Investigating new process-focused treatments for posttraumatic stress disorder : attentional bias modification and mindfulness-based cognitive therapy

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Investigating new process-focused treatments for posttraumatic stress disorder:
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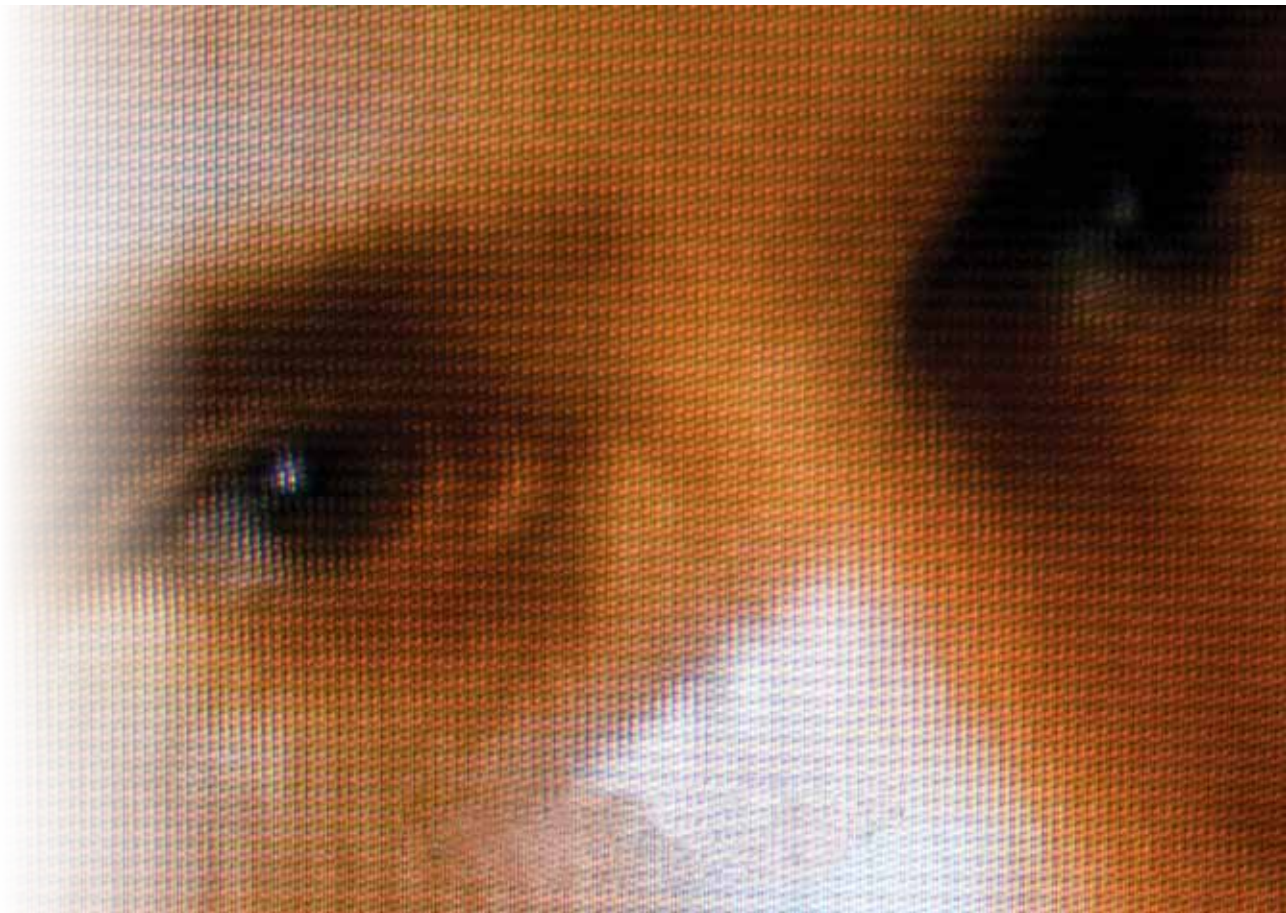
De eerste zes maanden heb ik niet gehuild. Toen merkte ik dat ik soms huilde in mijn slaap. Nu kan ik weer normaal huilen, net als iedereen. Ik wil leven. En de dood die me niet gewild heeft – nou ja, heeft-ie pech gehad.

Yolande Mukagasana (*De dood wil mij niet,* 1998)

1

General introduction



Introduction

Recently I moved into a new room at my workplace; a mental health care department for treatment of posttraumatic stress disorder (PTSD). Interestingly, this new office seems designed for detecting attentional problems in patients. Next to the door, there is a narrow window partly covered with foil. There is a small part uncovered, through which you can see the feet of people passing my office. During therapy, some patients are not able to ignore the images of these moving feet, and they turn their head almost every time someone passes by (which is actually quite often). Other patients don't even seem to notice the shadows.

Ms. B was a 21-year-old student from Nigeria. In childhood, she had been severely molested by her parents. Ms. B had nightmares, was afraid to go to sleep and had very vivid re-experiences of the occurred events. She had never talked to anyone about the physical abuse. Furthermore, she said she was ''unable to relax''. Her scores on a self-report questionnaire for PTSD were very high. When she first entered treatment (exposure therapy; Keijsers, van Minnen, & Hoogduin, 2004), she expressed the need to have the occurred events erased from her memory. She also indicated that her studies were very important to her, and that she felt competent at university, for the first time in her life.
At the start of treatment, I had noticed that Ms. B was very vigilant. She would keep her jacket and hat on and she sat on the edge of the seat. However, she was not distracted by the feet passing by.

Therapy did not result in quick symptom relief. We reached agreement on the treatment method but Ms. B stated that she hated to think back of the traumatic experiences, the details of which were indeed horrifying. Nonetheless, she did do her homework (listening to the audio taped version of the therapy sessions).
After the fourth session no progress seemed to have been made yet, as the scores on the self-report questionnaire for PTSD symptoms that she filled in every session were unchanged. Although I did not tell Ms. B, at that time I began to doubt that exposure therapy would help her. I noticed that I attributed this supposed failure of the therapy to the extremity and duration of the abuse.

Since the protocol for exposure therapy contains ten sessions, we continued therapy. When Ms. B came in for the fifth session, the scores on her homework showed that her anxiety had gone down for the first time after listening to the tapes. She confirmed this change, and told that she had also experienced fewer flashbacks during the past week.
Her improvement continued rapidly after this session. Her PTSD symptoms reduced and she was able to sleep and had fewer nightmares. She also reported that she experienced herself as more outgoing. She said she felt finally as a ''normal'' student; she went out with friends and had fun.

At the end of treatment we evaluated the therapy process. I mentioned the observation that I made at the start of treatment (her not being distracted) and Ms. B confirmed that she had a strong ability to stay focused, even when she was bothered by her PTSD symptoms. I wondered how her high level of attentional control might have contributed to the effect of therapy. But regardless of the mechanisms involved, this case illustrates the increasing awareness in clinical psychology that cognitive problems or strengths deserve more attention when diagnosing and treating patients.

Posttraumatic stress disorder

Posttraumatic stress disorder (PTSD) is a syndrome that may develop after exposure to a traumatic event. It is the only psychiatric disorder mentioned in the DSM-IV (APA, 2000) that is also defined by an etiologic factor. The event(s) have to involve life threatening danger or injury or have to have been physically threatening to oneself or others (for a description, see table 1). A subjective negative emotional reaction to the event is also part of the diagnostic criteria.

In the Netherlands, about 80% of all individuals experience one or more traumatic event(s) during lifetime. About 7% of these individuals develop symptoms as described in table 1 (De Vries & Olff, 2009). In the United States (US), about 90% of the population is exposed to at least one traumatic event during lifetime. Lifetime prevalence of PTSD is an estimated 6.8% (Kessler et al., 2005) to 9.2% (Breslau et al., 1998), depending on the nature of the traumatic event. Assaultive or interpersonal violence is associated with the highest rate of subsequent PTSD (20.9% chance). However, the type of trauma most likely to cause PTSD is the sudden unexpected death of a loved one; about 60% of all individuals in the US experience this type of event during lifetime, and the chance of consequently developing PTSD is 14.3% (Breslau et al., 1998).

Approximately 82% of all individuals diagnosed with PTSD fulfil the criterion of chronicity (duration at least three months) and about 74% continue to have symptoms after 6 months (Breslau, 2001). Median time to remission of PTSD is an estimated 24.9 months, and PTSD persists for more than 60 months in more than one third of the diagnosed cases (Breslau et al., 1998).

Of all patients diagnosed with PTSD, 92% also meet the diagnostic criteria of another Axis I disorder, e.g., major depressive disorder (MDD, 77%), generalized anxiety disorder (GAD, 38%), or alcohol abuse/dependence (31%; Friedman, Keane, & Resick, 2007). PTSD has a large impact on most patients; debilitating effects of the disorder are reported in several life areas (family, work, financial and health problems) (e.g., Foa, Keane, & Friedman, 2004).

Risk factors include biological factors (genetic factors, neuroendocrine responses), cognitive factors (e.g., premorbid intelligence, cognitive functioning and cognitive

biases) but also characteristics of the event(s), peri-traumatic responses, premorbid psychiatric diagnosis and family history, (a lack of) social support, and the experience of traumatic events in childhood (Brewin, Andrews, & Valentine, 2000; Ozer, Best, Lipsey, & Weiss, 2003, Bomeay, Risbrough, & Lang, 2012).

Treatment

Effective treatments for chronic post-traumatic stress disorder (PTSD) include pharmacotherapy (antidepressants) and cognitive-behavioral therapy (CBT) (Foa et al., 2004). CBT can be applied in several different ways and under different labels; most frequently used methods are exposure therapy (Dancu & Foa, 1992), cognitive processing therapy (Resick & Schnicke, 1993) and Eye Movement Desensitization and Reprocessing (EMDR; Shapiro, 1995).

However, a significant proportion of patients fail to respond or show only partial improvement (Sherman, 1998; van Etten & Taylor, 1998). Twenty-five to 45% of patients treated for PTSD continue to meet the criteria at the end of exposure treatment (CBT) (Van Minnen & Hagenaars, 2002). Although only a few studies on PTSD treatments examined exacerbation, results are not encouraging; rates as high as 10% in CBT are reported (Schottenbauer, Glass, Arnkhoff, Tendick, & Hafter Gray, 2008). Moreover, problems with treatment tolerability are common. Drop out rates vary from 21% (CBT) to 32% (antidepressants) (Hembree et al., 2003), and overall drop out rates from PTSD treatments range from 0 to 50% (Schottenbauer et al., 2008; Imel, Laska, Jakupcak, & Simpson, 2013).

One of the underlying reasons for suboptimal treatment outcomes is suggested in research into attitudes of PTSD therapists. It was observed that a significant proportion of clinicians feel uncomfortable or not capable when using exposure techniques (Van Minnen, Hendriks, & Olff, 2010). Infrequent use of this empirically validated intervention is likely to have negative clinical consequences.

The development of additional effective therapies for PTSD therefore seems imperative. For both clinicians and patients, therapy feasibility is an important focus in designing novel therapy approaches. Furthermore, recent theoretical developments in cognitive research offer promising insights in working mechanisms of anxiety which are currently applied to new treatments (Bomyea & Lang, 2012).

Information processing in PTSD

Criteria of PTSD

From a clinical perspective, all anxiety disorders are characterized by problems with attention and concentration. In PTSD, these phenomena are part of the diagnostic criteria (APA [DSM-IV-TR], 2000, see table 1). Problems in cognitive functioning are

Table 1. Diagnostic criteria for posttraumatic stress disorder according to the DSM-IV (APA, 2000)

Criterion A: stressor
The person has been exposed to a traumatic event in which both of the following have been present:

1. The person has experienced, witnessed, or been confronted with an event or events that involve actual or threatened death or serious injury, or a threat to the physical integrity of oneself or others.
2. The person's response involved intense fear, helplessness, or horror. Note: in children, it may be expressed instead by disorganized or agitated behavior.

Criterion B: intrusive recollection
The traumatic event is persistently re-experienced in at least **one** of the following ways:
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.

1. Recurrent distressing dreams of the event. Note: in children, there may be frightening dreams without recognizable content
2. 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 upon awakening or when intoxicated). Note: in children, trauma-specific reenactment may occur.
3. Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.
4. Physiologic reactivity upon exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event

Criterion C: avoidant/numbing
Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by at least **three** 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 foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span)

Criterion D: hyper-arousal
Persistent symptoms of increasing arousal (not present before the trauma), indicated by at least **two** of the following:

1. Difficulty falling or staying asleep
2. Irritability or outbursts of anger
3. Difficulty concentrating
4. Hyper-vigilance

Exaggerated startle response

Criterion E: duration
Duration of the disturbance (symptoms in B, C, and D) is more than one month.

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

included in all three symptom clusters. First, involuntary intrusive recollections can alter perception and disturb a normal sense of reality.
These experiences are often described as sensory, vivid flashes of the traumatic event, overwhelming normal cognitive processing and causing a sense of current ongoing threat (Ehlers & Clark, 2000). For a clinical example of severe re-experiencing, see the case description of Mr. X.

Mr. X

Mr. X is a 25-year-old student. He seeks treatment after being exposed to a violent attack in his house, during which he was held hostage by three masked men for a few hours. They were looking for drugs and when they could not find any, they threatened to kill him with their guns. He was badly injured with a knife. The police released him, but not after he thought he was going to die and said specific prayers related to dying. The police told him later that the attackers mistook him for his neighbor.

After the events, Mr. X was no longer able to sleep for more than three hours consecutively. He had severe nightmares and only slept during daytime, surrounded with weapons. At night, he would stay awake to watch over the house. He experienced intrusive recollections and he sometimes found himself fighting an imaginary attacker.

Mr. X was no longer able to concentrate and discontinued his studies soon after the event. He had severe memory problems. He forgot for example that he had to stop his study grant and as a consequence had to pay a large fine. His mother had to help him with his mail and she called him every morning to help him remember his appointments for that day.

Mr. X started treatment a year after the traumatic events. During intake he expressed serious doubts about the effects of therapy. He was preoccupied by his financial problems and asked for direct help with these problems. He also felt ashamed about seeking mental help for his problems. I observed that he had trouble sitting still on his chair and he could not concentrate when he had to fill in a self-report questionnaire for PTSD.
After three sessions preparing for exposure-based therapy, mr. X did not show up for his appointment. Despite several attempts, I was not able to reach him by phone, mail or letters, and he had to be considered a drop out. I contacted his general practitioner and informed him about the diagnosis and therapy drop out of mr. X. I also emphasized that mr. X should be encouraged to enter therapy again.

One of the criteria defining the second cluster of PTSD symptoms (i.e., pervasive avoidance) is a form of thought suppression; the attempt to avoid cognitions about the traumatic event(s). Furthermore, behavioral avoidance is often observed in

patients; most often places and people that remind of the occurred event(s) are no longer visited. Avoidance also comprises the inability to remember important aspects of the experienced events. Although research in this field is characterized by controversy and inconclusive evidence (e.g., recovered memories, dissociaton, see Bennet & Wells, 2010), this form of amnesia seems typically reported by individuals with early onset trauma (Goodman et al., 2003). In a recent study, memories of the worst moments of the experienced events were found to be disorganized (Jelinek et al., 2010). Interestingly, in clinical practice, a substantial amount of patients respond emotionally when they are asked whether they forgot details of the event(s); an often heard reaction is, ''I wish I could''.

The last cluster of PTSD symptoms is increased or excessive arousal, thought to maintain and even exacerbate other PTSD symptoms (Constans, 2005). One of the five criteria is concentration problems. In clinical practice, it is noticed that these symptoms often lead to severe impairments in (occupational) functioning. Although treatment can improve symptoms, clinical experience indicates that attention and concentration problems are still frequently reported at the end of treatment. For a clinical example of these problems, see the case description of Mrs. A.

Mrs. A

Mrs. A is a 32-year-old single mom. Her boyfriend had recently left her and she since then lost her job as a nursing assistant because she repeatedly forgot her work schedule. From the age of 4 she suffered from severe physical abuse from her stepfather that only stopped when she was sixteen and moved out of the house.

She did not show up for intake because she forgot the appointment. During the second appointment, Mrs. A wanted to keep her jacket on, although it was quite warm in the therapy room. She clearly had problems focusing on the questions framed and asked the therapist to repeat them several times. Mrs. A also was distracted easily and looked at the covered window of the room whenever she saw a shadow of a person passing by. She reported severe sleeping problems because she was afraid of nightmares when she would finally fall asleep. She also avoided getting close in relationships and she had never told anyone about the violence she had experienced in childhood. A decline in her symptoms had occurred when her boyfriend recently left her.

During therapy, Mrs. A had trouble telling about the occurred events, which was the main goal of treatment. Also, most of the time she forgot to listen to the audiotaped therapy sessions at home. We decided to take a pause in treatment and we first focused on practical ways to help her in doing her homework. Although after two sessions Mrs. A reported that she forgot less appointments and she was better able to do her homework, her concentration during the sessions seemed not improved when we continued exposure therapy.

However, mrs. A experienced significantly less sleeping problems after ten sessions. Furthermore, she finally confided in her best friend about the abuse of her stepfather. She felt she was doing much better, but she still was not able to read a book or watch a movie and stay concentrated, in the way she was before (e.g., at school). Extra sessions of exposure therapy did not bring about any further change. Mrs. A found a new job and together we discussed how to deal with her ''handicap''; the concentration problems. She would discuss this with her new boss, and she hoped that her being aware of these problems would help her to prevent mistakes. At the last appointment, two months after she started her new job, she reported that she still couldn't concentrate in the way she was used to. But the planned strategy was very helpful and she felt she was able to accept the remaining problem.

Hyper-vigilance is defined by excessive alertness and a constant attitude of being ''on guard''. Patients often display ''safety seeking behavior'', e.g., they check the locks in their homes continuously or sit with their back to the wall in public places to be able to oversee the room. This attentional vigilance for potential threat is thought to occupy working memory. Also, debilitating effects on the ability to focus attention are consequences of this alert mode; simply stated, an individual with these symptoms is constantly shifting attention away from goal-related information to inspect the surroundings.
Exaggerated startle response is another automatic reaction to (perceived) threat. The symptom seems determined by reflexive threat association, followed by a misinterpretation of the stimulus involved (looming, see below), which in turn activates a range of physiological reactions. The case description of Mr. V illustrates the clinical presentation of hyperarousal symptoms.

Mr. V

A 48-year-old male veteran seeks help for his trauma-related problems. He has served on two peacekeeping missions in Libanon and Bosnia. Especially in Bosnia, he experienced an intense form of helplessness when he had to witness the deportation of muslim men. Later he found out that the men were executed.

Since then Mr. V had trouble functioning in the army. He was aggressive and came in conflict with his superiors several times. He had trouble falling asleep and had nightmares every night, which in turn made him more irritable. He was on sickness leave for two years now. He felt alienated from his family and frequently visited internet discussions to find support from other veterans.

Mr. V mentioned feeling as if he was still living in a war zone. During long walks through the woods, to stay in shape, he would inspect his surroundings constantly. Small movements (e.g., a bird) would immediately lead to a feeling of being attacked. He also noticed that his perceptions were disturbed; one time during a walk, he had perceived a falling leave for a hand grenade and he had ducked to the ground.

During intake, the fire alarm unexpectedly went off. Mr. V jumped up, looked around, and inspected the room, with his back to the wall. Although almost immediately it became clear that the fire alarm was false, Mr. V was not able to continue the intake procedure because he felt very upset.
In the next appointment, we were able to finish the intake. But Mr. V indicated that he was very angry about what had happened during the first appointment. He wandered if this would happen again during treatment (''this is very unprofessional in a clinical setting'', he stated) and my reassurance did not seem to make a difference. He was referred for exposure therapy to a colleague, but I found out a few weeks later that he had ended therapy prematurely.

