treatment, immediately after treatment and at 35 months. The

only exception was the scores of the Social Disability Index which in this study indicates that it takes time to transform improvement in psychiatric symptoms and well-being into changes in everyday life functioning. The large effect sizes in psychiatric symptoms and well-being immediately after treatment were well maintained at the 35 months assessment, underscoring the stability of initial treatment effects.

On the whole, the group of immediate non-remitters did not recover, even if there was a significant improvement in the IES scores during the 35 months follow-up. The non-remitters had a significantly higher adult trauma load than the non-remitters. Otherwise the psycho-social characteristics did not significantly differ. As the EMDR treatment refractory group is chronic and is severely socially disabled, future study of this group should look into new treatment strategies. It may be that these individuals need more EMDR-therapy, an additional treatment or another kind of treatment altogether.

Fig 3. Scores on Global Assessment of Functioning in immediate remitters and non-remitters. Mean (95% CI).



Working capacity

Our finding of a significantly increased, as compared with the situation before treatment, working capacity at 35 months in the remitters is important. This result shows real life improvement in functioning.

Heart rate and blood pressure (Paper VI)

Differences between traumatised subjects with and without PTSD (Paper VI)

In contrast to the findings regarding psychiatric symptoms, well-being and social functioning, the physiological measures of heart rate, systolic blood pressure and diastolic blood pressure in the standardised supine resting setting did not manifest any significant differences between subjects with and without PTSD. This result differs from the meta-analysis by Pole (2007), where there was a difference between subjects with and without PTSD, especially in heart rate. Reasons for this discrepancy could be that 90% of the participants in the meta-analysis were Vietnam War veterans with a different trauma type and subsequent treatment history as well as a longer duration of the disorder than those in our sample.

Further knowledge about the physiological response in our full sample was possible to gain during the script-driven symptom provocation when the physiological response was measured before and after the provocation. There was a robust increase in heart rate, and systolic and diastolic blood pressure after the symptom provocation. This indicates both an adrenaline increase affecting heart rate and systolic blood pressure as well as a noradrenergic increase affecting the diastolic blood pressure (Pole, 2007). This was true both for the PTSD and the non-PTSD group. The interpretation of this is that the physiological reaction is indicative of a conditioned reaction to danger, a fear reaction, which was provoked by the script evoking a reliving of a previously experienced dangerous situation.

The SUD scores measure subjective anxiety, which increased after provocation in the PTSD subjects; and although SUD scores in the non-PTSD group were significantly lower than in the PTSD group, there was still a significant increase in heart rate and blood pressure upon script provocation. As the physiological reaction, but not the SUD-scores, were similar in both PTSD and non-PTSD subjects it could be hypothesised that the physiological reaction mirrors an adaptive reaction to danger in these traumatised subjects and that in the PTSD subjects there was an added experience of anxiety.

Comparing with other studies using symptom provocation concomitantly with brain imaging and physiological monitoring, results are disparate. Lanius *et al.* (2004) and Liberzon *et al.* (1999) found an increase in heart rate in PTSD subjects whereas Shin *et al.* (1999) reported increased heart rate in both PTSD subjects and controls. Finally Shin *et al.* (2004) recorded increased heart rate in PTSD subjects but in both PTSD subjects and controls an increase in systolic and diastolic blood pressure. These findings suggest that the script provocation activates both a fear and an anxiety reaction in varying combinations.

Heart rate and blood pressure before and after therapy (Paper VI)

During the symptom provocation there was a significant increase in heart rate and blood pressure both before and after the EMDR treatment. This physiological activation occurred both in subjects who lost the PTSD diagnosis and those who still suffered from

PTSD. By contrast, the subjective disturbance (SUD) changed significantly in the direction of normality in the subjects who lost the PTSD diagnosis. One explanation for this could be that the symptom provocation activates two systems. One is a system of conditioned fear reaction triggered by the trauma script in all subjects and shown in the physiological reaction. The other reaction is the pathological anxiety-reaction present only in the PTSD group. There is an emerging field of making a distinction between an immediate cue-specific fear reaction and a more generalised longer context-related anxiety reaction. It is also proposed that the fear reaction is connected to activation of the amygdala whereas the anxiety reaction is related to the adjacent structure of the bed nucleus of the stria terminalis (Ahearn *et al.*, 2007; Lang *et al.*, 2000). If those two systems exist and function somewhat independently this might explain our finding of dissociation between subjective anxiety and physiological response on trigger exposure.