Cognitive phenomena in PTSD

Many cognitive experimental studies have also reported attention (and memory) abnormalities in PTSD (for reviews, see Buckley, Blanchard, & Neill, 2000; McNally, 2006, Moore, 2008). These difficulties appear to be related to both the development and the maintenance of the disorder. In addition, cognitive impairments might have negative effects on therapy outcome (Buckley et al., 2000).

Memory deficits

Many forms of memory dysfunction have been examined in PTSD. The most consistent finding is that PTSD is associated with poor verbal memory (Brewin, Kleiner, Vasterling, & Field, 2007; Ferreri, Lapp, & Peretti, 2011). It is hypothesized that executive control may buffer against these specific memory problems which are developed immediately after exposure to a traumatic event (Vasterling, Brailey, Constans, & Sutker, 1998; Johnson & Asbjornsen, 2009). Other evidence indicates that reduced verbal memory is a pre-existing risk factor for PTSD (Moore, 2008).
Another memory process associated with PTSD is autobiographical memory (for a review, see Moore & Zoellner, 2007). Patients with PTSD tend to have difficulties in producing specific, personal memories, and instead generate more overgeneral memories. This memory bias is also found to be related to depressive disorders (Williams et al., 2007). Since depressed individuals are not capable of retrieving specific positive personal memories to counteract against their negative personal schemata activated by the depressive symptomatology, impaired autobiographical memory might also maintain depression. There is considerable evidence suggesting that memory impairments in general are (co-)dependent of comorbid depressive symptomatology, or related to symptoms that are overlapping in depressive disorder and PTSD (Moore, 2008; Johnson, Kanagaratnam, & Asbjornsen, 2008b; Johnson & Asbjornsen, 2009).

Attentional biases

Automatic threat processing

Patients with anxiety disorders demonstrate distinctive patterns of attentional bias (AB); attention is drawn automatically to information relevant to patients' current concerns (MacLeod, Campbell, Rutherford, & Wilson, 2004; Yiend & Mackintosh, 2004). This tendency is thought to consume valuable cognitive resources and strong evidence exists that this bias is associated with anxiety vulnerability, although AB tends to be smaller or even absent in recovered anxiety patients after treatment (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenbrug, & IJzendoorn, 2007).

AB has been demonstrated in many anxiety disorders to the extent that in a meta-analysis, the authors state: ''With over 150 studies that have established the existence and typical magnitude of the threat-related bias in anxious individuals from different populations and with a variety of experimental conditions, it appears as if little will be gained from additional studies of threat-related bias […]'' (Bar-Haim et al., 2007, p. 18).

Different paradigms have been used to measure AB. One of the most widely used tasks is the Emotional Stroop Task (EST, Devineni, Blanchard, Hickling, & Buckley, 2004). In this task, emotional and neutral words are presented consecutively in different colors on a computer screen. Participants are required to name the color of the presented words as quickly as possible. Anxious individuals name colors of negative and threatening words which are relevant to their conditions more slowly than colors of neutral words. AB is then defined as the difference in reaction times needed to name the color of the emotional and the neutral words (interference). This interference is thought to represent increased selective attention to the anxiety-related information, at the cost of task-relevant processing (i.e. colour-naming). Williams and colleagues (1996) concluded that the effect size for AB in PTSD appeared to be much larger than in any other anxiety disorder. A more recent meta-analysis of data of all existing studies on AB in PTSD based on 22 studies (of which 19 EST studies) showed an effect size of 0.36 (small to moderate)(Bar Haim et al., 2007).

Over the years, the EST has been criticized. In particular, it was pointed out that the increase in interference could arise from several non-attentional processes (MacLeod, Mathews, & Tata, 1986; Harvey, Watkins, Mansell, & Shafran, 2004). For example, a longer response time to the stimulus may reflect a mood-dependent response bias of the participant. MacLeod, Mathews, and Tata (1986) adapted the Dot-probe task (DPT; Posner, Snyder, & Davidson, 1980) to measure AB in a more direct way. The DPT is regarded as a better method for measuring selective spatial attention, because it is indexed by a shorter response time and does not suffer from interpretative difficulties (Harvey et al., 2004). Nowadays, multiple different but conceptually similar DPT's exist. In the most widely used adaptation of the DPT (Mathews & Macleod, 2002), two words (one neutral and one threat-related word) are presented simultaneously for 500ms, one above and one below the fixation

location. The next screen shows a target in the spatial location of either word. In half of the trials the target appears in the location of the threat-related word, and in half of the trials in the location of the neutral word. Participants are instructed to discriminate the target as fast as possible by pressing one of two response keys.

Figure 1. Schematic example of one trial of the Dot-probe test

Note: time in milliseconds

Figure 1 is an example of a trial with pictorial stimuli (see chapter 2). If attention is drawn towards threat-related information, reaction times will be shorter in trials
drawn towards threat-related information, reaction times will be shorter in trials where the target replaces the threat-related word (a so-called congruent trial) than in trials where it replaces the neutral word (an incongruent trial). AB score is calculated by deducting the mean reaction time to congruent trials from the mean reaction time to incongruent trials; a positive bias score reflects AB toward threat-related stimuli (vigilance), and negative congruency scores reflect attentional avoidance of threat.

Research shows that participants with pathological anxiety, as well as non-clinical individuals with high trait anxiety, are quicker to detect the probe in the same spatial location as the threatening word than to detect the probe in the spatial location of the neutral word (Mathews & Macleod, 2002). Individuals with PTSD after a motor vehicle accident also demonstrated AB to mildly threatening words (Bryant & Harvey, 1997). However, in another study, no significant group differences in AB on the DPT were observed among patients with PTSD, trauma victims with acute stress disorder (ASD) and healthy controls (Elsesser et al., 2004). Moreover, AB as measured with the DPT was not demonstrated in recent trauma victims and AB also was not found to predict PTSD symptom development after trauma (Elsesser et al., 2005).

Mathews and MacLeod (2002) were the first who tried to induce AB. The participants in their study were students with medium range trait anxiety. The

training task was an adapted version of the DPT described above. In the positive training condition, the probe always appeared in the location of the neutral word. In the negative training condition, the probe almost always appeared in the location of the threatening word. Positive and negative biases were successfully induced.
MacLeod, Rutherford, Campbell, Ebsworthy, and Holker (2002) did a similar experiment, also with middle range trait anxiety students. A stress task was added before and after the training session, to investigate if the training influenced emotional vulnerability. The results of Mathews and MacLeod (2002) were replicated: positive and negative AB was successfully induced. Furthermore, compared to the negatively trained group, the group in the positive training condition showed a smaller increase in anxious mood during the stress task. These results suggested that AB can be trained, and that AB *causally* affects emotional vulnerability. Based on these results, the first clinical trials into the effects of attentional bias modification (ABM) in anxiety disorders were initiated (Amir, Beard, Burns,& Bomyea, 2009a; Amir et al., 2009b, Schmidt, Richey, Buckner, & Timpano, 2009, see below).

Effortful threat processing
The first studies on sustained attention in PTSD were based on neuropsychological tests. Compared to veterans without PTSD, veterans with PTSD were found to be less capable maintaining focused attention (Vasterling, 1998; Vasterling, 2002).
Recent theories (see below) suggest that attentional control (AC) might be of much importance in the regulation of attentional bias (Eysenck, Santos, Derakshan, & Calvo, 2007; Derakshan & Eysenck, 2009). AC is defined as the ability to use voluntary and effortful attention to constrain cognitive and affective responses to emotional stimuli (Derryberry & Rothbart, 1997). It is hypothesized that AC is a top-down regulatory process, whereas AB can be seen as a habitual, reflexive response to threatening stimuli. Derryberry and Reed (2002) developed the Attentional Control Scale (ACS), a self-report questionnaire measuring AC, to investigate such issues. They observed that AB in high trait anxious participants was moderated by their self-reported AC. High AC in anxious participants was found to limit the impact of threatening information (Derryberry & Reed, 2002).
Several experimental studies also focused on the link between involuntary intrusion, AB and AC. For example, a significant relationship between AC and unwanted memories was found in undergraduate students, independent from trait depression and coping styles, suggesting a unique contribution of AC to this PTSD-related phenomenon (Verwoerd & Wessel, 2007).
Verwoerd, De Jong and Wessel (2008) asked a small group of students to keep a diary for a week after watching a stressful film fragment. Results demonstrated that low AC predicted self-reported intrusive recollection. In a next study (Verwoerd, Wessel, De Jong, & Nieuwenhuis, 2009), ''pre-film'' AC predicted the relationship between later preferential processing of threatening stimuli and intrusive

recollection. The authors suggest that individual AC can influence the development of AB related to traumatic events, by inhibiting intrusive recollection.
In another analogue study (Bardeen & Orcutt, 2011) the relationship between AC, AB (as measured with the DPT) and PTSD symptoms were investigated in a student sample. AC was found to moderate the relationship between symptoms and AB. Participants low in AC and high in symptoms demonstrated AB (vigilance), also identifying low AC as a risk factor for AB in PTSD.
Taken together, accumulating laboratory evidence suggests that AC might play a role in PTSD, possibly through inhibiting unwanted intrusive memories, and/or by attenuating automatic attentional reactions in the aftermath of a traumatic event. Although multiple risk factors for PTSD are identified (see above), little is known about the underlying mechanisms. Research into the role of AC in the development of AB and intrusions in the aftermath of trauma can add importantly to this field. More specifically, replication of the abovementioned analogue results in clinical trials would strengthen the recent theoretical considerations on the significance of strategic information processing in anxiety.

Cognitive biases

There is compelling evidence that cognitive biases contribute to PTSD. Negative perceptions of the self and/or of the world are linked to PTSD (Foa et al., 2004) and multiple theoretic models indicate that these negative cognitions account for the sense of ongoing threat that characterizes PTSD patients (e.g., Ehlers & Clark, 2000, Janoff-Bulman, 1992).
Recently, focus in research on cognitive biases is shifting towards cognitive styles and metacognitions to explain the development and maintenance of PTSD symptoms. For example, specific negative attributional styles are found to be related to symptoms of PTSD in both cross-sectional and longitudinal studies. Rumination and looming cognitive style (the anticipation that threatening stimuli are rapidly approaching and intensifying) are also marked as cognitive vulnerability factors in PTSD (for an overview, see Bomeay et al., 2012).
An example of metacognition – the thoughts and beliefs about one's thoughts and beliefs – is anxiety sensitivity (AS); the fear of fear and of anxiety related symptoms. AS is also considered as a vulnerability factor in the development of PTSD (Bomyea et al., 2012). In a prospective design, AS was measured before childbirth and found to predict PTSD postpartum (Keogh, Ayers, & Francis, 2002). Moreover, AS measured immediately after a traumatic event predicted subsequent PTSD symptom severity, independent from early symptom development (Marshall, Miles, & Stewart, 2010), (for a review on AS and PTSD, see Elwood, Hahn, Olatunji, & Williams, 2009).

Information processing theories

Cognitive theories on PTSD

Several theoretical models on cognitive processing in PTSD have been proposed in the past three decades (e.g., Ehlers & Clark, 2000, Resick & Schnicke, 1993; Brewin, Dalgleish, & Joseph, 1996). One of the most influential is emotional processing theory (EFT, Dancu & Foa, 1992). According to this theory, patients with PTSD develop pathological fear networks related to the traumatic event(s). When one trigger activates this network, a pattern of fear reactions is enrolled. Moreover, it is hypothesized that in PTSD a large set of stimuli can activate the complete fear network (i.e., lead to all PTSD symptoms), and this leaves an individual extremely vulnerable to outside stimuli (Foa, Steketee, & Rothbaum, 1989).
Exposure therapy was hypothesized to weaken the associations in the network in the absence of expected outcomes (i.e., the traumatic events); a process of unlearning. More recent evidence suggests an inhibiting role of new pathways formed through therapy, preventing the range of stimulus-driven fear reactions (McNally, 2007). Consequently, as Bardeen & Orcutt (2011) suggest, although emotional processing theory has contributed largely to the understanding of PTSD by accounting for the bottom-up, reflexive processing, more elaborated models are necessary that incorporate top-down threat processing.

Recent models for anxiety: dual process model for anxiety and attention control theory

Ouimet, Gawronski, and Dozois (2009) propose a dual process model to account for both associative, automatic information processing in anxiety and more rule-based, strategic cognitive functioning. Instead of focusing on a specific form or stage of information processing (e.g., attentional vigilance or avoidance or cognitive biases), the model integrates these phenomena into either an automatic or a strategic system. Individual differences in central executive functioning are proposed to function as a vulnerability factor; e.g., limited attentional control can influence the rule-based system. Instead of inhibiting activated threat associations, an individual is more likely to act on these associations in a fear-driven way (both behaviorally and cognitively). A focus on enhancement of executive functioning is suggested as a useful strategy for improving therapy in anxiety disorders.
Attentional control theory (ACT; Eysenck, Santos, Derakshan, & Calvo, 2007) was designed to explain the effect of anxiety specifically on attentional control, not on all cognitive performance. The underlying central assumption is that the effect of anxiety on attentional processes is crucial in understanding impaired cognitive performance (efficiency). Attentional control comprises attentional focus, which renders an individual capable of inhibiting distractions by task-irrelevant stimuli, and attentional shifting. Shifting is the ability to flexibly switch attention between and within tasks (Derakshan & Eysenck, 2009).

Anxious individuals then tend to be distracted by task-irrelevant emotional information more easily (i.e., demonstrate AB). Anxiety is also considered to affect the attentional inhibition function, while inhibition of task-irrelevant distraction is crucial to remain focused and/or ''correct'' AB. In this way, anxiety disrupts the balance between two ways of information processing. Bottom-up processing (i.e. AB) is increased while top-down processing is decreased. In an individual facing threatening stimuli, this leads to debilitating effects; inhibition of the attentional bias is disrupted while reflexive attentional processing is enhanced.
Although ACT is set up as a conceptual framework to understand different levels of information processing, it is not clear on how these two processes interact. For example, is high ability to control attention thought to buffer against the development of AB? Empirical research into the relationships between the two systems may further clarify this interaction.

Process focused therapies

Inspired both by theoretical as well as experimental evidence, novel therapies have recently been developed with a focus on cognitive processing, both on the automatic and strategic aspects. In this thesis, we investigate the effectiveness of two of these new treatments in patients with PTSD.

Attentional bias modification

Several studies have investigated the role of attention training in clinical samples. In a randomized controlled trial (RCT), Schmidt and colleagues (2009) assigned 36 patients with general social phobia (GSP) to ABM or a control condition. At post-treatment, 72% of the participants in the ABM condition no longer met diagnostic criteria for GSP, compared with 11% of participants in the control group. These results were maintained at four-month follow up (Schmidt et al., 2009). In another RCT (Amir et al., 2009a), 44 GSP patients were randomly assigned to ABM or a placebo condition. Interviewer ratings of Social Avoidance showed a remarkable decline after treatment, and treatment gains were maintained during a follow up period. Importantly, change in symptoms in the training condition was related to change in AB.
Amir and colleagues (2009b) also examined the effects of ABM in patients with generalized anxiety disorder (GAD). In this study, fifty percent of participants in the training condition were classified as responders, compared with 13% of the participants in the placebo condition.
In summary: there are reasons to expect that ABM can reduce AB and that ABM can influence clinical symptoms. Three clinical studies with 8 or more sessions of ABM

claim a reduction of social or general anxiety symptoms. Since AB is also observed in PTSD (see above), we aimed to investigate the effects of ABM in PTSD in a large RCT.

Mindfulness-based cognitive therapy

In 1995, when mindfulness interventions were first introduced as psychological treatments, they were referred to as ''attentional control training'' (Teasdale, Segal, & Williams, 1995). Later on, mindfulness-based cognitive therapy (MBCT) (Segal, Williams, & Teasdale, 2002) was developed; a manualized 8-week treatment program firmly based in cognitive theory of depression. The model assumes that recovered depressed patients differ from never-depressed people in that when the former group experiences dysphoria, depressogenic thinking patterns are more likely to be activated, which may ultimately lead to relapse (Teasdale et al., 1995). In MBCT, patients learn techniques to turn attention towards potential difficulties instead of avoiding, combined with an attitude of acceptance. Thus, MBCT aims at reducing relapse risk by increasing awareness of negative thinking patterns and by promoting the disengagement from ruminative thinking, which is also a core problem in PTSD. In this way, MBCT might also be a promising treatment for PTSD, since the focus of treatment is specifically on enhancing attentional control combined with decreasing maladaptive metacognitive patterns through acceptance.
Two meta-analyses concluded that MBCT is an effective treatment for patients with recurrent depression (Piet & Hougaard, 2011; Fjorback, Arendt, Ørnbøl, Fink, & Walach, 2011). However, MBCT seems beneficial for patients with two prior episodes, but not in patients with three or more prior episodes of depression. Ma and Teasdale (2004) investigated the role of adverse childhood experiences in an attempt to explain this difference in effect. Patients with three or more episodes were found to be more characterized by adverse childhood experiences (abuse and/or indifference) compared to patients with two episodes. Supposedly, the autonomous cognitive and affective ruminative processes that are often experienced in this population are disrupted by mindfulness techniques (Ma & Teasdale, 2004).
Kabat-Zinn and colleagues (1992) also found that mindfulness-based stress reduction (MBSR, on which MBCT is based) has significant positive effects on symptoms of anxiety disorders (GAD and panic disorder, PD), both at post-treatment and at 3-month follow up. In addition, a recent meta-analysis (Chiesa & Serreti, 2011) concluded that treatment augmented with MBCT has a beneficial effect on symptoms of PD, GAD and bipolar disorder in remission.

Research aims

The present project is concerned with the testing and implementation of two novel treatments that have recently been developed in the field of anxiety disorders and depression, respectively.
ABM is the translation of experimental psychological findings in anxiety disorders into a treatment program. The central question of this study is: is ABM more effective than the control condition in changing AB and alleviating PTSD symptoms in patients with PTSD? In a RCT, participants will be asked to follow 8 sessions of ABM (training or control/placebo condition). In a following case series we examined a personalized version of ABM, based on the same hypotheses.
The relationship between AB and AC will be investigated in the same patient group, to examine whether the earlier mentioned relations between these two types of information processing can be replicated in a clinical sample.
We will examine the associations between the different potential working mechanisms (mindfulness skills and metacognitions) and PTSD symptoms in a cross-sectional study with PTSD patients. Next, we will investigate an adapted version of the MBCT protocol of Segal and colleagues (2002) in a pilot study with PTSD patients.. Our focus is to explore the feasibility, safety and the effect of MBCT on symptoms of PTSD.

Outline of this thesis

In Chapter 2, results of a large RCT for ABM in PTSD are reported Chapter 3 is concerned with the association between AB and AC in PTSD patients. Chapter 4 is the report of a case series in male veterans with PTSD, in which we tested individualized ABM. The next chapter concerns a cross-sectional study on the relation between mindfulness skills, reactivity and PTSD symptoms. Chapter 6 describes a pilot study (case series) on the effect of MBCT in patients with PTSD. The last chapter contains a summary and general discussion of the main findings, clinical implications and directions for future research.