Our finding of a disconnection between treatment outcome and physiological response is in line with the findings of Rokicki *et al.* (1997) who studied subjects with tension headache. The tension in relevant muscles was measured with electromyography. The subjects learnt relaxation exercises and were treated with a bio-feedback procedure. Fifty percent of the subjects no longer suffered from headache post-treatment but the muscle tension as measured by electromyogram did not change.

The human emotional system is not easily compared to that of animals, as man in contrast to other mammals can control the facial muscles that express feelings. Thus, there is an element of control in thinking and modification of emotional responses, enabling coalitions, deceptions, social play, innovation and social learning (Dunbar & Schultz, 2007). It is therefore no surprise that the concept of control is paramount in understanding pathological emotional reactions. Rotter (1966), for one, expounded on this with his concept of outer or inner locus of control, as did Horowitz (1983), who viewed PTSD as a disrupted control of emotional imagery. Our results may indicate that a key element in treatment progress is the change in the perception of internal control of the physiological arousal – not the change of the autonomic arousal proper.

Risks in symptom provocation

The use of script-driven symptom provocation is well established. However, the event of an extreme physiological reaction in one subject underscores the need to conduct such studies in safe medical settings.

Cerebral blood flow (Papers I, IV and V)

The differences in rCBF between the PTSD and the non-PTSD group

Differences in memory-related areas of the brain

In this study we focused on the cardinal symptom of PTSD, the reliving on encounter with trauma related triggers. This focus has assisted us in increasing the understanding of the biology of PTSD. We found a general fear component that was akin in both the PTSD and the non-PTSD group. This general fear reaction on encounter with a trigger connected to a personally experienced traumatic event – elicited a physiological reaction with script-related increase in heart rate and blood pressure (**Paper VI**). In the brain, this general reaction in PTSD and non-PTSD subjects was manifested by a higher relative CBF distribution in the right hemisphere as compared to the left hemisphere

(**Paper I**). But in the realm of subjective experience this reaction was unrelated to the subjective fear and discomfort as recorded by SUD during the symptom provocation (**Paper VI**). The PTSD group by contrast manifested a relatively higher CBF distribution as compared to the non-PTSD group. The left temporal lobe had an increased rCBF in the PTSD subjects (**Paper V**) and there was, when SPM was used, also in the PTSD-subjects in comparison with the non PTSD group, a significantly increased tracer uptake in the temporal pole (BA 38), the parahippocampal gyrus (BA 36) and orbito-frontal cortex BA11). These findings might be related to the specific anxiety-reaction of the PTSD-subjects.

The temporal pole is part of the paralimbic belt (Mesulam, 1985) and is adjacent to and has bilateral connections with among other areas the sensory systems in the temporal lobe, the prefrontal cortex and the hypothalamus. Its function is suggested to comprise multimodal perceptual analysis and socio-emotional processing and to be activated in emotions and emotional autobiographical memory (Dolan *et al.*, 2000; Olsen *et al.*, 2007). The orbitofrontal cortex is implicated in sensory integration, judging of emotional valence of stimuli, emotional learning, motivational state, modulation of autonomic reaction and motor action preparation and decision (Mega *et al.* 1997, Kringelbach, 2005; O'Doherty, 2007), and the parahippocampal gyrus with its proximity to the hippocampus is involved in encoding of new memory (Wagner *et al.*, 1998). Our findings suggest in PTSD an activated functional network including the temporal lobe, especially the temporal pole, the orbitofrontal cortex and the parahippocampal gyrus.

Taken together, these regions are relevant in social interaction, discrimination of people and interpretation of situations, new memory encoding and fear-conditioning. Our results suggest that in PTSD there is a novelty reaction to trauma-related trigger exposure, with exploration of context and emotional valence and an ensuing memory encoding. This is in line with the concept of PTSD as a disturbance of memory where reactions to trauma-related triggers cause new trauma memories that uphold the PTSD symptomatology.

Other studies

The only study that is similar to ours with regard to study sample, script-driven symptom provocation and SPECT is the one by Lindauer *et al.* (2004) of 30 police officers with and without PTSD. They used SPM for the analysis of SPECT data which highlights small regions but cannot identify diffuse CBF changes. That study found a significant increase in rCBF activity in the right cuneus (occipital lobe) in the PTSD subjects upon provocation. However, as compared to **Paper IV**, Lindauer *et al.* used much more liberal statistical and cluster-extent thresholds, resulting in regional differences much smaller than the ones we found. Other studies using symptom provocation in PTSD subjects have found activations in the limbic system in comparison with controls, but the findings vary between studies (Francati *et al.*, 2006). This variability could be explained by differences in samples, methods and individual reactions to the symptom provocation. For instance, Lanius *et al.* (2006) described that PTSD subjects during script-driven symptom provocation could react with either hyperarousal or with dissociation, producing different patterns of brain activation. The dissociation response was more common in subjects with childhood trauma of abuse and neglect.

Differences between the right and the left cerebral hemisphere

The finding of a laterality in the reaction to the emotions evoked by the trauma script supports the findings from other areas of research that suggest an increased activity in the right hemisphere of the brain in negative emotional states. Observed emotional reactions in hemiplegia led Juys as early as 1881 to propose a right hemispheric lateralisation of feelings in general, as the subjects with damage in the left hemisphere showed strong anxiety reactions, whereas persons with right-lateralised damage often displayed passivity and seemingly loss of affect.

A further hypothesis, to a large extent based on affective experiments and EEG-recording, is a right-hemispheric lateralisation of negative affect. In PTSD subjects, resting EEG showed increased right-sided parietal activation (Metzger, 2004). In adults who had experienced childhood maltreatment there was enhanced right hemispheric activation when traumatic memories were remembered (Teicher, 2006). Varying hemispheric laterality of emotional processing was suggested to be an existing individual trait with right-sided hemispheric activation caused by negative emotions in about 70% of the cases, while about 30% had a left-sided hemispheric negative emotional valence (Schiffer *et al.*, 2007). Another study where subjects had one hemisphere anesthetized by intracarotid amobarbital showed strong negative emotional reactions with right-sided lateralization in two subjects and left-sided in two (Masia *et al.*, 2000). Our study combined with the findings from other studies suggests a hemispheric lateralization of negative emotions, and in our study, preponderantly to the right.

The amygdala

The amygdala are strongly implicated in fear conditioning but were not activated in our study; the reason for which may be both related to the low reliability in segmenting the amygdala in SPECT studies, and to the fact that a main function of the amygdala is the swift early recognition of the emotional valence of a stimulus. In our study, therefore, such activation might have preceeded the infusion of $^{99m}\text{TcHMPAO}$ (Büchel *et al.*, 1998). Such an interpretation is supported by the fact that amygdala often is not activated in script-driven symptom provocation studies (Reiman *et al.*, 1997).

Changes in cerebral blood flow after EMDR therapy (Paper IV)

Although we did not find significant within-subject changes in rCBF before and after treatment there were pre- and post-treatment differences in comparison with non-PTSD subjects and between remitters and non-remitters. These differences indicate an effect of EMDR therapy in affecting rCBF. When the PTSD subjects were treated with EMDR, the previously increased uptake in the medial temporal cortex (parahippocampal gyrus) disappeared. Considering the importance of this area for encoding of new memory this might indicate that therapy resulted in a neurophysiological change reducing the reliving caused by the trauma-related provocation. In addition, there was an extension of tracer uptake to the lateral temporal cortex and the hypothalamus.