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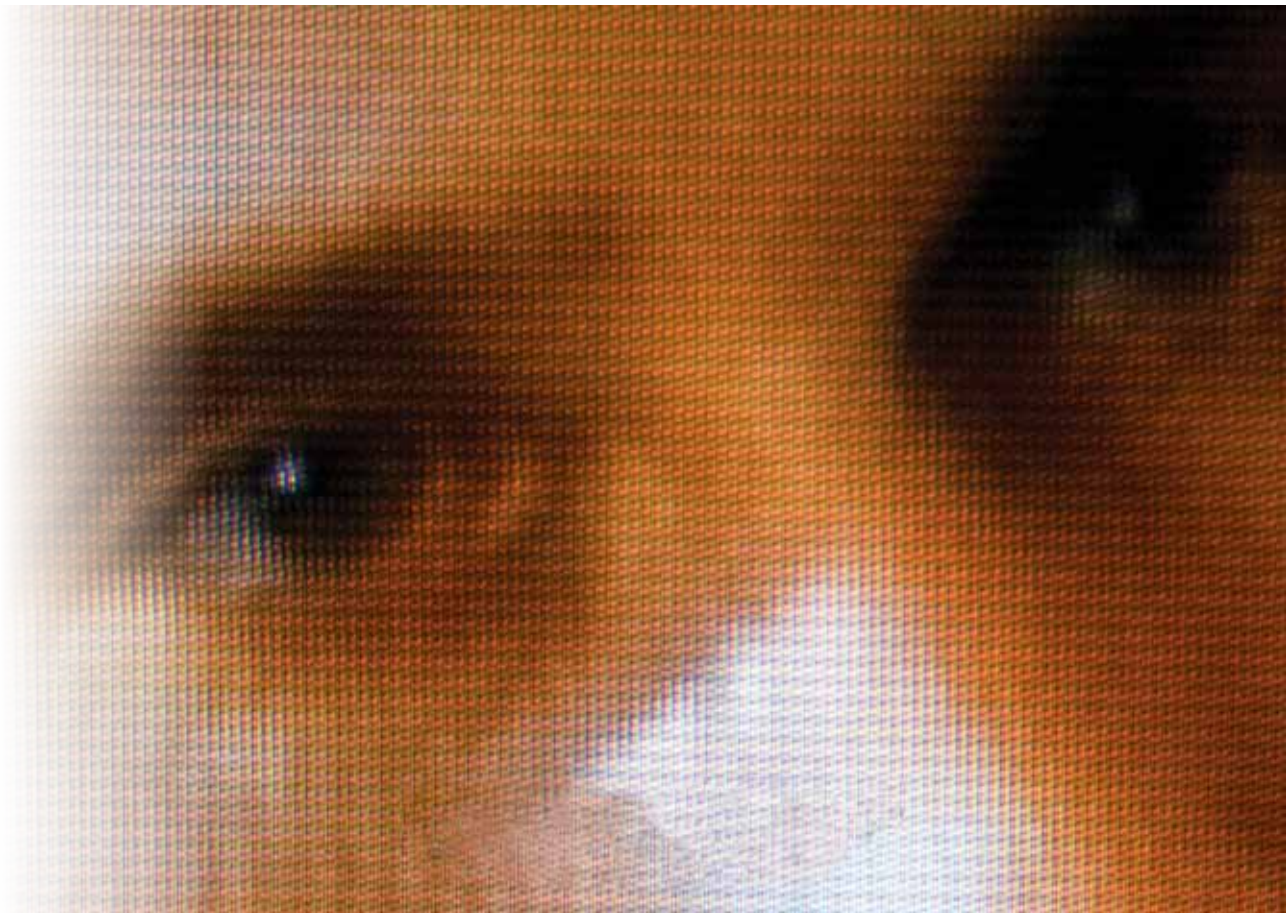
2

Attentional bias modification in posttraumatic stress disorder: A randomized controlled trial

M. Schoorl, P. Putman, & W. Van Der Does (2013). *Psychotherapy and Psychosomatics (82),* 99–105*,* doi: 10.1159/000341920.



Abstract

Attentional Bias Modification (ABM) is a new treatment for anxiety disorders. Three randomized controlled clinical trials have shown positive effects of ABM in social anxiety disorder and generalized anxiety disorder. This study investigated the efficacy of ABM in outpatients (N = 102) with chronic posttraumatic stress disorder (PTSD) in a randomized controlled double-blind trial. ABM and control treatment consisted of eight 20-minute sessions over the course of three weeks. Symptoms and attentional bias were assessed pre- and post-treatment and at three-week follow up. ABM and the control treatment were equally effective in reducing the symptoms of PTSD. The effect sizes of the improvement (pre-post) were 0.66 for ABM and 0.46 for the control treatment, which is comparable to the effect sizes of pill-placebos in pharmacotherapy trials of chronic PTSD. Both treatments did not affect attentional bias. The acceptability and tolerability of ABM were moderate.
We conclude that this version of ABM is not an effective treatment of PTSD.

Introduction

A large body of evidence has shown that patients with anxiety disorders selectively attend to threatening information (Bar-Haim, Lamy Pergamin, Bakermans-Kranenburg, & Van IJzendoorn, 2007). This increased cognitive processing of threatening information may increase and maintain symptoms. (Mathews & MacLeod, 2002). Attentional Bias Modification (ABM) is a novel computerized treatment for anxiety disorders. It involves brief (approximately 20-minutes) sessions in which participants are trained to keep their attention away from the threatening stimuli to which they automatically attend.

Recent randomized clinical trials suggest that ABM may be effective in patients with anxiety disorders. A meta-analysis called the approach promising (Hakamata et al., 2010), but was based on the results of only three relatively small trials that have been conducted in clinical populations. Two of the ABM trials have examined the treatment's effectiveness in patients with generalized social anxiety disorder (SAD). The first study randomly assigned 36 patients to eight sessions of ABM or control training over the course of four weeks (Schmidt, Richey, Buckner, & Timpano, 2009). In the ABM condition, 72% of the patients no longer met diagnostic criteria for SAD, compared with 11% in the control group. These results were largely maintained at a four-month follow up. Another study in 44 SAD patients (Amir et al, 2009b) found 50% responders in the ABM condition and 14% in the control condition. These treatment gains were also maintained at four-month follow up. The third reported trial of ABM tested the treatment in 29 patients with generalized anxiety disorder (GAD) (Amir, Beard, Burns, & Bomyea, 2009a). Fifty percent of the participants in the ABM condition were classified as responders, compared with 13% in the control condition.

Since AB has also been observed in posttraumatic stress disorder (PTSD) (Bar-Haim et al, 2007; Williams, Mathews, & MacLeod, 1996) and ABM seems to generate positive results in anxiety disorders, the goal of the present study was to investigate the effects of ABM in patients with PTSD. The primary outcome was clinician-rated improvement of PTSD symptoms. The secondary outcome was self-reported symptoms. Attentional bias change was assessed as the potential mediator of treatment effects.

Methods

Design and randomization

We carried out a double-blind randomized controlled trial, comparing a three-week attention training program with a control treatment. The randomization was done using a computerized randomization sequence of permutated blocks of 20 patients and was coordinated by a person independent of the study. All researchers, assessors, hospital staff and patients remained blind to treatment condition until completion of the project.

Participants

Patients were recruited while they were on the waiting list for treatment at a mental health care department for PTSD. Inclusion criterion was diagnosis of chronic PTSD (duration at least three months). Exclusion criteria were a psychotic disorder (lifetime); alcohol or drug dependency (current); deficits in motor skills prohibiting the use of a computer keyboard; color blindness. Participants also had to be able to complete the measurements in Dutch or English. Medication usage was checked at each assessment.

Instruments

Diagnoses

The Mini-International Neuropsychiatric Interview 5.0 (Sheehan et al., 1998) was used to assess DSM-IV Axis I psychiatric diagnoses.

Symptoms

Frequency and intensity of PTSD symptoms were assessed at pre- and post-treatment and follow-up with the Clinician Administered PTSD scale (CAPS) (Blake et al., 1990), a semi-structured interview that has been validated in a Dutch population (Hovens, Luinge, & Van Minnen, 2005). Symptom severity was also assessed with the Self-Rating Inventory for Posttraumatic Stress Disorder (SRIP) at pre-treatment and at follow up. Test-retest for the scale was 0.92 and coefficient alpha was 0.90-0.94 (Hovens, Bramsen, & Van Der Ploeg , 2000). The Hospital Anxiety and Depression scale (HADS) (Zigmond, & Snaith, 1983; Spinhoven et al., 1997) was used to measure depressive and anxiety symptoms. Both the MINI and CAPS interviews were conducted by the first author, who is a licensed and experienced clinical psychologist, and two trained junior psychologists. The training protocol consisted of several training interviews and role-plays. Next, they co-rated a live interview by the first author and conducted at least two interviews in her presence. Interrater reliability was not assessed, however the junior interviewers received weekly supervision

during which the assessments were discussed. Feedback on audiotaped interviews was provided in approximately 15% of the CAPS interviews.

Attentional bias (AB)

AB Assessment

Each of the 96 trials of the Dot-probe Test (DPT) started with a fixation cross that lasted 500 ms. Next, two pictures (one neutral and one trauma-related) were presented simultaneously for 500 ms, above and below the fixation location. Next, a target ('E' or 'F') appeared in the spatial location of either picture. Patients were instructed to discriminate the target as fast as possible by pressing one of two response keys. Target, target position (top or bottom) and picture type (neutral or trauma-related) were fully counterbalanced. AB was calculated by subtracting the mean reaction time to congruent trials from the mean reaction time to incongruent trials.

AB Modification

Both treatment conditions consisted of eight sessions over the course of three weeks. Each session lasted approximately 15 minutes and consisted of 200 trials. Of these, 80% were neutral/trauma-related pairs, and 20% were neutral/neutral pairs. In the ABM condition, the target always appeared in the location of the neutral picture. In the neutral/trauma-related pairs in the control condition, the target appeared in the location of the neutral picture in 50% of the trials. The control treatment was similar to the AB assessment but lasted 200 instead of 96 trials, and the assessment did not contain neutral/neutral trials. Different sets of pictures were used in the training and assessment DPT, to test for generalizability of the training to a new set of stimuli.

We used pictures as stimuli instead of words, to make the project feasible for patients from different cultural backgrounds for whom Dutch was not their first language. To create two sets of interchangeable stimuli, we first conducted a pilot study in which we selected 105 pictures taken from the International Affective Picture System (IAPS) (Lang, Bradley, & Cuthbert, 1999). Next, five PTSD-patients rated the pictures on valence and arousal levels on 0 – 5 scales. Nine pictures with very low (≤ 2) average valence rating (0 = happy, 5 = sad) or very low or very high (≤2 or > 4) average arousal ratings were excluded. The mean valence and arousal ratings of the 48 trauma-related pictures in both set A and B were 3.6 and 3.2, respectively. A list of the selected IAPS pictures is presented in appendix A. The pre- and post-assessments were programmed and presented in E-Prime V1, the training was programmed using PHP, Flash AS3 and MySQL.

Procedure

The trial was carried out in a double-blind fashion. Assessments took place at pre- and post-treatment and at a three-week follow-up. Therapists screened patients during intake, and if eligible, patients received a letter of information. If they decided to participate, the first assessment was planned. Assessments lasted approximately 2.5 hours. Assessments were performed at the clinic but participants could do all of the treatment sessions at home on a secured website. Treatment adherence (date, time and duration of the sessions) was monitored through the secured internet connection.
The study was approved by an independent medical ethics committee (METIGG, Utrecht). All patients gave informed consent before any assessment took place. Patients received €10 for participating. Traveling costs were also reimbursed.

Data reduction and statistics

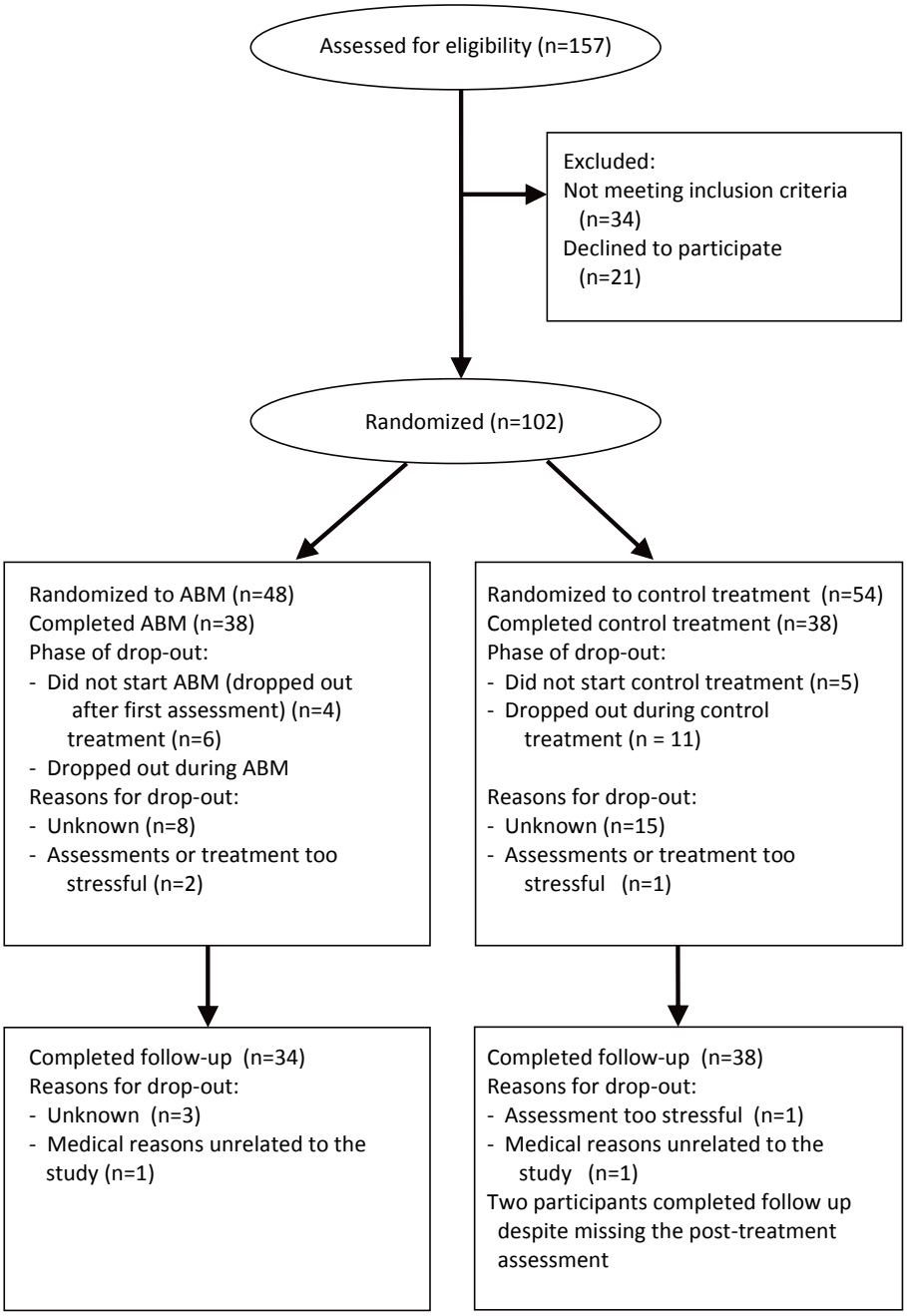
All analyses were performed on the intention-to-treat sample. Demographic and baseline clinical characteristics were compared between groups, using independent samples t-tests for continuous variables and chi-square tests for categorical variables. The effects of the interventions were analyzed using a repeated measures general linear model. Attentional bias scores were calculated by first excluding erroneous responses from analyses. Furthermore, trials with reaction times ≤ 300 ms or more than three standard deviations above the mean were also removed. This led to elimination of 5.5% of the trials at pre-treatment assessment and 5% and 4.8% of the trials at post-treatment and follow-up assessments, respectively. At the time when the present study was designed, no published data were available on the effects of attention training in patient samples on which to base a power analysis. At conferences however, significant effects had been presented in relatively small samples (N = 29 and N = 44; now published (Amir et al., 2009b; Amir et al., 2009a). We aimed to recruit 100 participants (50 per group), which gives a power of 0.80 to detect an effect size of 0.75 (between medium and large) with alpha set at 0.05.

Results

Participant flow

Figure 1 summarizes the flow of participants. 157 patients were screened, 102 of whom (65%) were randomized. Of the 55 patients who were excluded, 34 did not meet inclusion criteria. Twenty-one eligible patients declined to participate. In the ABM condition, 38 patients (79.2%) completed the training, compared to 70.4% in the control condition. Four patients in the ABM condition and two patients in the

Figure 1. Flow chart



control condition did not show up for the follow-up assessment. In two cases this was due to medical reasons unrelated to the project or to their psychiatric condition. Two patients who had completed treatment but missed their post-treatment assessment could be assessed at follow-up.

Data screening

Prior to analysis, all data were screened for accuracy of data-entry, missing values, normal distribution and outliers. We replaced missing values (last observation carried forward). The distribution of the scores on the CAPS, SRIP and HADS was explored with a Kolmogorov-Smirnov test. For both the ABM and control conditions the CAPS, SRIP and HADS scores at baseline, post-treatment and follow-up were normally distributed and there were no outliers. Six cases were outliers on the DPT at one or more of the assessments. These cases were removed for analyses involving the DPT, but not for the main study questions.

Patient characteristics

The baseline characteristics of both samples are summarized in table 1. The two samples had similar gender distributions, mean age, level of education, and ethnic backgrounds. The majority of participants were Dutch. The others were migrants from Morocco, Turkey and the former Dutch colonies who had been living in The Netherlands for many years, sometimes decades. Refugees represented 14.6% of the sample in the ABM condition, and 9.3% in the control condition. Most of these people had also been living in The Netherlands for several years. All participants completed all assessments in Dutch, except one who filled in an English version of the questionnaires.

Most of the patients had experienced multiple traumas (93.1%). More than half (56.9%) of the patients had been traumatized in childhood and 40.6% had experienced both childhood trauma and more recent trauma. Almost half (48%) of the patients received medication while they participated in the study, most of this group were prescribed antidepressants. There were no significant differences between groups in number of co-morbid clinical diagnoses ($t(99) = 0.61$; $p = 0.55$). The total number of additional diagnoses varied between zero and seven, with an average of 2.6 diagnoses per patient. At baseline the groups did not differ significantly on any of the symptom scores nor on attentional bias score ($t(97) = 1.14$; $p = 0.26$).