A final observation that contributes to the understanding of the biology of PTSD is the difference in rCBF concerning VOIs between the immediate treatment remitters and the non-remitters. There was a significant decrease in rCBF in the remitters in the occipital cortex, the temporo-occipital cortex and the hippocampus and an increase in

the dorsolateral prefrontal cortex (DLPFC). This result was shown in Figure 2. The decrease in the temporo-occipital and occipital cortex might be correlated to the loss of reliving after script provocation when EMDR therapy was successful as these areas are activated in visual tasks and recognition of humans (Peelen & Downing, 2005). The DLPFC is implicated in the network of mirror neurons with important functions in imitating, preparing and executing actions in relation to the environment. DLPFC is also involved in observational learning and self-selection of intended action (Torriero *et al.*, 2007; Owen *et al.*, 1996). The activation of this region after successful EMDR treatment could be interpreted as an equivalent of increased response-flexibility (spontaneity) in subjects who are no longer haunted by the stereotypic reactions inherent in the repetitive relivings during PTSD.

A study that is in line with our results was carried out by Cohen *et al.* (2004), who found transient symptom improvement in PTSD subjects after transcranial magnetic stimulation at an activating frequency of the right DLPFC. Other studies of cerebral blood flow after successful treatment found, in comparison with pre-treatment, rCBF increases in the left inferior frontal gyrus (including DLPFC), left frontal lobe, parietal lobes, left hippocampus, thalamus, left prefrontal cortex, and the anterior cingulate cortex (Lansing *et al.*, 2005; Levin *et al.*, 1999; Peres *et al.* 2007) (Table 1). Decreases were noted in the left occipital lobe, the parietal lobes and the right prefrontal lobe. Common to all studies was an increase in the frontal/prefrontal cortex and this might indicate increased frontal control after successful treatment. This might help to restore the balance between inhibitory and excitatory impulses upon trauma triggers. The variability of results across studies might be explained by sample differences such as level of comorbidity and medication, different statistical methods, different symptom provocation techniques and differences of trauma types.

Brain volumetrics (Paper V)

Previous volumetric studies of the temporal lobe have shown neither significant side-to-side effects (Bhatia *et al.*, 1993), nor a larger left temporal lobe (Geschwind & Levitsky, 1968), nor a larger temporal lobe in the right hemisphere (Jack *et al.*, 1989). Our finding in both PTSD and non-PTSD subjects of a smaller left-sided temporal lobe is in line with the findings of Jack. Considering the uncertainty of normative data on temporal lobe lateralisation, the most important aspect of our finding is that we found no difference between PTSD and non-PTSD subjects.

The hippocampi of our PTSD and non-PTSD subjects did not significantly differ in size. This finding indicates that changes in hippocampal volume are not at hand in occupationally related PTSD.

The finding of smaller hippocampi limited to the subjects who did not respond to treatment, even if in a small sample of patients, speaks in favour of a more severely affected hippocampus in some of the PTSD subjects. The non-remitters had experienced more adult trauma and had a higher sum of the total trauma load, which might be the effect of more traumatic work incidents. Thus the variability across studies of the hippocampi and PTSD might be explained by different trauma loads and duration of stressful trauma memories.

Suggested mechanism of change in EMDR

This section is speculative as the matter of why EMDR works has not been addressed in this study.

EMDR unlearns the anxiety response to trauma-related triggers

The basic mechanism of pathology in PTSD is suggested to be a disturbance of memory when it comes to trauma-related triggers. This disturbed memory reaction, the reliving, is related to the anxiety present in PTSD. In this study EMDR succeeded in unlearning the anxiety response upon exposure to the symptom provocation. EMDR might establish new functional learning since de-conditioning of fear reactions is generally perceived as new ‘no-fear’ learning. The EMDR therapy in our study did eliminate the anxiety reaction but did not affect the fear reaction. This can be considered appropriate, as a natural level of reaction to fear signals is important in order to avoid and to handle danger at work.

Dismantling studies

The cognitive elements in EMDR were excluded in one study (Cusack & Spates, 1999) but this did not affect outcome, suggesting that cognitive restructuring is not essential to the efficacy of the method. Sanderson & Carpenter (1992) treated subjects with phobic symptoms with a single seven-set session of EMD or with a single seven-set session of image confrontation with eyes closed, *i.e.* EMD without eye movements, and both groups improved substantially.

Studies of clinical and non-clinical anxiety found that alternative eye activation such as fixating a point (Renfrey & Spates, 1994; Foley & Spates, 1995; Dunn *et al.*, 1996; Pitman *et al.* 1996; Lytle *et al.* 2002) had as good effect on outcome as EMDR with the ordinary bilateral eye movements.

The putative special value of the eye movements in EMDR

Although EMDR might function without the eye movements there are indications of eye involvement in PTSD (Hermann Oppenheim, 1892). About half of his cases showed contraction of the visual fields and a similar observation was made by Myers (1915). Kardiner (1947) commented on the findings of 40 cases of psychiatric casualties of war: “The most common visual disturbance was the contraction of the visual fields so that the vision was almost tubular.”

Clinicians who practice EMDR report that the eyes at the beginning of a session might be locked in a fearful gaze but that by moving the eyes there comes a softening and access to feelings. Another observation reported is that when aversive emotional memories emerge there are irregular eye movements but when the therapist makes the eyes follow a smooth rhythm the anxiety wanes. A third observation is that breathing seems related to eye movements (Wilson *et al.*, 1996) and that with smooth bilateral eye movements the breathing also becomes deeper and more even.

Multiple counter-conditioning sets as the proposed key element

What then, if EMDR anyhow works without cognitive re-structuring and without eye movements? What is left is the *set*, meaning the short activation of trauma memory, much like the script-driven symptom provocation in this study, which aims at

maximising the emotional memory. The set is a very brief imaginal trauma exposure as compared to the 20 – 100 minutes prolonged exposure to trauma-related cues in traditional exposure based psychotherapy (Rogers & Silver, 2002). In EMDR the evoked emotional memory is combined with sensory stimulation and after a short time of half a minute or so is interrupted by a brief report from the patient on the present emotional and autonomic status including new associated emotional memories. There is active stopping of associative talk followed by new immersion into the emotional memory. Each set could be considered to be a unit of counterconditioning as defined by Wolpe (1958): “If a response antagonistic to anxiety can be made to occur in the presence of anxiety-evoking stimuli so that it is accompanied by a complete or partial suppression of the anxiety responses, the bond between these stimuli and the anxiety responses will be weakened”. A counterconditioning mechanism in EMDR was also suggested by among others Hedstrom (1991), Shapiro (1995), Wilson *et al.* (1996), and MacCulloch & Feldman (1996). The short duration of the exposure to the traumatic memory might be a factor that is patient-friendly and increases the control of the subject as might also the fact that disclosure by the patient of emerging emotional memories is not obligatory in the process of repeated sets.

The observant reader will have noticed the similarity between the script-driven symptom provocation and the *set* in EMDR. This means that studies using imagery as symptom provocation can also be seen as studies of the key element of EMDR therapy. Both aim at evoking as strongly as possible an emotional memory. In EMDR the aim of emotional imagery is to achieve a positive transformation of the content and the techniques used are to combine the emotional imagery with positive sensory stimulation. In the present study the sensory stimulation during a set was bilateral eye movement, bilateral alternating hand tapping or bilateral alternating sound. These sensory stimuli had been positively conditioned before, both by the treatment rationale and by association to relaxation and safe-place exercises. And touch, rhythm and eye movements (Hedstrom, 1991; MacCulloch & Feldman, 1996; Barrowcliff *et al.*, 2003) are of themselves relaxing, for instance bilateral eye movements are a part of Yoga practice.

A very special feature of EMDR is the number of short sets during a treatment session, usually numbering about 10-20. Several sets enable associative processes to take place and the content of the sets often drift away from the target trauma which is then later returned to. This associative quality of the chain of sets could enhance the treatment effect as traumas from different times could add up to the pathology of PTSD.