Table 1. Demographic and clinical characteristics of the samples

	Attention training (N = 48)	Control Training (N = 54)	*p*-value
Gender (N, % women)	37 (77.1)	40 (74.1)	0.7
Age *(SD*)	36.8 *(11.4)*	37.3 *(11.7)*	0.8
Education *(SD)*	1.9 *(0.8)*	1.7*(0.8)*	0.4
Ethnicity (N, %)			
Dutch	28 (58.3)	29 (53.7)	0.6
Migrants	13 (27.1)	19 (35.2)	0.4
Refugees	7 (14.6)	5 (9.3)	0.6
Trauma (N, %)			
Two or more events	43 (89.6)	52 (96.3)	0.2
Age 12 or younger	27 (56.2)	31 (57.4)	0.9
Comorbidity (N, %)			
Depression	34 (70.8)	37 (68.5)	0.9
Dysthymia	7 (14.6)	6 (11.1)	0.6
Panic disorder	15 (31.2)	19 (35.8)	0.6
Social anxiety disorder	15 (31.2)	22 (40.7)	0.3
General anxiety disorder	18 (37.5)	21 (38.9)	0.8
Obsessive-compulsive disorder	10 (20.8)	6 (11.1)	0.4
Somatization disorder	5 (10.9)	3 (5.8)	0.1

Note: Education: 1=low, 2=moderate 3=high educational level

Treatment effects on primary and secondary outcomes

Table 2 presents the means and standard deviations of the outcome variables and the results of the GLM analyses. Results revealed significant main effects of Time on clinician-rated symptoms (CAPS) ($F(1.86, 185.56) = 40.38$; $p < 0.001$) and on self-reported posttraumatic symptoms (SRIP) ($F(1, 98) = 31.15$; $p < 0.001$) and anxiety (HADS-A) ($F(2, 194) = 29.37$; $p < 0.001$). The main effect of Time on self-reported depression severity (HADS-D) did not reach significance ($F(2, 194) = 2.20$; $p = 0.11$). The effect sizes of the improvement (pre-post) on the CAPS were d = 0.66 for ABM and d = 0.46 for the control treatment. Post-hoc analyses with medication use and

Table 2. Primary and secondary outcomes

	Baseline		Post-treatment		Follow-up		
	ABM	Control	ABM	Control	ABM	Control	Time x Treatment effect
CAPS	80.7 *(16.4)*	80.5 *(18.7)*	65.1 *(23.3)*	70.4 *(21.7)*	64.3 *(23.7)*	66.9 *(24.1)*	F(1.9,185.56) = 1.18; p = 0.31
SRIP	62.1 *(9.6)*	63.9 *(8.3)*	-	-	57.2 *(13.7)*	58.6 *(11.5)*	F(1,98) = 0.07; p = 0.79
HADS-A	15.2 *(2.8)*	15.3 *(2.5)*	13.4 *(3.7)*	13.6 *(4.1)*	12.5 *(4.2)*	13.2 *(4.0)*	F(2,94) = 0.36; p = 0.70
HADS-D	12.0 *(2.8)*	11.5 *(3.2)*	11.7 *(4.9)*	11.7 *(4.2)*	11.0 *(4.7)*	11.3 *(4.4)*	F(2,94) = 0.91; p = 0.40
DPT	-4.9 *(53.5)*	3.2 *(58.5)*	-1.0 *(37.8)*	-0.1 *(34.7)*	-3.4 *(41.4)*	-3.3 *(35.5)*	F(1.8,142.79) = 0.24; p = 0.76

Note: Means *(Standard Deviations). Abbreviations:* ABM = Attentional Bias Modification; CAPS = Clinician Administered PTSD Scale; SRIP = Self-Rating Inventory for PTSD; HADS-A = Hospital Anxiety and Depression Scale – Anxiety; HADS-D = Hospital Anxiety and Depression Scale – Depression; DPT = Dot-probe Test

depression history as covariates did not change this pattern of results, nor did an analysis of treatment completers

GLM analyses on DPT scores did not reveal any significant main or interaction effects of Time or Treatment. However, the mean DPT score in both groups at pre-treatment was close to zero with a large standard deviation. We therefore conducted unplanned post-hoc analyses only in patients who showed at least moderate attentional bias (i.e., positive congruency scores) to threat (n=46). This revealed the same pattern of results.

Discussion

The aim of this study was to investigate the effects of ABM on symptoms and attentional bias in patients with PTSD. Although ABM led to a reduction of symptoms with a moderately high effect size (d = 0.66), the reduction was not significantly larger than in the control treatment (d = 0.46). Theoretically, this could mean that both treatments were effective, since we cannot be sure that the control condition acted as a real (neutral) placebo. For patients with anxiety disorders who have attentional bias towards threat, one could speculate that training at 50/50 contingency may actually be a low-dose version of ABM. However, this interpretation is untenable. Both effect sizes are below published effect sizes of pill-placebo in pharmacotherapy trials of chronic PTSD (Marshall, Beebe, Oldham, & Zaninelli, 2001; Davidson, Rothbaum, van der Kolk, Sikes, & Farfel, 2001; Brady et al., 2000). In one study an effect size of d = 0.81 was found for pill-placebo, even after a two-week placebo lead-in (Brady et al., 2000). In another study (Davidson et al., 2001) the same decline in CAPS-scores was observed after pill-placebo as in the present study for ABM. These effects were reached in the first four weeks of the pharmacotherapy trials. Consequently, we cannot even exclude the possibility that both the ABM and control treatment are less effective than placebo. The lack of effect was unexpected since positive effects of ABM had been shown in generalized anxiety disorder (GAD) (Amir et al., 2009a) and in social anxiety disorder (SAD) (Amir et al., 2009b).

Although previous research has shown that AB to threat is also a feature of PTSD, we did not observe a mean positive AB score in the present sample at pre-treatment. We did not test a healthy control group, matched for age, gender and education with the present version of the DPT, so the AB scores of our patients may still be different from healthy controls. Although healthy participants do not show AB on average (Bar Haim et al, 2007), some studies that assessed AB in anxiety disorders found *avoidance* of threat in the control group (Mogg et al.,2000).

Furthermore, in previous ABM studies the absence of AB has not been crucial in producing positive results (Amir et al., 2009a). The lack of AB at pre-treatment in the present study does not affect our conclusion that this version of ABM is ineffective for PTSD. The treatment has been investigated in and is being advocated for

patients with anxiety disorders, not only those who show high DPT scores. Moreover, a post-hoc analysis in the subgroup of patients who did show AB at baseline revealed the same pattern of results.

The feasibility and acceptability of the training was lower than expected. Given the fact that this treatment was short and could be carried out at home, we expected fewer drop-outs compared to traditional treatments for PTSD (i.e., Cognitive Behavioral Therapy, CBT). However, our mean drop-out rate (25.2%) fell within the range of drop-out rates in CBT (e.g., 32% (Van Emmerik, Kamphuis, & Emmelkamp, 2008) and 15% (Hensel-Dittmann et al., 2011; Dorrepaal et al., 2012).

The present study is the first study that was carried out in patients with PTSD. Participants were recruited in a mental health care setting. Previous studies in GAD and SAD included younger and more highly educated patients and may be less representative. The sample sizes of these studies were also notably smaller. About 70% of our patients also met criteria for a depressive episode. In the ABM-study on GAD (Amir et al., 2009a), however, the positive effects of ABM treatment were not limited to anxiety but extended to depressive symptoms, implying that these symptoms may also be sensitive to AB manipulation.

Our sample was relatively heterogeneous: some patients had suffered from childhood traumas and others were traumatized later in life. Since we aimed to test a representative clinical sample, we decided not to exclude patients based on the nature of the traumatic event.

Limitations of this study include the fact that we did not assess interrater reliabilities for the standardized diagnostic interviews and that we did not measure Axis II diagnoses. Regular supervision sessions for the diagnostic interviews were held however, and patients were only invited for participation if they had been diagnosed with PTSD in a clinical interview during the intake procedure of the outpatient clinic.

Research on cognitive-behavioral treatment shows that anxiety disorder patients with and without personality disorders benefit equally well (Mersch, Jansen, & Arntz, 1995). The relatively short follow-up period (three weeks) may also be seen as a limitation, but a delayed effect on symptoms after a longer time period is theoretically implausible.

In conclusion, we found no evidence that this version of ABM is effective in patients with chronic PTSD. A change of AB, which is the presumed mechanism of action, was also not observed. The field of ABM research is in its infancy and instead of continuing with more randomized controlled trials for new indications, we think that it will be more useful to further investigate the presumed mechanism of action in order to understand what the effects of this treatment are. This question is urgent. ABM is already commercially available (www.managingyouranxiety.com, 2012) for SAD, GAD and obsessive-compulsive disorder and given the number and the size of the studies we think that this is premature.

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Appendix A. IAPS numbers

Test (Set A)

Neutral		Trauma	
1333	5764	2703	9041
1419	578-	2799	9050
1450	7035	3022	9230
1540	7037	3181	9250
1590	7038	3215	9252
1603	7052	3500	9402
1670	7057	3550.1	9404
1810	7090	5970	9419
2235	7130	6010	9424
2514	7140	6021	9425
2980	7150	6190	9427
5010	7161	6210	9429
5200	7175	6241	9435
5390	7185	6243	9470
5471	7190	6250	9471
5500	7205	6313	9495
5531	7230	6540	9594
5534	7233	6821	9611
5600	7234	6836	9620
5621	7490	6840	9630
5628	7491	6940	9900
5629	7547	7361	9902
5660	7595	9000	9910
5700	7950	9010	9912

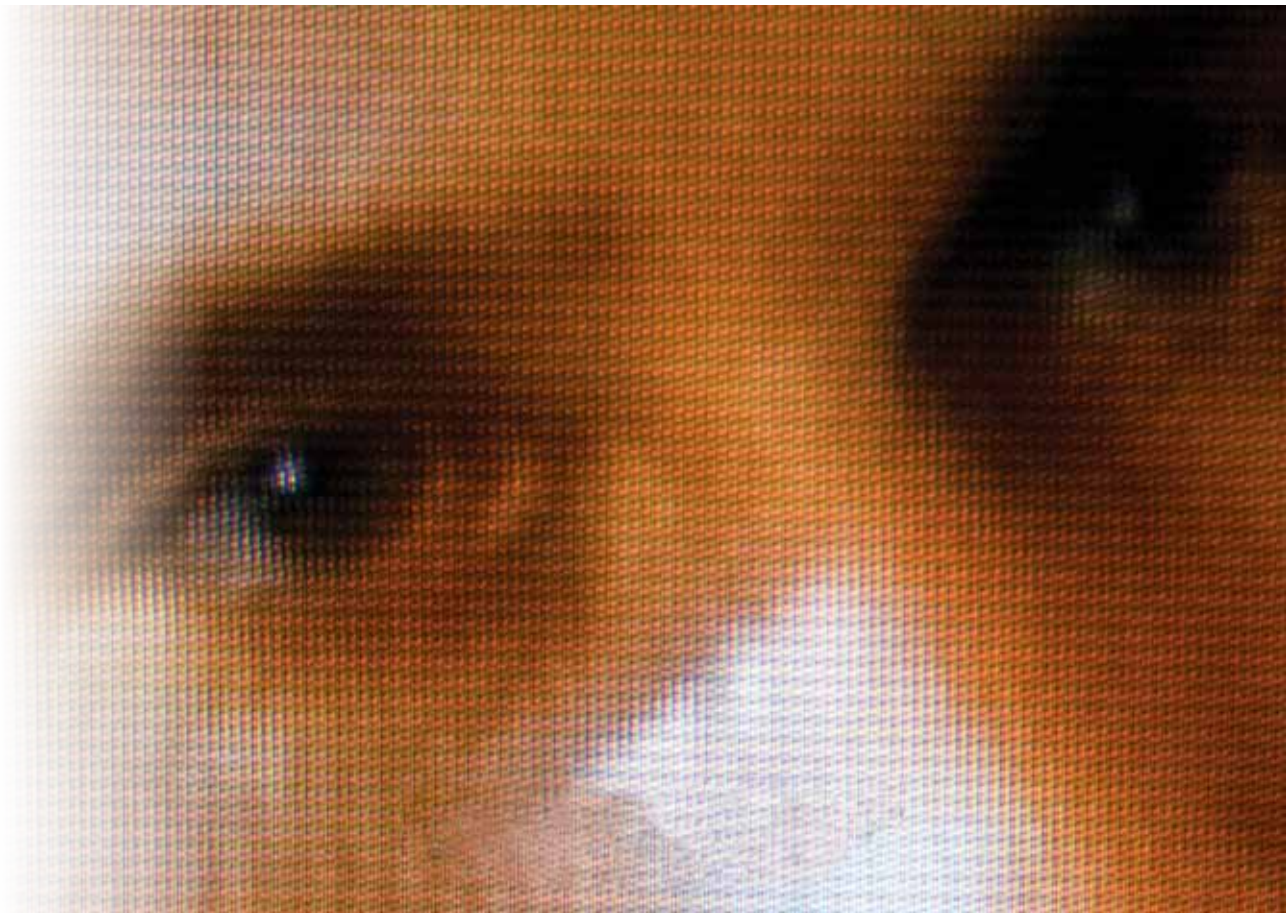
Training (Set B)

Neutral		Trauma	
1500	5631	2811	6550
1600	5635	2900	6560
1602	5711	3180	6561
1604	5720	3210	6562
1620	5731	3216	6570
1740	5750	3225	6571
1812	5760	3530	6610
1910	5800	5972	6800
1920	5811	6020	6825
2191	5870	6022	6830
2383	5891	6200	6834
2745.1	7002	6211	6838
5000	7004	6230	9007
5020	7006	6242	9160
5130	7009	6260	9254
5201	7010	6311	9421
5300	7036	6312	9426
5510	7041	6314	9428
5520	7059	6315	9592
5530	7080	6350	9622
5532	7160	6360	9635.2
5535	7179	6370	9901
5623	7211	6510	9903
5626	7260	6530	9911

3

Attentional bias and attentional control in posttraumatic stress disorder

M. Schoorl, P. Putman, S. Van Der Werff & W. Van Der Does (2013). *Journal of Anxiety Disorders*, under revision



Abstract

Extensive evidence exists for an association between attentional bias (AB; attentional vigilance or avoidance) and anxiety. Recent studies in healthy participants suggest that attentional control (AC) may facilitate inhibition of automatic attentional processes associated with anxiety.

To investigate relationships among AC, trauma-related AB, symptom severity and trait anxiety in patients with Posttraumatic Stress Disorder (PTSD), participants (N=91) completed self-report measures of AC, posttraumatic stress symptoms (PTSS) and trait anxiety. AB was measured with a pictorial version of the Dot-probe Test.

AC moderated the relationship between PTSS and AB (threat avoidance). Patients high in PTSS and low in AC showed attentional avoidance. No significant association between PTSS and AB in patients with medium or high levels of AC was found. A similar pattern of results was observed for the relationship between trait anxiety, AC and AB. These results suggest that a low ability to control attention is a risk factor for AB in PTSD. This first clinical study corroborates the accumulating evidence from analogue studies that individual differences in top-down attentional control are of considerable importance in the expression of AB in anxious psychopathology.

Introduction

Problems with attention and concentration are important characteristics of anxiety disorders. In posttraumatic stress disorder (PTSD), these problems are in fact part of the diagnostic criteria (American Psychiatric Association [DSM-IV-TR], 2000). A well known anxiety-related phenomenon is attentional bias (AB), which operates automatically to favor the processing of emotionally negative information in early stages of information processing (Williams, Mathews, & MacLeod, 1996). Attentional bias has been demonstrated in all anxiety disorders, including PTSD, with medium to large effect sizes (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & IJzendoorn, 2007).

Attentional bias

The adapted Dot-probe Task (DPT; Posner, Snyder, & Davidson, 1980; MacLeod, Mathews, & Tata, 1986) is considered the most direct and versatile measure of selective attention in psychological disorders (Harvey, Watkins, Mansell, & Shafran, 2004). In the DPT, a neutral and a threatening stimulus are presented simultaneously on a computer screen, in two separated locations. After a cue-target interval (e.g. 500 ms), a probe appears in one of the two locations. Participants are instructed to respond to the probe as fast as possible. If attention is selectively allocated to threatening information, RTs will be shorter in trials where the target replaces the threatening picture (a so-called congruent trial) than in trials where it replaces the neutral picture (an incongruent trial). Therefore, attentional bias in the DPT is defined as the congruency effect (RT incongruent minus RT congruent). Positive congruency scores reflect vigilant attentional bias towards threat and negative congruency scores reflect attentional avoidance of threat.

AB seems specific, in the sense that patients with PTSD selectively attend to trauma-related words (Kaspi, McNally, & Amir, 1995), whereas patients with social anxiety disorder respond strongest to words related to social judgment (Musa, Lépine, Clark, Mansell, & Ehlers, 2003), for instance. Although the majority of studies reports a relationship between vigilance and anxiety, selective attention away from threatening information has also often been reported, which is thought to reflect maladaptive avoidance of threat in later stages of processing (Cisler & Koster, 2010, Mogg, Mathews, & Weinman, 1987, Mathews, 1990). For instance, high trait anxious participants demonstrated vigilance after a cue-target delay of 100 ms but avoidance after 200 and 500 ms in an exogenous cueing task (ECT) with neutral and threatening pictorial stimuli (Koster, Crombez, Verschuere, Vanvolsem, & De Houwer, 2007). In healthy participants, avoidance of threatening pictures was also observed with the ECT at 200 ms and was correlated with trait anxiety (Putman, Verkuil, Ruissen & Hagenaars, 2012a). Such anxiety-driven attentional avoidance effects are also found using the DPT. For example, participants with blood-injury fear demonstrated attentional avoidance of threat scenes at longer stimulus durations (i.e., 1500 ms) in

a DPT (Mogg, Bradley, Miles, & Dixon, 2004). In healthy participants, greater attentional avoidance as measured with the DPT at 500 ms was also positively related to self-reported trait anxiety (Putman, 2011). More DPT studies using pictorial cues with 500 ms delays have demonstrated such anxiety-related avoidance (e.g., Mansell, Clark, Ehlers, & Chen, 1999, Musa et al., 2003, Chen, Ehlers, Clark, & Mansell, 2002, Pine et al., 2005, Monk et al., 2006).

Attentional control

The central assumption of attentional control theory (Eysenck et al., 2007) is that anxiety affects the central executive cognitive function of attentional inhibition and attentional shift. Anxious individuals are more easily distracted by task-irrelevant internal (e.g., worrying thoughts) or external (threatening) stimuli (Hirsch & Mathews, 2012; Mogg & Bradley, 1998). Attentional control then is defined as the ability to use voluntary and effortful attention to constrain these cognitive responses to goal-irrelevant (emotional) stimuli (Derryberry & Rothbart, 1997). Weak attentional control may reflect a more general cognitive deficit (trait) that might be of much importance in the regulation of attentional bias (Eysenck et al., 2007, Derakshan & Eysenck, 2009). Individuals with greater attentional control are less easily distracted by goal-irrelevant stimuli and should be better able to inhibit stimulus-driven attentional processes as probed by tests of attentional bias.
This has indeed been demonstrated several times now. Derryberry and Reed (2002) tested threat-selective attention in four groups of participants who scored high or low on trait anxiety and high or low on attentional control as measured with the Attentional Control Scale (ACS), a 20-item self-report questionnaire that measures the ability to focus and shift attention. Results of this study showed that a relationship between trait anxiety and threat bias was moderated by attentional control; high levels of attentional control enabled anxious participants to constrain the impact of threatening information on their performance of a spatial attention task. Putman and colleagues (Putman et al., 2012a) also found relationships between trait anxiety, attentional control and attentional avoidance of threat in healthy students using an emotional cueing task. However, only ACS was independently associated with avoidance (controlling for anxiety). This finding was recently replicated with an Emotional Stroop Task (EST). In a large student sample (n = 80), attentional control was found to predict threat interference as measured with the EST (Putman, Arias-Garcia, Pantazi, & Van Schie, 2012b). Furthermore, results of a recent analogue study by Bardeen and Orcutt (2011) demonstrated a moderating effect of attentional control on the relationship between posttraumatic symptoms (PTSS) and attentional bias, in line with the results from the original Derryberry and Reed study. These findings suggest an important but hitherto much overlooked role for AC in attentional processes and affect regulation. However, since the participants in these studies were all unselected students, the extent to which these results generalize to patients with anxious psychopathology has yet to be determined.

Present study

The goal of the present study was to investigate the association between attentional bias, attentional control, PTSS and trait anxiety in a large clinical sample of PTSD patients. Based on the extant literature and theory, we expected an association between PTSS and trait anxiety and attentional bias. However, if this relationship should take the form of either vigilance or avoidance seems hard to predict. It is very likely that the direction of the relationship between attentional bias and anxious constructs depends strongly on various methodological variables (e.g., stimulus-type, cue-target delay; see Koster et al., 2007) but the influence of these parameters has not been sufficiently charted to make a firm prediction.
Regardless of the direction of attentional orienting, our main interest was the association between attentional control and attentional threat-processing. We expected that attentional control should be related to attentional bias in an opposite manner than posttraumatic stress symptoms or trait anxiety, reflecting the previously reported buffering effect of attentional control (c.f. Derryberry & Reed, 2002, Bardeen & Orcutt, 2011; Putman et al., 2012a, Putman et al., 2012b). Higher attentional control was predicted to be associated with reduced automatic influence of threat information on attentional performance. This led to the following hypotheses. First, we expected to find a negative relationship between posttraumatic stress symptoms as well as trait anxiety and attentional control as measured with the ACS. Second, we expected opposite relationships between PTSS as well as trait anxiety and attentional bias, compared to the relationship between attentional control and attentional bias. Lastly, based on previous findings (Derryberry & Reed, 2002, Bardeen & Orcutt, 2011), we tested the hypothesis that attentional control might moderate relationships between PTSS or trait anxiety and attentional bias.

Method

Participants

Participants were included while they were on a waiting list for treatment in a specialized mental health care department for patients with PTSD. Eligible participants had a diagnosis of chronic PTSD (duration at least three months). Exclusion criteria were a psychotic disorder (lifetime); alcohol or drug dependency (current); deficits in motor skills prohibiting the use of a computer keyboard; color blindness. Information was collected regarding the participant's age, living circumstances, ethnic background and trauma history. The data reported in this paper were collected at the pre-treatment phase of a clinical trial for a novel treatment (Schoorl, Putman & Van Der Does, 2013). DPT data were collected for 99 patients.

Measures

Posttraumatic Stress Disorder

The Mini-International Neuropsychiatric Interview 5.0 (Sheehan et al., 1998) was used to assess DSM-IV Axis I psychiatric diagnoses. Patients were included for the study when they fulfilled the criteria of PTSD.

Self-Rating Inventory for Posttraumatic Stress Disorder (SRIP). Symptom severity was assessed with the Self-Rating Inventory for Posttraumatic Stress Disorder (Hovens, Bramsen, & Van Der Ploeg, 2000). This instrument asks participants to rate each of the PTSD symptoms on a scale ranging from 0 (not at all) to 4 (very severe). The SRIP has three sub-scales (Re-experiencing, Avoidance and Hyperarousal) and a total score. Internal consistency ranges from 0.76 to 0.94 for the four scales. Test-retest reliability is 0.92 and coefficient alpha is 0.90-0.94 (Hovens, Bramsen, & Van Der Ploeg, 2000). The SRIP correlates highly (around r = 0.80) with other self-report questionnaires for PTSD, for instance the Impact of Event Scale (IES, Horowitz, Wilner, & Alvarez, 1979)(Hovens et al., 2000).

Anxiety proneness

Spielberger State/Trait Anxiety Inventory (STAI-t). Participants completed the trait version of the Spielberger State/Trait Anxiety Inventory (Spielberger, 1983, Van der Ploeg, Defares, & Spielberger, 1980). The STAI-t measures anxiety proneness and consists of 20 items scored on 4-point Likert scale, such as ''I feel nervous and restless''. The STAI-t has high internal consistency (Cronbach's α = .90), good test-retest reliability (r = .70 - .76) and good concurrent validity with other anxiety measures (Spielberger, 1983). The STAI-t is correlated with PTSD symptomatology (r = .33, Collimore, McCabe, Nicholas Carlton, & Asmundson, 2008).

Attentional Control

Attentional Control Scale (ACS). The Attentional Control Scale (Derryberry & Reed, 2002, Verwoerd, De Jong, & Wessel, 2006) is a 20-item questionnaire measuring voluntary attentional inhibition attentional shifting and the ability to flexibly control thought with a 4-point Likert scale. Example items are ''When I need to concentrate and solve a problem, I have trouble focusing my attention'', "When a distracting thought comes to mind, it is easy for me to shift my attention away from it'', or "I can become interested in a new topic very quickly when I need to''. Previous reports show that the ACS has a good internal consistency (Cronbach's α from .71 to .82; Putman et al., 2012a, Verwoerd, De Jong, & Wessel, 2008). Due to a human error, we used a 19-item version of the ACS in the present study. The first item of the questionnaire, ''It's very hard for me to concentrate on a difficult task when there

are noises around''; an item that measures attentional inhibition, was missing[1].

Attentional Bias

Attentional bias was measured with a version of the DPT (MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002) modeled after the adaptation used by Amir et al. (2009). Each trial of the DPT starts with a fixation cross that appears in the center of a computer screen for 500 ms. Next, two pictures (always one neutral and one threat-related picture) are presented simultaneously for 500 ms, above and below the fixation location. The next screen shows a target ('E' or 'F') in the spatial location of either picture. Participants were instructed to discriminate the target as fast as possible by pressing one of two response keys (E = left arrow, F = right arrow). If attention is allocated towards threat-related information, RTs will be shorter in trials where the target replaces the threat-related picture (a congruent trial) than in trials where it replaces the neutral picture (an incongruent trial). The 96 trials consisted of various, fully counterbalanced combinations of target type (E or F), target position (top or bottom) and location of the threatening picture, presented in a random order. Attentional bias score (AB score) is calculated by subtracting the mean reaction time in congruent trials from the mean reaction time in incongruent trials. A positive AB score indicates threat vigilance, a negative score indicates threat avoidance.

We used pictures as stimuli instead of words (following the design of Koster, Crombez, Verschuere, & De Houwer, 2004). We first selected 105 threat pictures taken from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 1999). Next, five PTSD patients and five senior psychotherapists selected 96 pictures based on valence and arousal level. For ethical reasons and feasibility, we removed pictures that were considered too highly threatening. Examples of the used pictures; a person holding a gun, a man strangling a woman, car accident, or a hospital scene. A list of the selected IAPS pictures is presented in appendix A.

Procedure

The study was approved by an independent certified medical ethics committee (METIGG, Utrecht, The Netherlands). All patients provided written informed consent before any assessments took place. The DPT and questionnaires were programmed and presented in E-Prime V1. The DPT was presented on a 17'' CRT monitor.

[1] In another sample from the same population, 25 PTSD patients filled out the complete ACS. Correlations between the complete ACS Total and the ACS total with one item missing was high (r = 0.996). Internal consistency was also high (complete version α = .82, incomplete version α = .81). When we treated the missing item as an at random missing value and imputated the mean of the rest of the items (within subject), correlation between this corrected score and the score on the incomplete version of the ACS was 1.0. In other words, omitting this one item does not affect psychometric properties of the scale. For reasons of across-study comparability, we report scores for the imputed scale when providing descriptive data, but for correlations and regression analysis we use the results for the incomplete version.

Results

Data reduction and analyses

First all trials with erroneous responses and trials with RTs < 300 ms were removed (mean number of errors 3.7, *SD* = 6.2). This procedure removes the most extreme outliers and allows better use of distribution parameters of the remaining RTs for a subsequent more precise data-driven outlier removal procedure (Putman, Hermans, & Van Honk, 2006). In this following step, all trials with RTs below or above an individual threshold set at the mean +/- three standard deviations were removed as outliers. This filtering procedure resulted in exclusion of an average 1.6% of the correct trials.

Table 1. Demographic and clinical characteristics of the sample

Variable	Outcome
Gender (N, % women)	70 (76.9)
Age (N, range, *SD*)	37 (18-61, *11.6*)
Trauma (N, %)	
Three or more events	58 (63.7)
Age 12 or younger	42 (46.2)
Comorbidity (N, %)	
Depressive disorder	63 (69.2)
Dysthymia	22 (24.2)
Panic disorder	27 (29.7)
Social anxiety disorder	33 (36.3)
General anxiety disorder	35 (38.5)
Obsessive-compulsive disorder	14 (5.4)
Somatization disorder	11 (12.1)

Next, we excluded two participants based on behavioral observations during the test. These participants were unable to follow the instructions. We then screened the participants for outliers (scores more than 3 *SD* above or below group mean) based on mean AB score, number of incorrect responses, and total number of trials left for analysis. This resulted in exclusion of another six participants. Because of technical difficulties, STAI-data of one patient were lost.

Patient characteristics

Of the 91 remaining participants, 76.9% was female (see table 1). Average age was 37 years. All of the patients had experienced multiple traumas and 46.2% of the sample had been traumatized in childhood (under the age of 12). Traumatic events most mentioned were non-consensual, unpleasant or violent sexual experiences (75.9%), physical violence (65%), being attacked with a weapon (29.7%) and the sudden unexpected death of a loved one (16.5%).

Bivariate correlations

For means, *SD*s and intercorrelations, see table 2. AB was not significantly correlated to any of the demographic variables. In the whole sample, the overall (negative) attentional bias score did not differ significantly from zero (mean AB score = -10 ms (*SD* = 66.5), *t* (90) = -1.45; *p* = .15).
As expected, ACS was negatively correlated with SRIP Total. All subscales, SRIP Re-experiencing, Avoidance and Hyperarousal, showed very similar relations with ACS. Furthermore, SRIP Total and SRIP Re-experiencing were significantly negatively related to AB score and ACS was positively correlated with AB score. ACS was significantly negatively associated with STAI-t, showing similar relations between trait anxiety and PTSS with attentional control. No significant correlation was found between STAI-t and AB score. These results confirm our first two hypotheses.

Table 2. Descriptive statistics and correlations

	Variable	M *(SD)*	1	2	3	4	5	6	7
1	SRIP Total	62.8 *(8.4)*	-	.77**	.91**	.85**	-.50**	.51**	-.21*
2	SRIP Re-experiencing	16.8.*(2.6)*		-	.57**	.49**	-.41**	.24**	-.21*
3	SRIP Avoidance	26.1 *(4.0)*			-	.65**	-.41**	.52**	-.15
4	SRIP Hyperarousal	20.0 *(3.3)*				-	-.46**	.49**	-.20
5	ACS	40.9 *(7.4)*					-	-.52**	.31**
6	STAI-t	63.8 *(8.7)*						-	-.14
7	AB score	-.10 *(.67)*							-

Note: SRIP Total = Self-Rating Inventory for Posttraumatic stress disorder Total score; SRIP Re-experiencing = SRIP Re-experiencing subscale score; SRIP Avoidance = SRIP Avoidance subscale score; SRIP Hyperarousal = SRIP Hyperarousal subscale score; ACS = Attentional Control Scale; STAI-t = State-Trait Anxiety Inventory trait scale; AB score = Attentional Bias score
* p < .05
**p < .01

Multiple regression analyses

To examine moderation, hierarchical linear regression was performed. The predictor variables and moderator were centered to maximize interpretability and reduce multicollinearity (Frazier, Tix, & Barron, 2004). AB score served as outcome variable. In the first step of the model, ACS and SRIP served as predictor variables. The interaction term (ACS X SRIP) was entered as predictor in the final step (see table 3).
In the first step, ACS and SRIP predicted 10% of the observed variance of the AB score (p = .009). Only ACS predicted attentional bias independently. Adding the interaction term in the 2nd block improved the model significantly: ΔR^2 = .10, β = .28, p = .002. This confirms that ACS has a moderating effect on the relationship between SRIP and AB score.
The analyses were repeated with STAI-t as predictor in the first block. Results indicated that there was no main effect of trait anxiety in the first step, but ACS predicted attentional bias significantly (p = .006). When the interaction term (ACS X STAI-t) was entered in the second step, ACS still predicted attentional bias, and the interaction between attentional control and trait anxiety also predicted attentional bias significantly (ΔR^2 = .08, β = .31, p = .005).

Table 3. Hierarchical multiple regression with attentional bias as outcome variable

Predictor	β	ΔR^2	p
Step 1			.10
SRIP	.08		.515
ACS	.17		.022
Step 2		.10	
SRIP	.07		.520
ACS	.24		.034
SRIP X ACS	.31		.002
Step 1		.11	
STAI-t	.04		.723
ACS	.35		.004
Step 2		.08	
STAI-t	.05		.659
ACS	.37		.002
STAI-t X ACS	.28		.005

Note: SRIP = Self-Rating Inventory for Posttraumatic stress disorder; ACS = Attentional Control Scale; SRIP X ACS = interaction term; STAI-t = State-Trait Anxiety Inventory trait scale; STAI-t X ACS = interaction term

To clarify the nature of the significant interactions, we performed simple slope analyses (Aiken & West, 1991). A significant positive association was demonstrated between AB score and SRIP in patients with low ACS scores (B = -2.9, β = -.37, *p* = .012) (see figure 1); patients with low AC and high PTSS showed more avoidance of the trauma-related stimuli, suggesting that a low ability to control attention is a risk factor for attentional bias in PTSD. At medium and high levels of ACS no significant association between AB score and SRIP was found (*p* = .521 and *p* = .126 respectively). Results for STAI-t revealed a similar pattern of results (see figure 2). The association between AB score and trait anxiety was not significant in patients with low (*p* = .128) or medium ACS (*p* = .625), but results revealed a significant positive association between AB score and trait anxiety for patients with high ACS (B = 2.6, β = .34, *p* = .030); patients high in ACS and high in STAI-t showed attentional vigilance.

In summary, AC is related to AB independently from PTSS or trait anxiety. Moreover, AC moderates the relationship between AB and PTSS and trait anxiety. Patients with a low ability to control attention and high in PTSS show attentional avoidance, and patients with high attentional control and high trait anxiety demonstrate opposite attentional bias.

Figure 1. Interaction between attentional bias, attentional control and posttraumatic stress symptoms

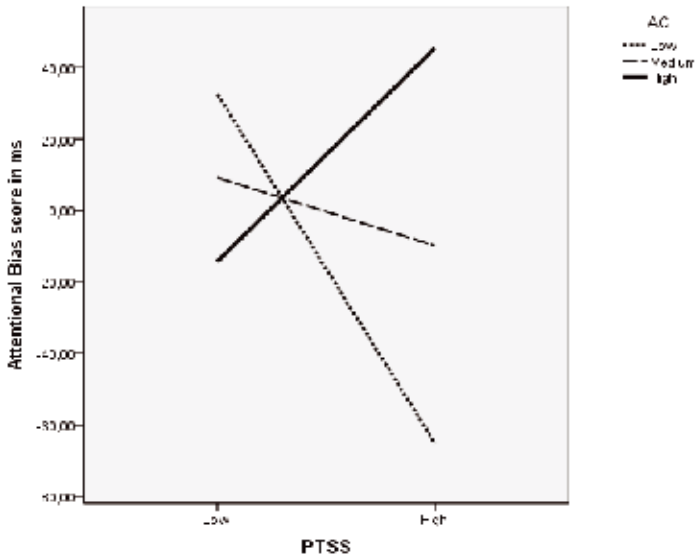
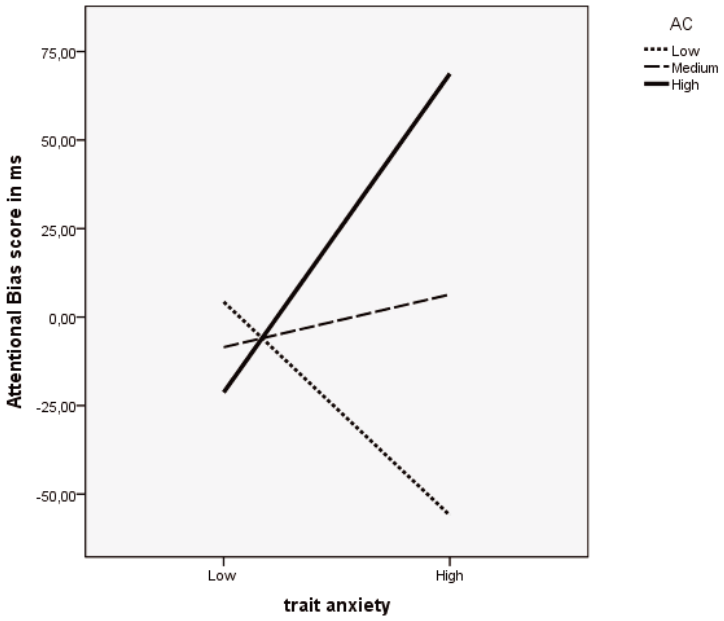


Figure 2. Interaction between attentional bias,attentional control and trait anxiety



Discussion

The main goal of this study was to investigate the relationship between attentional bias, attentional control and PTSS in a large patient sample. As predicted, significant associations were demonstrated between PTSS, attentional bias and attentional control. More importantly, our results showed that AC is associated with attentional avoidance in PTSD patients and moderates the relationship between PTSS and attentional avoidance, indicating that individual differences in attentional control contribute importantly to the occurrence of anxiety-related abberations in attentional functioning as seen in PTSD (Buckley, Blanchard, & Neill, 2000). AC also related to AB independently from trait anxiety and moderated the association between AB and trait anxiety, suggesting that AC also overrides the effect of trait anxiety on AB in clinical patients.

When investigating the specific direction of the effect of attentional control, both expected and unexpected results emerged. PTSD patients with high symptom levels and low levels of attentional control showed attentional avoidance, and medium or high levels of AC seem to inhibit this co-occurrence of posttraumatic stress symptoms and AB. A very similar pattern of results related to trait anxiety was found. Follow up tests showed that the relation between low AC and avoidance only came

close to significance (p = .128), but this time there was significance for a relationship whereby high AC was related to vigilance in high anxious patients. We can only speculate about the underlying mechanisms. Possibly, high attentional control ''overcorrects'' the naturally occurring tendency to avoid associated with both posttraumatic and trait anxiety. When accounting for the difference in results, it can also be hypothesized that posttraumatic anxiety but not ''general'' anxiety is related to attentional avoidance. A hallmark characteristic of PTSD is pervasive behavioral and cognitive avoidance, in contrast with trait anxiety, as measured by the STAI-t, which is defined in terms of being nervous and worrisome and repetitively engaging in threatening cognitions (Andrews et al., 2010). Regardless of conjectures about the direction of attentional bias (Bar-Haim et al., 2007, Chen et al., 2002; Monk et al., 2006, Mansell et al., 1999, Pine et al., 2005, Putman et al., 2012a), the present data clearly show the important role of attentional control in its expression.

Our results demonstrate some suggestion of overall avoidance, but far from significant. However, absence of such a significant group-level effect does not preclude further study because individual differences in anxiety and attentional control may influence the manifestation of selective attention to threat. Indeed, our results showed that PTSD patients with a low ability to control attention displayed attentional avoidance, in contrast with patients with a medium or good ability to control attention.

Avoidance of threatening stimuli is demonstrated in a study in unselected participants using this version of the DPT with the same pictorial stimuli and cue-target delay, demonstrating that attentional avoidance was related to trait anxiety and reduced frontal cortical regulation of affect (Putman, 2011). Furthermore, attentional avoidance has also been observed in maltreated children with PTSD (Pine et al., 2005). In that study, children demonstrated attentional avoidance of pictures of angry and threatening faces presented for 500 ms. The extent of this bias was associated with the severity of physical abuse and diagnosis of PTSD, comparable to the presently observed relation between avoidance and PTSD symptom severity. Moreover, attentional avoidance at this timeframe is not limited to PTSD, as some studies in social anxiety disorder have found the same pattern using a DPT with pictorial stimuli (faces) at a cue-target delay of 500 ms (Chen et al., 2002; Mansell et al., 1999). Attentional avoidance was also observed in adolescents with Generalized Anxiety Disorder (Monk et al., 2006).

To summarize, automatic anxious responding to threatening stimuli can take the form of attentional avoidance. This has been demonstrated in healthy participants as well as in patient samples, particularly with tasks measuring spatial attention and pictorial stimuli. More importantly, attentional avoidance was associated with low levels of attentional control in this sample, replicating findings with an emotional cueing task-study with pictorial stimuli (Putman et al., 2012a). The present results suggest that the influence of task-irrelevant threatening information has on attentional performance can be inhibited by attentional control.