A third reflection on the mechanism of action in EMDR is that each set is also a combination of a hypnotic induction and de-induction. Actually both strokes and eye movements are classical methods in order to induce a state of hypnotic trance. Liebhafetz (1823-1904) of the hypnotherapy ‘School of Nancy’, for instance, had the subject watch his finger move in an oval in front of the face of the subject. Thus the beginning of a set can be seen as a brief trance induction entering a state of inner focus and re-experiencing, to be influenced by the sensory stimulation and changed in affective valence. After about one-half to one and a half minutes this process is interrupted and the subject is de-inducted by stopping the sensory stimulation and asking the client direct concrete questions about present sensations. This in and out of trance could serve as a brain exercise in switching between inner memory experience mode and actual sensations mode, thus perhaps switching between temporal lobe and prefrontal activity

in the brain. The result could be increased prefrontal cortical tonic inhibition, leading to decreased anxiety and a bettered sense of control. This quality of intensive, repetitive counterconditioning sets is a unique feature of EMDR and, considering the effectiveness of EMDR, the invention of associative short sets of emotional imagery combined with sensory stimulation might prove to be a major contribution to psychotherapy.

CONCLUSIONS

Occupational health hazards such as person under train accidents and threats and violence at work are risk factors for the development of occupationally related PTSD. In this study, the PTSD group had a much higher psychiatric symptom load and lower levels of well-being and social functioning than the group of traumatised subjects without PTSD.

Five sessions of EMDR proved to be a psychotherapy that gave good results with 60% initial remission rate that was stable over time and a remission at 35 months of 65%. After therapy there was an immediate, significant improvement in psychiatric symptoms and well-being and this improvement was stable over the follow-up period. The only exception was the scale of social functioning, which compared with the scores before therapy changed significantly first at the 35 months assessment. Full working capacity improved from 20% to 60% (in the remitters to 83%) at 35 months. The effect sizes (Cohen's *d*) for EMDR therapy varied for the secondary outcome measures between 0.3 and 1.3 at 35 months. The corresponding effect sizes for the remitters were between 1.0 and 3.0 at 35 months. The group of non-remitters did not deteriorate but remained fairly stable over time. As the non-remitters might run a chronic course, further research to develop effective therapy for this group is warranted.

Since high drop-out rates in therapy are a practical problem, it is important to note that all subjects completed therapy. As to gender, it is concluded that in this sample the proportion of men and women was the same regarding PTSD diagnosis and successful therapy.

The use of personalized trauma scripts in order to provoke symptoms in the subjects was successful but warrants caution. One subject experienced an extreme physiological reaction. Symptom provocation was related to physiological changes in the peripheral autonomic nervous system as well as in the regulation of cerebral blood flow. However, the changes were observable at group level and are, at the present state of development, not of use in diagnosis or treatment evaluation.

Heart rate and blood pressure increased during symptom provocation without any significant difference between PTSD and non-PTSD subjects. This means that other psychophysiological variables must be found for diagnostic differentiation. Our finding that anxiety and perceived autonomic reactions during symptom provocation disappeared after EMDR therapy, but not the rise in heart rate and blood pressure values, indicates dissociation between anxiety and fear reactions.

Our understanding of the neurobiology of PTSD has developed through: (A) the finding of increased regional cerebral blood flow in the right cerebral hemisphere upon symptom provocation; (B) findings in the PTSD subjects of increased rCBF in areas involved in memory encoding, and (C) a trend towards normalisation of rCBF after EMDR therapy with a decrease in areas implied in memory encoding and an increase in frontal areas involved in conscious choices.

SAMMANFATTNING

Denna studie syftade till att utvärdera en ny terapimetod, eye movement desensitization and reprocessing (EMDR), för att behandla posttraumatisk stress (PTSD), samt att studera biologiska reaktioner i PTSD vid symptomprovokation.

PTSD är en sjukdom som kan uppstå efter ett allvarligt psykiskt trauma. Tillståndet utmärks av de påträngande återupplevelsorna som återför personen till upplevelser och känslor som fanns vid det ursprungliga traumatillfället. Återupplevelsorna följs ofta av undvikande av triggers som påminner om traumat, irritabilitet och känslomässig avtrubbnings. Sjukdomen är långvarig, ofta kronisk, och bidrar avsevärt till den psykiatriska sjukligheten.