Peers and Lawrence (2009) showed that high attentional control might buffer against the influence of emotional distraction in rapid serial visual presentations, whereas state anxiety was not associated with emotional distraction. Putman et al. (2012b) similarly report a negative relation between emotional Stroop interference for threat words and AC but not between interference and anxiety. These results are in line with our findings on the significance of attentional control. Attentional bias has for long been conceptualized primarily in terms of affective processes such as stimulus appraisal (see e.g. Mogg & Bradley, 1998). Recent findings, including the present results, demonstrate that ''cold'' cognitive factors (attentional control) have considerable impact on biased attentional processing of threatening information. These cognitive factors may be even more important than negative affective states or traits and might even explain the sometimes mixed results of studies on attentional bias in anxiety (Cisler & Koster, 2010).

Deficits in attentional control may constitute a general risk factor for developing affective disorders. From a developmental perspective, non-emotional effortful attentional control is found to influence self-regulating capacities (Rothbart, Ahadi, & Evans, 2000). Strong attentional control may ''override'' the effects of anxiety on automatic attention and children who do not acquire the ability to inhibit stimulus-driven attentional responding to threat may be more prone to develop anxiety disorders in childhood (Kindt & Van den Hout, 2001).

Although we know of no earlier reports of studies investigating the role of attentional control in PTSD patients, Verwoerd and Wessel (2007) showed a relationship between self-reported unwanted intrusive memories and distractibility in a large sample of undergraduate students. Unwanted intrusive memories are a core feature of PTSD (i.e. re-experiencing). Results indicated a significant relationship between distractibility and involuntary memories independent of both trait depression and 'repressive coping'. In a study by Hagenaars and Putman (2011), further evidence for the relationship between intrusive memories and AC (also measured with the ACS) was found. In healthy participants low in attentional control, self-perceived tonic immobility (a state of physical immobility and muscular rigidity that can occur after encountering a traumatic event) during film viewing predicted intrusion frequency in a week after watching the aversive film, but people with higher AC seemed inoculated against this relationship. Bardeen and Orcutt (2011) recently investigated the relationship between AC, attentional bias (as measured with the DPT) and PTSS in a student sample. In this study, AC was also found to moderate the relationship between PTSS and attentional bias but only when the threatening stimulus was presented for 150 ms (note that in that study, using a short CTOA, higher AC was associated with a positive relationship between PTSS and AB). In line with results of the present study, participants low in AC and high in PTSS demonstrated attentional bias (vigilance), also identifying low AC as a risk factor for AB in PTSD. Contrary to our findings, this moderating effect of AC was not present when a 500 ms time-interval was used in the DPT. These differences in results might be explained by the design of the DPT involved (general threat stimuli vs trauma

specific stimuli in the present study) and characteristics of the samples involved (undergraduate students vs clinical patients).

Our results show that in patients with PTSD poor attentional control is associated with attentional avoidance. The three symptoms clusters of PTSD are re-experiencing of the traumatic event(s), avoidance and hypervigilance. More commonly, attentional bias is associated with hypervigilance towards threatening information. Our study accentuates the role of attentional avoidance of ''triggers''; reminders of the traumatic experience(s). This cognitive strategy prevents a change in dysfunctional appraisals of the experienced event(s); individuals deprive themselves of the opportunity to discover that the traumatic event(s) will not happen again. In this way, attentional avoidance contributes to a "sense of serious current threat'' (Ehlers & Clark, 2000). By both inoculating against intrusive memories directly and through attentional avoidance, attentional control could play a crucial role in two of the core symptoms of PTSD.

The clinical implication of the present results is that attentional control seems to have an important relationship with supposedly maladaptive early cognitive processing of threatening information in PTSD. Although our cross-sectional design leaves no room for speculations about causality, these data warrant further investigation whether individual differences in attentional control may be a risk factor for developing PTSD after experiencing a traumatic event. It also may encourage further research into the preventive or therapeutic effects of attentional control training. Existing therapeutic interventions for PTSD should take into account that poor attentional control might interfere with treatment. New clinical developments such as Mindfulness-Based Cognitive Therapy (MBCT; Segal, Williams, & Teasdale, 2002) and metacognitive therapy (MCT; Wells, 2008) specifically focus on enhancing attentional control and seem therefore suitable for PTSD.

A suggestion for future research is to include trials in the DPT with only neutral stimuli (Koster, et al., 2004), which would allow a more precise investigation of the attentional processes involved (reduced engagement or facilitated disengagement of the threatening stimuli). Furthermore, comorbidity with depression might have influenced our results since patients with depressive disorder are hypothesized to demonstrate AB at later stages of processing (Mogg, Bradley, & Williams, 1995). However, in all anxiety disorders comorbidity with depression is high and our sample therefore represents clinical reality.

Another limitation of the present study is the reliance on self-report questionnaires to measure anxiety and attentional control. Future research could also include an objective measure of attentional control or physiological measures or neural correlates of attentional control.

In conclusion, a unique feature of this study is that we were able to investigate the relationship between attentional control and attentional bias for the first time in a large clinical sample. Implications for other anxiety disorders seem evident and future research into attentional bias could greatly benefit from incorporating measures of attentional control into their design. Our results confirm the hypothesis

that in patients high in anxiety (whether trait anxiety or posttraumatic stress symptoms) attentional control predicts attentional bias. Moreover, attentional control moderates the relationship between posttraumatic stress symptoms and AB. Only when attentional control is low, patients high in PTSS demonstrate characteristic attentional avoidance. However, results also indicate that high trait anxiety and high attentional control are related to attentional vigilance. This latter effect seems less straightforward to interpret, but these results unmistakably demonstrate the importance of attentional control in relationships between anxious symptomatology and cognitive processing of threatening information in PTSD patients.

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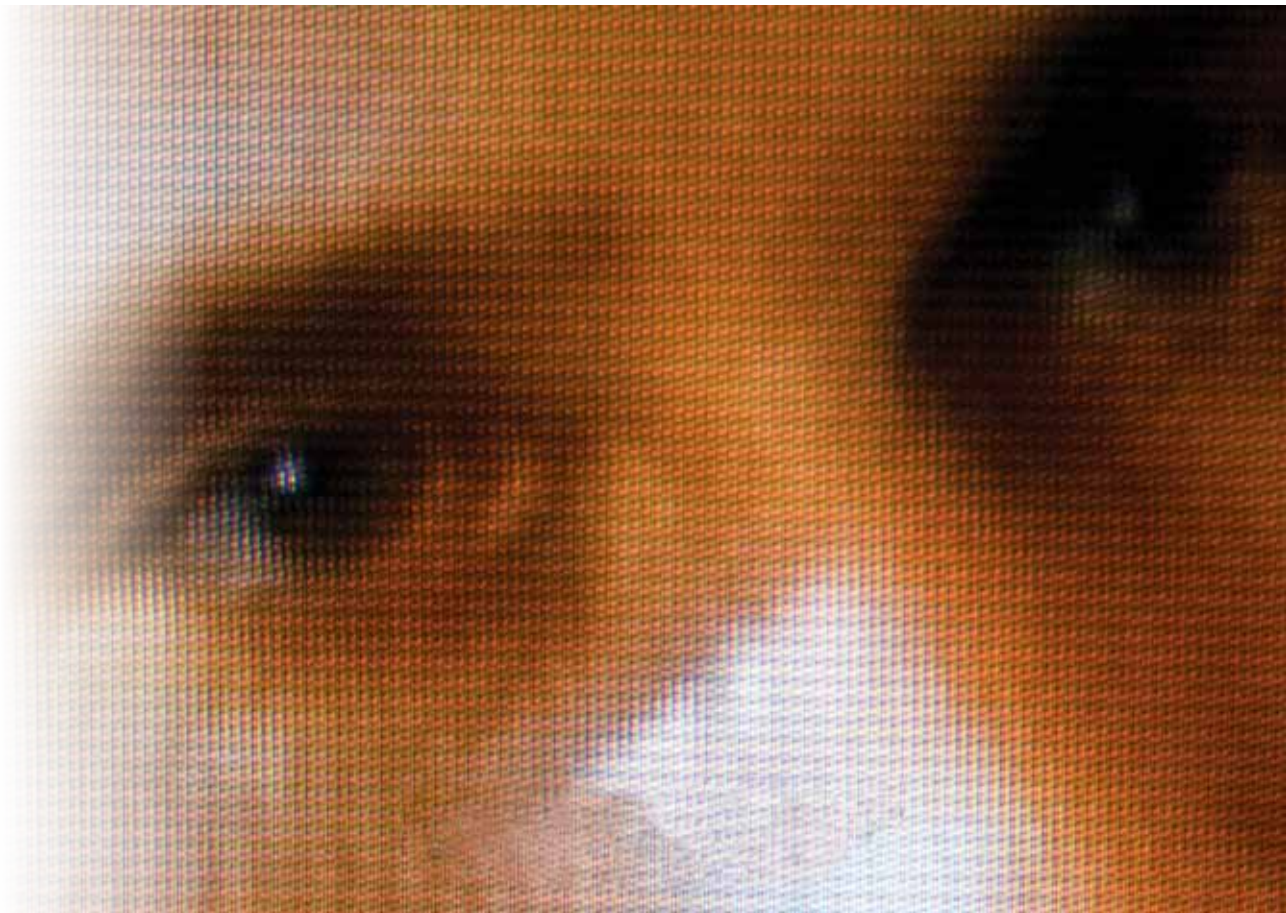
4

Attentional bias modification in veterans with posttraumatic stress disorder: a case series with a personalized treatment version

M. Schoorl, P. Putman, T.M. Mooren, S. Van Der Werff & W. Van Der Does (2013). *Journal of Traumatic Stress*, under revision



Abstract

Beneficial effects of Attentional Bias Modification (ABM) have been claimed in a number of anxiety disorders, but the results are variable. A recent trial in patients with posttraumatic stress disorder (PTSD) showed no therapeutic effects. The use of personally relevant stimuli in patients might increase the efficacy of ABM. In an A-B case series design, we explored whether individualized ABM led to changes in attentional bias and to symptom reduction in six war veterans with PTSD. No therapeutic effects were observed. Inter- and intra-individual attentional bias scores varied widely and did not respond to ABM as hypothesized. This study provides no evidence that individualized ABM is an effective treatment for PTSD.

Introduction

Attentional bias (AB) for threatening information is a characteristic of anxiety disorders, including PTSD (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & IJzendoorn, 2007). Attentional Bias Modification (ABM) is a novel, computerized treatment that aims to treat anxiety disorders by changing AB. ABM involves eight to ten 15-minute sessions in which participants are trained to direct their attention away from the threatening stimuli that automatically attract their attention.

Two meta-analyses have concluded that ABM positively affects anxiety (Hakamata et al., 2010; Hallion & Meron Ruscio, 2011). Reviewing twelve randomized controlled trials (RCTs), an effect size of .61 (medium) was calculated for ABM as compared to a control training (Hakamata et al., 2010). Three of these RCTs were clinical trials, demonstrating therapeutic effects of ABM in patients with generalized anxiety disorder (GAD) (Amir, Beard, Burns, & Bomyea, 2009a) and social anxiety disorder (SAD) (Amir et al., 2009b; Schmidt, Richey, Buckner, & Timpano, 2009). The number of patients in each RCT was limited however and a recent clinical trial on the effect of ABM on PTSD had disappointing results (Schoorl, Putman, & Van Der Does, 2013). This trial was by far the largest RCT to date (n = 102) and revealed that ABM and control treatment reduced PTSD symptoms with effect sizes of 0.66 and 0.46 respectively, comparable to or lower than the effect sizes of pill-placebos in pharmacotherapy trials in PTSD (e.g., Davidson et al., 2001). Moreover, ABM did not affect AB.

The lack of effect might be explained by the use of pictorial stimuli, since verbal stimuli are thought to generate better results (Hakamata et al., 2010). Furthermore, our stimuli might not have been personally relevant enough. ABM may be more effective when the stimuli are tailored to patients' idiosyncratic experiences (MacLeod, Koster, & Fox, 2009).

At a conference presentation, Amir (2010) presented preliminary positive results of two studies in war veterans with PTSD, in which individualized ABM was used as an augmentation to regular treatment. We decided to investigate such a version of ABM in a case series design and measure the effect on both symptoms and AB. In only two RCTs (a change in) AB was measured (Amir et al., 2009a, Schoorl et al., 2013). Establishing mediation of symptom change by a change in AB is however crucial to attribute therapeutic impact to ABM. Therefore, our goal was to investigate the effects of individualized ABM on both AB and PTSD symptoms.

Methods

Participants

Participants were six war veterans administered in a clinic for PTSD treatment. Inclusion criteria were PTSD symptoms, measured by the Clinician Administered

PTSD scale (CAPS, Blake et al., 1990). Inclusion criterion was a CAPS score ≥ 45. Exclusion criteria were lifetime psychotic disorder, alcohol or drug abuse or dependence.

Measures

The Mini-International Neuropsychiatric Interview Plus (MINI Plus, Sheehan et al., 1998) was used to assess the presence of psychiatric disorders at baseline. PTSD symptoms were assessed with the CAPS.
AB was measured with a version of the Dot-probe Test (DPT; Amir et al., 2009a). Each trial starts with a fixation cross in the center of a computer screen for 500ms. Next, two words (one neutral and one trauma-related) appear for 500ms, above and below the fixation location. Then, a target ('E' or 'F') is shown in the location of either word. In half of the trials the target appears in the location of the trauma-related word, and in the other half in the location of the neutral word. Patients are instructed to discriminate the target as fast as possible by pressing a response key. The trials consisted of different, fully counterbalanced combinations of target type, position and location of the trauma-related word, presented in a random order. AB score is calculated by subtracting the mean reaction time (RT) in congruent trials from the mean RT in incongruent trials.
To collect idiographic relevant words, participants were interviewed about their traumatic experiences. A verbatim report of this audiotaped interview was made. The interviewer selected two sets of 20 meaningful words for test and training for each participant individually.

Treatment

Each of the eight ABM sessions consisted of 100 trials. Of these, 80% were neutral/trauma-related, and 20% neutral/neutral pairs. In ABM, the target always appeared in the location of the neutral word. In the control condition, the target appeared in the location of the neutral word in 50% of the trials, similar to AB assessment.

Design and procedure

A single-case series using an A-B design (Barlow & Hersen, 1984) with a 2-week follow up was implemented. Individual baselines and control treatment acted as control variables.
The study was approved by the local review board. Therapists informed their patients about the research and patients received an information letter. Patients were informed about the study, but they were unaware of the timing of the control treatment. If patients decided to participate, the first assessment (inclusion, Time 1) was planned. Written informed consent was obtained.

A one week baseline-period took place (baseline, Time 2), followed by one week control treatment (Time 3). Subsequently, all patients received ABM for two weeks (Time 4) with a one week follow-up (Time 5).
All assessments and interviews were done by an independent, well-trained experienced psychologist, supervised by the first author, a licensed clinical psychologist.

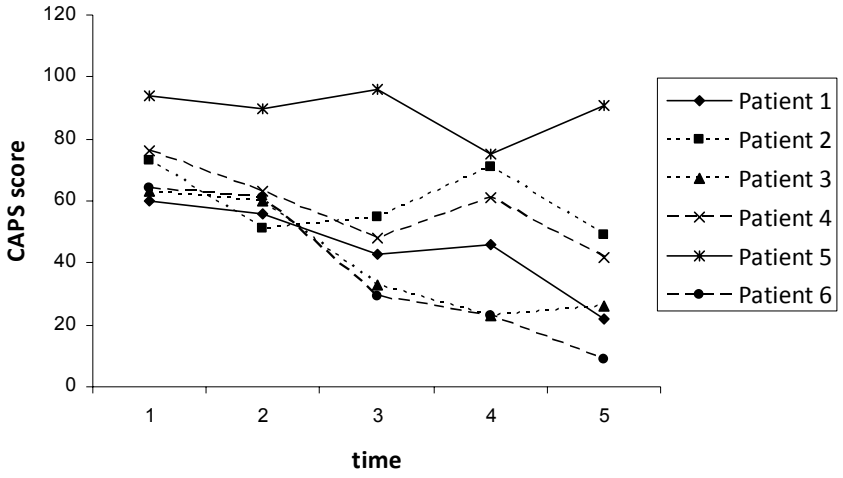
Data reduction and analyses

The DPT data from Time 1 of one patient were lost due to technical problems. One patient did not show up for follow-up and we were unable to contact him.
First, all DPT trials with erroneous responses and trials with RTs < 300 ms were removed (5 % of the data). In the following step, all trials with RTs below or above an individual threshold set at the mean +/- three standard deviations were removed as outliers (2 % of the data; Putman, Hermans, & Van Honk, 2006; Ratcliff, 1993).

Results

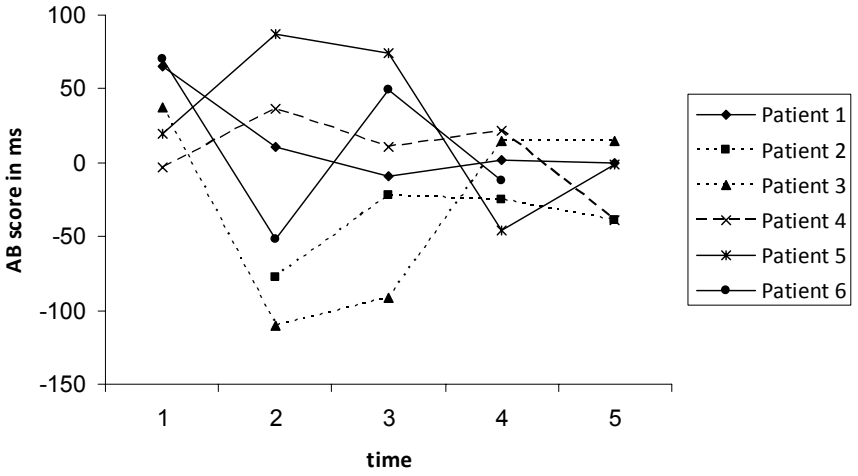
Average age of the six male participants was 39.3 years (*SD* = 8.2, range 27-49 years). According to the MINI Plus, two patients were diagnosed with current major depressive disorder, one with dysthymic disorder, one with panic disorder and two with GAD. Mean AB score was 3.7 ms (*SD* = 3.1ms). For the results on the CAPS, see figure 1. Positive effects were expected after the intervention or at follow-up (Time 4 or 5).
We used the Jacobson & Truax (1991) formula to compute criteria for clinically meaningful improvement. For the CAPS, we used norms of both a functional and a dysfunctional population (Resick, Nishith, Weaver, Astin, & Feuer, 2002); a clinically significant cut-off point of 56.5 was set.
According to this cut-off point, five patients showed recovery at follow-up. However, none of the patients were improved after ABM. Furthermore, in two patients (patient 2 and 4) PTSD symptoms increased during ABM although this effect disappeared at follow-up.
AB scores (see figure 2) varied widely, to the extent that the intra-individual change was larger than the inter-individual change during baseline. Moreover, at Time 1 all patients demonstrated AB towards threat at Time 1, but at Time 2 three patients showed attentional avoidance. Two patients demonstrated the expected attentional modification after ABM, but one of these patients showed a similar decline during baseline. In three other patients, AB did not change and one patient demonstrated less avoidance after ABM. In one patient (patient 5) a decline in symptoms, although not clinically meaningful, coincided with a shift in AB at time 4 compared to time 3, but both changes were lost at follow-up.

Figure 1. Posttraumatic stress symptoms



Note: CAPS score = Clinician Administered PTSD scale total score

Figure 2. Attentional bias



Note: AB score in ms = Attentional bias score in milliseconds

In conclusion, although five patients showed meaningful clinical improvement, this can not be related to ABM. Moreover, the individual AB scores vary largely, and changes in AB do not coincide with symptom change.

Discussion

Contrary to our expectations, we found no evidence that ABM was effective in reducing AB or PTSD symptoms.