I denna studie deltog femtiotre anställda vid Stockholms kollektivtrafik, varav en tredjedel kvinnor, som hade varit med om en överkörningsolycka eller blivit överfallna i arbetet. PTSD diagnosticerades genom intervju. Dessutom användes självskattningsskalor. Tjugoen av 53 hade PTSD. Dessa bägge grupper skiljde sig markant åt vad gäller psykiatriska symptom, socialt fungerande och välmående. PTSD-gruppen hade i jämförelse med icke-PTSD-gruppen varit med om fler trauman.

Deltagarna med PTSD blev randomiserade till en behandlingsgrupp och en vänteliste-grupp. Den förutbestämda primära utfallsvariabeln var remission av PTSD. Behandlingen med EMDR följde det gängse protokollet och deltagarna behandlades med fem 1,5 timmars sessioner. När sedan behandlingsgruppen jämfördes med vänteliste-gruppen noterades signifikanta skillnader mellan grupperna vad gällde remission (åtta av tolv i behandlingsgruppen och en av nio i vänteliste-gruppen), psykiatriska symptom och välbefinnande.

Även vänteliste-gruppen fick sedan EMDR-behandling och totalt fullföljde 20 personer behandlingen. Denna utvärderades genast efter behandlingen, efter 8 månader och efter 35 månader. Det ursprungliga positiva resultatet bibehölls och förstärktes. Under uppföljningstiden förbättrades även social funktion inklusive arbetsförmåga. Effektstorlek vid jämförelse mellan värdena före behandling och efter 35 månader bedömd efter GAF-skalan var för hela behandlingsgruppen 1,3. För de som blev av med sin PTSD diagnos genast efter behandlingen var motsvarande effektstorlek 3,0.

Hjärtfrekvens och blodtryck ökade signifikant vid symptomprovokation både i PTSD- och i icke-PTSD-gruppen. Detta gällde också före och efter EMDR behandlingen, oavsett behandlingsresultat. Detta bedömdes tyda på att det hos alla deltagare fanns en 'faro'-reaktion som inte var identisk med den ångestreaktion som enbart fanns hos PTSD-deltagarna.

Hela gruppen av deltagare fick efter symptomprovokationen ökad aktivitet i högra hjärnhalvan. Generellt ökad aktivitet i hjärnan noterades hos PTSD-gruppen samt allra kraftigast hos de deltagare som varit med om överfall. PTSD-gruppen hade ökad aktivitet i delar av det limbiska systemet relaterade till minnes- och känslofunktioner. Efter EMDR-behandlingen tenderade aktiviteten att minska i limbiska områden och öka i delar av framloben. Vad gäller storleken av hippocampus så fanns det ingen skillnad mellan PTSD-gruppen och icke-PTSD-gruppen. Däremot var de bägge hippocampi hos dem som inte blev bra efter behandlingen mindre än hos dem som tillfrisknade.

Sammanfattningsvis ger denna studie vid handen att EMDR är en fungerande behandling för denna grupp och vi fann även fysiologiska skillnader i hjärnaktiviteten hos de deltagare som hade PTSD.

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APPENDIX

The names of the Brodmann areas shown in Figure 1.

1 – intermediate postcentral	28 – entorhinal
2 – caudal postcentral	29 – granular retrolimbic
3 – rostral postcentral	30 – agranular retrolimbic
4 – gigantopyramidal	31– dorsal posterior cingulate
5 – preparietal	32 – dorsal anterior cingulate
6 – agranular frontal	33 – pregenual
7 – superior parietal	34 – dorsal entorhinal
8 – intermediate frontal	35 – perirhinal
9 – granular frontal	36 – ectorhinal
10 – frontopolar	37 – occipitotemporal
11 – prefrontal	38 – temporopolar
12 – prefrontal	39 – angular
17 - striate	40 - supramarginal
18 – parastriate	41 – anterior transverse temporal
19 – peristriate	42 – posterior transverse temporal
20 – inferior temporal	43 - subcentral
21 – middle temporal	44 - opercular
22 – superior temporal	45 - triangular
23 – ventral posterior cingulated	46 – middle frontal
24 – ventral anterior cingulated	47 - orbital
25 – subgenual	48 - retrosubicular
26 – ectosplenial	52 - parainsular