Our results fit the outcomes of recent RCTs on the effect of ABM in anxiety disorders (Boetcher, Berger & Renneberg, 2012; Carlbring et al., 2012; Neubauer et al., 2012; Schoorl et al., 2013), in which no therapeutic effect of ABM was demonstrated. When compared to the earlier positive results (Amir et al., 2009b; Schmidt et al., 2009), it is hard to explain the large differences in outcomes. An often heard argument is that null findings are due to the absence of AB at baseline; when an individual does not demonstrate attentional vigilance at the start of treatment, ABM (training avoidance) can not lead to beneficial effects. However, the absence of AB has not been crucial in producing positive results before (e.g., Amir et al, 2009a; Hazen, Vasey, & Schmidt, 2008). Moreover, a post-hoc analysis in a subgroup with PTSD patients demonstrating AB at baseline also showed no effect of ABM (Schoorl et al., 2013).

A noticeable feature of this study is the use of idiographic stimuli. Although carefully selected, this was of course a subjective procedure for which formal validation was not possible. Furthermore, the generalizability of the results is limited by the small amount of patients treated. However, since the present results are almost unequivocal, and confirm the outcomes of an earlier large RCT (Schoorl et al., 2013), reconsidering ABM as an effective treatment for PTSD seems inevitable.

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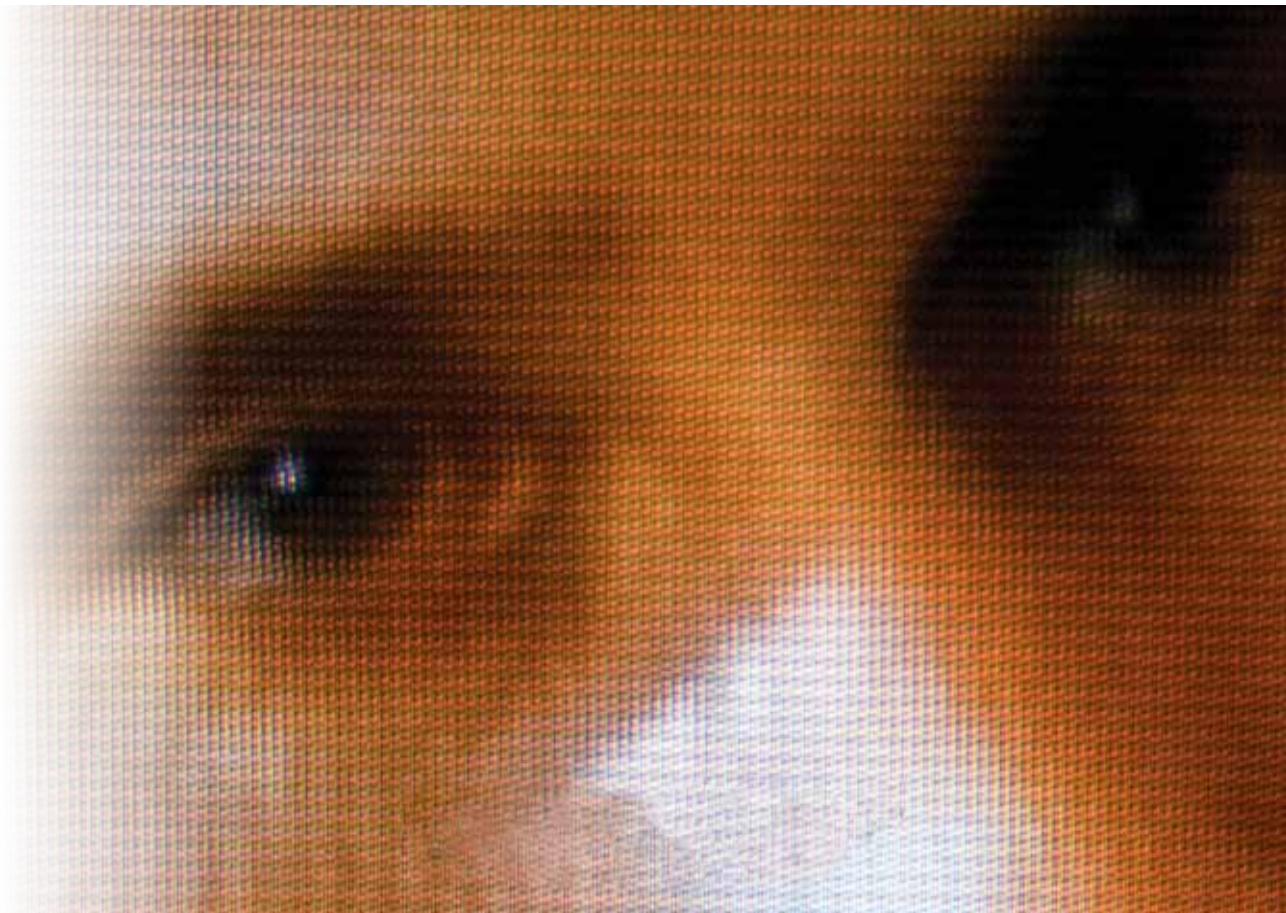
5

Relationships between mindfulness skills, anxiety sensitivity and cognitive reactivity in posttraumatic stress disorder

M. Schoorl, L. Van Mil-Klinkenberg & W. Van Der Does (2013).
Mindfulness, under revision



Abstract

Mindfulness interventions are effective in patients with recurrent depression. They might also be helpful in posttraumatic stress disorder (PTSD), since mindfulness skills have been associated with low levels of symptoms in trauma-exposed students and combat veterans. Anxiety sensitivity (AS) and cognitive reactivity (CR) are hypothesized to mediate the effects of mindfulness interventions and are also related to PTSD. To investigate the associations among mindfulness skills and anxiety and depression sensitivity and symptom severity in a clinical sample of patients with PTSD.

Outpatients with PTSD (N = 101), in treatment at a specialized center, filled out questionnaires. Mindfulness skills, particularly the facet non-judgment or acceptance, correlated negatively with sensitivity measures and with symptom severity. The relationship between mindfulness facet non-judgment and CR and AS remained statistically significant when controlling for PTSD and depression symptoms.

In conclusion, clinicians who attempt to increase mindfulness skills in patients with PTSD may be advised to pay particular attention to the aspect of non-judgment. It is also recommended to measure anxiety and depression sensitivity when evaluating effects of MBCT in patients with PTSD.

Introduction

Effective treatments for posttraumatic stress disorder (PTSD) include pharmacotherapy (antidepressants, AD) and cognitive-behavioral therapy (CBT) (Foa, Keane, & Friedman, 2004). There is, however, ample room for improvement of treatment. Twenty-five to 45% of patients treated for PTSD continue to meet the criteria at the end of exposure treatment (CBT) (Van Minnen & Hagenaars, 2002). Furthermore, CBT carries a risk of exacerbation that is estimated at 10% (Schottenbauer, Glass, Arnkhoff, Tendick, & Hafter Gray, 2008) and in a recent meta-analysis an average dropout rate of 18% was reported (Imel, Laska, Jakupcak, & Simpson, 2013).

Mindfulness-based cognitive therapy (MBCT), designed for patients with recurrent depressive episodes, may be an option to improve treatment efficacy in PTSD. MBCT is a prophylactic treatment that aims to reduce relapse risk by increasing the awareness of negative thinking patterns and by promoting an accepting instead of an avoiding attitude towards one's own thoughts (Teasdale, Segal, & Williams, 1995). The protocol includes attentional control exercises and training in mindfulness, integrated with components of cognitive therapy (Segal, Williams, & Teasdale, 2002). Meta-analyses have shown that MBCT protects against depressive relapse in patients with recurrent depression (Piet & Hougaard, 2011; Fjorback, Arendt, Ørnbøl, Fink, & Walach, 2011) and has positive effects on anxiety symptoms in patients with panic disorder, generalized anxiety disorder and bipolar disorder in remission (Chiesa & Serreti, 2011). Mindfulness Based Stress Reduction (MBSR; on which MBCT is based, Kabat-Zinn, 1982) was recently studied in an open trial with 27 adult survivors of child abuse, 15 of whom were diagnosed with PTSD (Kimbrough, Magyari, Langenberg, Chesney, & Berman, 2010). MBSR led to a 31% reduction of PTSD symptoms, significant reductions of anxiety and depression and an increase of mindfulness skills. We reported positive experiences with MBCT for chronic PTSD in a pilot study (Schoorl & Van Der Does, 2013).

A rationale for exploring MBCT in PTSD lies in the relationship between mindfulness skills and posttraumatic symptoms. In a population of trauma-exposed students without axis I diagnoses, the mindfulness facet non-judgment predicted PTSD symptoms above and beyond the number of experienced events and negative affectivity (Vujanovic, Youngwirth, Johnson, & Zvolensky, 2009). In another study in trauma-exposed students, mindful non-judgment predicted variance in PTSD-avoidance symptom severity beyond other measures of experiental avoidance (Thompson & Waltz, 2010). In a cross-sectional study with three groups of 15 veterans (with/without combat exposure and PTSD), higher scores on non-judgment were again associated with lower severity of PTSD (Wahbeh, Lu, & Oken, 2011). The first aim of the present study was to further investigate the relationship between mindfulness skills and PTSD symptom severity in a larger clinical sample of patients with PTSD of various (also non-combat-related) origins.

A second aim of this study was to investigate the association of two aspects of sensitivity for anxiety and depression with mindfulness skills and symptoms. Anxiety sensitivity (AS) is strongly related to PTSD severity, both cross-sectionally and reciprocally over time (Marshall, Miles, & Stewart, 2010; Naragon-Gainey, 2010). In a large community sample, the interaction between AS and mindfulness was found to predict anxious arousal symptoms and agoraphobic cognitions (Vujanovic, Zvolensky, Bernstein, Feldner, & McLeish, 2007). Results of an experimental study furthermore demonstrated that trait mindfulness predicted anxious responding to a laboratory stressor, above and beyond anxiety sensitivity and anxious symptoms (Arch & Craske, 2010).

High cognitive reactivity (CR) is the tendency to react with depressogenic thinking patterns to stress or a mild state of dysphoria (Lau, Segal, & Williams, 2004) and has been found to predict depressive relapse (Segal et al., 2005). CR was found to relate negatively to mindfulness in a student population, even after controlling for history of major depression and current depressive symptoms (Raes, Dewulf, Van Heeringen, & Williams, 2009). In a non-randomized, waiting list-controlled study, an increase in mindfulness mediated the change in CR after MBCT, supporting the view that changes in mindfulness can affect the first reactions to a low mood. Since the comorbidity with major depression in PTSD is estimated as high as 77% (Friedman, Keane, & Resick, 2007), we decided to include measures of both anxiety and depression sensitivity in our study.

In summary, the aim of the present study was to investigate the relationships among mindfulness skills, anxiety sensitivity, cognitive reactivity and symptom severity in a large clinical sample of PTSD patients. We expected to find positive correlations among AS, CR and depressive and posttraumatic symptoms, and negative correlations among mindfulness skills, AS and CR, also after statistically controlling for symptom severity.

Methods

Participants

Participants were outpatients of a specialized treatment center for PTSD. Patients who were unable to fill in the questionnaires for language reasons were excluded.

Measures

Exposure to trauma

Lifetime trauma exposure was assessed using the Life Events Checklist (LEC), the first part of the Clinician Administered PTSD Scale (CAPS) (Blake et al., 1990) (Dutch translation Hovens, Luinge, & van Minnen, 2005). The LEC consist of 17 potentially traumatic events (including a category ‘other stressful event or experience’) and patients were asked to indicate to which of the events they had been exposed.

Symptoms

The Self-Rating Inventory for Posttraumatic Stress Disorder (SRIP) (Hovens, Bramsen, & Van Der Ploeg, 2000) is a 22-item self-report questionnaire based on DSM-IV criteria. The SRIP has three subscales (re-experiencing, hyperarousal, avoidance) and a total score that ranges from 22-88. Internal consistency ranges from $r = 0.76$ to $r = 0.94$ for the four scales and the SRIP correlates highly (around $r = 0.80$) with other self-report questionnaires for PTSD, for instance the Impact of Event Scale (IES; Horowitz, Wilner, & Alvarez, 1979) (Hovens, Bramsen, & Van Der Ploeg, 2002).

The Beck Depression Inventory – 2nd edition (BDI-II) (Beck, Steer, & Brown, 1996) is a 21-item self-report measure of depressive symptoms. The Dutch translation was used (Van Der Does, 2002a).

Anxiety and Depression Sensitivity

AS was measured with the 16-item Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gurksky, & McNally, 1986; Dutch translation by Arrindell & Albersnagel, 1987) and CR with the Leiden Index of Depression Sensitivity - Revised (LEIDS-R) (Van Der Does, 2002b). Adequate reliability is reported for the LEIDS-R and internal consistencies of the subscales ranged from .64 to .84 (Williams, Van der Does, Barnhofer, Crane, & Segal, 2008).

Mindfulness skills

The Extended version of the Kentucky Inventory of Mindfulness Skills (KIMS-E) (Raes et al., 2009) is a 46-item self-report measure of five aspects of mindfulness: Observing (observe), Describing (describe), Act with Awareness (act), Accept without Judgment (non-judgment) and Non-Reactivity to Inner Experience (non-reactivity). Items are rated on a six-point scale (never or very rarely true till very often or always true). The KIMS-E consists of the original KIMS (Baer & Smith, 2004, De Keyser, Raes, Leijssen, Leysen, & Dewulf, 2008) and all seven items of Non-reactivity to Inner Experience scale from the Five Factor Mindfulness Questionnaire (FFMQ, Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006) The original KIMS has shown good reliability and validity (Baer & Smith, 2004). The values of the four factors from the original KIMS were comparable to the Dutch four factor KIMS (Dekeyser et al., 2008) and the value of the Non-reactivity to Inner Experience factor from the KIMS-E ($\alpha = 0.76$) was comparable to the alpha coefficient obtained for the original Non-reactivity to Inner Experience factor from the Five Factor Mindfulness Questionnaire ($\alpha = 0.75$) (Baer et al., 2006).

Procedure

All patients who were in treatment in the month of June and July in 2010 were given an envelope containing a booklet with the questionnaires by their therapists. They were asked to fill these out in private and return these to their therapists or the reception at the next visit. Participation was not registered and no reminders were

sent. The envelope also contained a written explanation of the purpose of the study and of the fact that participation was voluntary and anonymously. Patients received no financial reimbursement for their participation.

Data screening

Preliminary analyses were performed to check the normality of the distributions, linearity and homoscedasticity. Missing values were replaced with the mean value of other items of the particular subscale for that patient with a maximum of one missing value per five items.

Results

Participants

Three hundred and fifty envelopes were handed out to patients and 101 (29.5%) questionnaires were returned. Of the 101 patients (85 female, mean age 41.3 years), most (62.2%) had a low or middle level of education. Almost all patients had experienced multiple traumatic events (96.9%). Participants reported to have experienced an average of approximately seven potentially traumatic events (range 1-15, *SD* = 3.3). The events most often mentioned were physical violence, sexual violence, other non-consensual or unpleasant sexual experiences, the sudden unexpected death of a loved one and 'other stressful event or experience'.
The questionnaire data revealed high levels of symptoms in all domains. Participants' average score on the SRIP was in the high range and 60 participants (59%) scored above the cut off score for PTSD of 52. The average score on the BDI-II also indicated severe symptom levels. Seventy-seven patients (72.3%) scored above the cut-off score for moderately severe depression. Demographics and mean questionnaire scores are shown in table 1.

Data screening

The distributions of all variables were consistent with the assumptions for multivariate analysis. One person had too many missing items on the SRIP subscales avoidance, hyperarousal and total, and one person on the KIMS-E subscale non-reactivity, therefore scores for these (sub)scales were not calculated. Three patients did not indicate which type of traumatic event(s) they had experienced.

Reliability of the KIMS-E

The internal consistencies of the KIMS-E subscales in the present sample were as follows: observe (α = .83), describe (α = .88), act (α = .78), non-judgment (α = .87)

and non-reactivity (α = .79). Norms for the KIMS or the KIMS-E are not yet available. We compared the results on four of the five KIMS-E subscales with KIMS subscale scores of a large student sample (N = 215, Baer & Smith, 2004, sample 2), and a large heterogeneous patient sample (N = 234, Baum et al., 2009). On the subscale observe, average scores of the patients in our sample fell between the scores of the patient and the student sample; present sample M = 36.1 (*SD* = 7.1), patients M = 34.5 (*SD* = 7.8), students M = 38.6 (*SD* = 7.8). When comparing scores of the samples on the subscale describe, a similar pattern was observed. However, present scores

Table 1. Demographic and clinical characteristics of the sample

Sex (N, % women)	85 (84.5)
Age (mean, *SD*, range)	41.3 *(10.7)*, 20-60
Traumatic events (N, %)	
Physical violence	75 (74.3)
Sexual violence	67 (66.4)
Other non-consensual sexual exp	73 (72.3)
Sudden death loved one	62 (61.4)
Other	53 (52.5)
Symptoms (mean, *SD*)	
SRIP Reexperiencing	14.7 *(4.1)*
SRIP Avoidance	22.2 *(6.2)*
SRIP Hyperarousal	17.8 *(4.9)*
SRIP Total	54.6 *(14.4)*
BDI II	27.2 *(12.8)*
Reactivity (mean, *SD*)	
ASI	37.3 *(11.9)*
LEIDS-R	62.1 *(19.5)*
Mindfulness skills (mean, *SD*)	
Observe	36.2 *(7.1)*
Describe	23.5 *(5.5)*
Act with awareness	25.3 *(5.5)*
Non-judgment	25.4 *(6.4)*
Non-reactivity	17.3 *(4.1*)
KIMS-E Total	127.4 *(18.9)*

Note: Other non-consensual sexual exp = Other non-consensual or unpleasant sexual experiences; Sudden death loved one = Sudden unexpected death of a loved one; Other = Other stressful event or experience; SRIP = Self-Rating Inventory for Posttraumatic Stress Disorder; BDI II = Beck Depression Inventory – 2nd edition; ASI = Anxiety Sensitivity Index; LEIDS-R = Leiden Index of Depression Sensitivity – Revised; Observe = KIMS-E subscale Observing; Describe = KIMS subscale Describing; Act with Awareness = KIMS-E subscale Act with Awareness; Non-judgment = KIMS-E Accept without Judgment; Non-reactivity = KIMS-E subscale Non-Reactivity to Inner Experience; KIMS-E = Kentucky Inventory of Mindfulness Skills –Extended Version

Table 2. Correlations between mindfulness skills, cognitive reactivity and anxiety sensitivity symptoms

Variable	ASI	LEIDS-R	Observe	Describe	Act	Non-judg	Non-react	KIM-E Total
SRIP Reexp	.39**	.56**	-.16	-.34**	-.45**	-.42**	-.42**	-.57**
SRIP Avoid	.47**	.58**	-.17	-.41**	-.51**	-.46**	-.50**	-.63**
SRIP Hyper	.42**	.50**	-.12	-.42**	-.52**	-.36**	-.41**	-.58**
SRIP Total	.46**	.59**	-.15	-.42**	-.52**	-.45**	-.48**	-.64**
BDI II	.55**	.63**	-.17	-.51**	-.61**	-.49**	-.49**	-.69**

Table 3. Correlations and partial correlations between reactivity measures and mindfulness skills

	Variable	LEIDS-R	Observe	Describe	Act	Non-judg	Non-react	KIMS-E Total
Correlations								
	ASI	.52**	.02	-.26**	-.45**	-.46**	-.24*	-.40**
	LEIDS-R		-.06	-.27**	-.45**	-.52**	-.38**	-.50**
Partial correlations								
	ASI		.12	.02	-.19	-.27**	.04	-.08
	LEIDS-R		.06	.01	-.21*	-.35**	-.15	-.19

Note I: ASI = Anxiety Sensitivity Index; LEIDS-R = Leiden Index of Depression Sensitivity – Revised; Observe = KIMS-E subscale Observing; Describe = KIMS-E subscale Describing; Act = KIMS-E subscale Act with Awareness; Non-judg = KIMS-E subscale Accept without Judgment; Non-react = KIMS-E subscale Non-Reactivity to Inner Experience; KIMS-E = Kentucky Inventory of Mindfulness Skills – Extended Version

Note II: partial correlations; controlled for posttraumatic and depressive symptoms

* $p < .01$

** $p < .05$

on this subscale resembled the scores of the patient sample more than the scores of the student sample; present sample M = 23.5 (*SD* = 5.9), patients M = 22.4 (*SD* = 6.5), students M = 28.2 (*SD* = 5.5). Scores of the present sample and the patient sample were comparable on both subscales act and non-judgment; act, present sample M = 25.3 (*SD* = 6.4), patients M = 24.7 (*SD* = 6), students M = 29.2 (*SD* = 5.4) and non-judgment, present sample M = 25.3 (*SD* = 6.4), patients M = 25.3 (*SD* = 6.6), students M = 29.6 (*SD* = 6.5). The KIMS-E was extended with the subscale non-reactivity, but Raes et al. (2009) report no mean scores for this subscale. However, scores on the KIMS-E Total scale were reported, showing a large difference (>1 *SD*) between the student sample and scores of the present sample; mean score respectively M = 145.6 (*SD* = 14.2) (Raes et al., 2009) and M = 127.6 (*SD* = 18.9).

Relationships between mindfulness skills and symptoms

With the exception of the KIMS-E subscale observe, all correlations between KIMS-E Total and subscales scores with PTSD symptom dimensions were negative, moderately high and statistically significant (see table 2). The correlations between KIMS-E dimensions and depressive symptoms (BDI-II) were also significant (r = -0.66, p < .01). Again, the subscale observe diverged from the pattern and did not correlate significantly with depressive symptoms.

Relationships between mindfulness and reactivity

Mindfulness skills had significant negative correlations with AS (r = -.41, p < .01) and CR (r = -.49, p < .01) (see table 3). All subscales of the KIMS-E had moderately high correlations with both sensitivity measures, except subscale observe. The highest correlations with both AS and CR were observed for non-judgment.
The partial correlation between total mindfulness skills and AS, controlling for PTSD severity and depression symptoms was not significant. But for the non-judgment subscale, this partial correlation was r = -.27 (p = .008). The partial correlation between total mindfulness skills and LEIDS-R, controlling for posttraumatic and depression symptoms was r = -.16 (p = .06) and for subscales act r = -.21 (p = .04) and non-judgment r = -.35 (p < .001) (see table 3).

Discussion

In this sample of outpatients with PTSD, we observed a negative association between mindfulness skills and AS. This relation remained significant for the mindfulness skill non-judgment after controlling for symptoms of PTSD and for depression. A similar pattern was observed for the association between CR and non-judgment. Our findings are in line with cross-sectional studies in non-clinical samples and combat veterans (Thompson & Waltz, 2010, Wahbeh et al., 2011, Vujanovic et al., 2009).

Theoretically, an attitude of acceptance or non-judgment is a key concept in the definition of mindfulness (Bishop et al., 2004). In addition, there is ample clinical and empirical evidence that patients with PTSD are typically highly judgmental of themselves, the outside world and their symptoms, up to the point of self-blame (Foa, Tolin, Ehlers, Clark, & Orsillo, 1999). An open attitude of non-judgment is the opposite of avoidance, which is a key mechanism in the development and maintenance of PTSD. Our results support the idea that acquiring a more accepting attitude towards inner thoughts, emotions and physical sensations but also towards the experienced traumatic event(s) might be helpful in reducing sensitivity and eventually in the development and maintenance of symptoms of PTSD and depression. Clinicians who would like to adapt an MBCT or MBSR protocol for use in PTSD may be advised to pay particular attention to modules focusing on acceptance and non-judgment (see also Wahbeh et al., 2011; Schoorl & Van Der Does, 2013).

We also found that the mindfulness skill observe did not correlate with any symptom or reactivity measure. This suggests that awareness itself may not contribute much to psychological wellbeing (Cardaciotto, Herbert, Forman, Moitra, & Farrow, 2008). Clinicians are sometimes reluctant to apply exposure-based treatments for PTSD because patients may become even more aware of their memories and subsequently feel overwhelmed by their own anxious reactions (Van Minnen, Hendriks, & Olff, 2010). However, the correlations, although non-significant, were still in the direction of higher observational skills associated with lower symptom severity.

A limitation of this study is the reliance on self-report measures. An interview-based measure of mindfulness skills or anxiety sensitivity is not available, however. CR may also be measured using mood inductions and some researchers consider this the golden standard. However, mood inductions are fraught with methodological difficulties, including regular non-replications, which have not been reported yet for the LEIDS-R. Because of the cross-sectional design of this study, conclusions about the causality of the demonstrated relationships cannot be drawn.

In conclusion, the mindfulness skill non-judgment is inversely associated with AS, independently from posttraumatic symptoms. Increasing non-judgment or mindful acceptance might have a beneficial effect on PTSD by affecting an important underlying working mechanism of PTSD. We observed similar relationships between non-judgment and CR, extending earlier results of Raes et al. (2009) in students to a clinical sample of PTSD patients. Studies on the effect of MBCT on symptoms of PTSD and/or depression should include measures of AS and CR, to be able to further investigate the mediating role of mindfulness skills in reducing sensitivity for anxiety and depression.

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6

Mindfulness-based cognitive therapy in posttraumatic stress disorder: a pilot study

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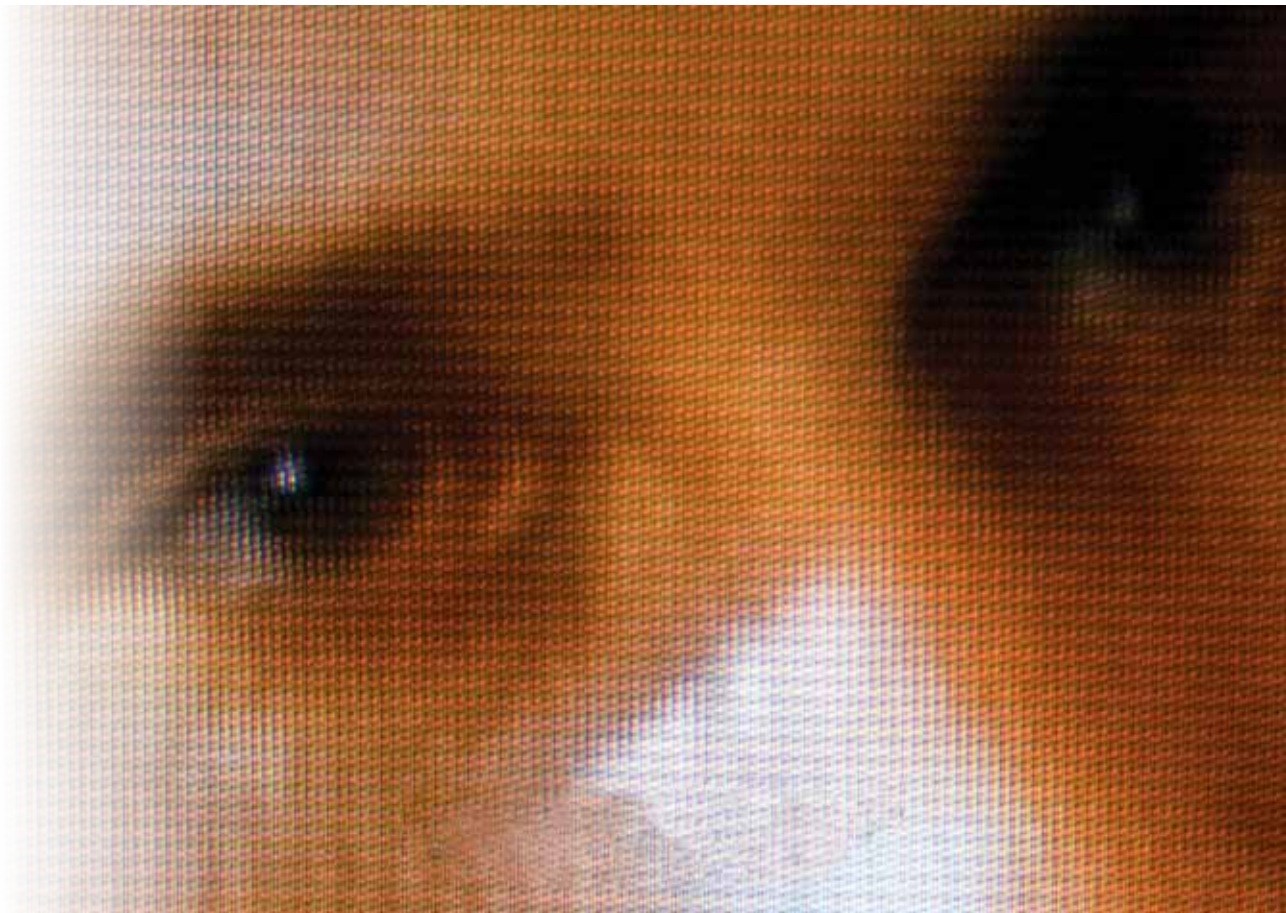


Abstract

Meta-analyses demonstrated positive effects of mindfulness-based therapies in mood and anxiety disorders. One uncontrolled study suggests that mindfulness-based stress reduction is useful in the treatment of posttraumatic stress disorder (PTSD). We explored the therapeutic potential, safety and feasibility of mindfulness-based cognitive therapy (MBCT) in a pilot study with PTSD patients. Mindfulness skills and symptoms were assessed before, at pre- and post-treatment and at follow up.

Fourteen patients started MBCT and nine completed the whole study. All patients had been in treatment for a long time when they started MBCT. Participants evaluated MBCT as positive, however significant symptomatic improvement was observed in only four patients. Mindfulness skills were increased, but depressive symptoms were unchanged. No adverse effects were observed.

In conclusion, these treatment-resistant patients experienced MBCT as positive and safe. Clinical improvements were observed in almost half of the completers. Considering the early dropout rate, acceptability was not high.

Introduction

Mindfulness-based cognitive therapy (MBCT) is a new prophylactic treatment for patients with recurrent depressive episodes (see for meta-analyses Piet & Hougaard, 2011; Fjorback, Arendt, Ørnbøl, Fink, & Walach, 2011). MBCT includes attentional control exercises and training in mindfulness integrated with components of cognitive therapy (Segal, Williams, & Teasdale, 2002). In MBCT, participants learn to disengage from negative thoughts and ruminative thinking that often remain active during periods of remission and that may trigger recurrences of depression. In patients with three or more episodes of major depression, MBCT leads to a reduction of relapse risk of approximately 43%. No risk reduction was found in patients with only one or two episodes (Piet & Hougaard, 2011). Possibly, MBCT has a specific beneficial effect on the autonomous ruminative processes formed through negative childhood experiences that more often characterize patients with multiple episodes and early first onsets of depression (Ma & Teasdale, 2004).

MBCT also has beneficial effects in panic disorder, generalized anxiety disorder and bipolar disorder in remission (Chiesa & Serreti, 2011). Furthermore, an open trial of mindfulness based stress reduction (MBSR; Kabat-Zinn, 1982) with 27 survivors of child abuse had encouraging results. At the end of the eight-week program, a 65% reduction of depressive symptoms, a 47% reduction of anxiety symptoms, and a 31% reduction of PTSD symptoms (effect size d = 1.2) were reported (Kimbrough, Magyari, Langenberg, Chesney, & Berman, 2010). Mindfulness skills were significantly increased and 8 of the 15 participants with PTSD no longer met these diagnostic criteria at the end of the program. All the therapeutic gains were maintained at a 24-week follow up. The authors recommend a randomized controlled trial (RCT) to further test the effect of the intervention in traumatized patients.

MBCT differs from MBSR in that it contains cognitive educational elements, such as information on diagnostic criteria and exercises to learn to identify negative thought patterns. In MBSR, more yoga practice is offered. Because of the more therapeutic rationale, it seems that MBCT could have more profound effects on PTSD than MBSR. On the other hand, it cannot be ruled out that mindfulness-based treatments may have negative effects in some patients. In patients with PTSD, meditating might bring on overwhelming emotional experiences, for example flashbacks or intrusions (Dobkin, Irving, & Amar, 2012).

We conducted an open study to explore the therapeutic effects, feasibility and safety of MBCT in patients with PTSD. We made several adjustments to the published protocol of MBCT for depression (Segal et al., 2002), based on our clinical experience in working with patients with chronic PTSD. We measured mindfulness skills and symptoms before and after an eight-week course of MBCT.

Methods

Participants

Participants were outpatients of a specialized mental health care department for patients with PTSD. No exclusion criteria were set, since this was an open pilot trial. Patients participated in one of two MBCT training groups, either from October to December 2010 or from January to April 2011. Pharmacotherapy and/or supportive counseling were to be continued during MBCT.

Instruments

Diagnoses

The Mini-International Neuropsychiatric Interview Plus (MINI Plus, Sheehan et al., 1998, Dutch version, Van Vliet & De Beurs, 2000) was used to assess the presence of psychiatric disorders. The MINI Plus contains 120 questions and screens 17 DSM-IV axis I disorders.

Symptoms

The frequency and intensity of PTSD symptoms were assessed with the Clinician Administered PTSD scale (CAPS, Blake et al., 1990; Hovens, Luinge, & Van Minnen, 2005). We also used the Self-Rating Inventory for PTSD (SRIP) (Hovens, Bramsen, & Van Der Ploeg, 2000), a 22-item self-report questionnaire covering DSM-IV criteria (APA, 2000). The SRIP has three subscales (re-experiencing, hyperarousal, avoidance) and a Total Score. Internal consistency ranges from r = 0.76 to r = 0.94 and test-retest reliability from r = 0.47 to r = 0.97.

The 14-item Hospital Anxiety and Depression scale (HADS, Zigmond & Snaith, 1983; Spinhoven et al., 1997) was used to measure depressive symptoms. Cronbach's alpha's for subscales and total scale shows are satisfactory to good (range .71 to .90) and test-retest reliability ranges from r = .86 to r = .91.

Mindfulness skills

The Extended version of the Kentucky Inventory of Mindfulness Skills (KIMS-E) (Raes, Dewulf, Van Heeringen, & Williams, 2009) is a 46-item self-report measure of 5 aspects of mindfulness: Observing (observe), Describing (describe), Act with Awareness (act), Accept without Judgment (non-judgment) and Non-Reactivity to Inner Experience (non-reactivity). Internal consistency ranged from α= .78 to α = .88 for all subscales and total score (Schoorl, van Mil-Klinkenberg, & Van Der Does, 2013).

Exit interview

A semi-structured exit interview was held to ask patients about their experiences with the program and the possible effects of MBCT on their symptoms or quality of life. Adherence to home practice was also assessed.

Procedure

Patients were recruited through their therapists and through information leaflets in the waiting room. MBCT was not presented as a treatment but as a course of meditation and attentional control exercises that could be followed in addition to ongoing treatments. Patients who expressed interest in participating were contacted by the researcher and received written information about the program. Possible participants were invited for an intake meeting (Segal et al., 2002), in which they were further informed about the program and the project. If they were still interested in participation, patients were invited for a baseline assessment after written informed consent for the measurements was obtained. Patients then received the questionnaires, except for the HADS, and were asked to fill these out and return them by mail.

After four weeks, patients completed a second assessment visit (pre-treatment) consisting of the two clinical interviews and questionnaires. At the end of the program, patients completed a third assessment session (post-treatment). Ten weeks later, patients were invited for a booster session and the final assessment (follow up). At the post-treatment and follow-up assessments the CAPS and all self-report questionnaires were administered. The exit interview was administered at follow-up. All assessments were done by an independent, well-trained junior psychologist.

Intervention

We made several adjustments to the eight-week MBCT-protocol for depression (Segal et al., 2002), based on our experiences with two earlier pilot groups. We added an introductory session in which a basic meditation exercise was practiced and additional information on MBCT was provided. Home practice was explained. Patients in our clinic usually had no experience with group treatment and were sometimes reluctant to enter group therapy since they anticipate possible distressing effects of listening to traumatic experiences of other group members (Allen, 2001). Therefore, we explained in this session that MBCT is a course and not group therapy. Furthermore, we paid extra attention to the specific fears PTSD patients can have about reliving their traumatic experiences. The introductory session was meant as a ''try out'' session, and patients could afterwards decide whether or not to participate. Throughout the eight sessions we added diagnostic information on PTSD when the protocol provided information on depression and we focused on current symptoms instead of symptoms in the past. In the fourth session

patients were asked to fill in questionnaires on automatic negative – depressive – thoughts to become more aware of their own thought patterns. We added the Posttraumatic Cognitions Inventory (PTCI) (Foa, Tolin, Ehlers, Clark, & Orsillo, 1999, Van Emmerik, Schoorl, Emmelkamp, & Kamphuis, 2006) to identify PTSD-related negative thoughts.

In line with the idea that mindfulness skill non-judgment could be particularly helpful for patients with PTSD (Wahbeh, Lu, & Oken, 2011; Thompson & Waltz, 2010), we paid extra attention to teaching an accepting attitude towards all inner and outer experiences. We emphasized and modeled this non-judgmental attitude during discussions of meditation experiences. We also spend relatively more time on the modules focusing on acceptance (e.g., dealing with barriers, session 1; thoughts are not facts, session 6). We were already trained in the sensitive attitude that is necessary for working with patients with PTSD. Meditation or exercises were always done sitting, and patients were encouraged to make a conscious choice to continue, pull back or even step out during exercises to maintain an optimal level of anxious arousal (Van Minnen & Hagenaars, 2002). In contrast with the standard protocol, we started with shorter meditations (e.g., 15 minutes), gradually introducing longer meditations (Germer, 2005). During the sessions we consequently alternated between meditations and periods of verbal explanations or information providing. We expected that highly structured sessions would create a greater sense of control for the participants. Furthermore, we introduced the meditation exercise ''focus on a problematic situation'' earlier in the protocol (in session 4 instead of 5) and this specific meditation was repeated in each of the following sessions. Our goal was to help participants to allow and accept negative or trauma-related thoughts, emotions or physical experiences instead of avoiding them. Lastly, since problems with attention, concentration and memory are important characteristics of PTSD (Schoorl, Putman, & Van Der Does, 2013), we spent more time on summarizing and repeating the provided information, both within and at the start of the sessions.

Both classes were taught by two MBCT trainers. One was a clinical psychologist educated in MBCT who had two years of experience in MBCT and over 10 years experience in working with PTSD patients. The co-trainer was a MSc-level clinical psychologist with four years of experience in working with PTSD patients, who was trained in MBCT but had little experience yet. The sessions were videotaped and both trainers were supervised regularly by a highly experienced MBCT teacher, who had received her training at the Dutch Institute for Mindfulness and had participated in other MBCT research projects.

Results

Patient flow

Figure 1 summarizes the flow of participants. Twenty-five potential participants were invited for an intake session. Three patients were not interested in participation after hearing more about MBCT and two patients did not show up for baseline assessments. Of the 20 patients who participated in the baseline assessments, two did not show up for pre-treatment assessment twelve weeks later. One patient indicated that the measurements were too stressful, and one patient thought that combining MBCT with his regular treatment would be too demanding. Four patients left the course after the introductory session. One patient thought he would not be able to do the homework involved in MBCT, one indicated that she had expected MBCT to be more spiritual and one patient indicated that she was doing much better on a new medication. One patient declined to comment.

Of the fourteen patients who started MBCT, five dropped out. One participant stopped for medical reasons unrelated to the study or her psychiatric condition and three patients did not attend at least six of the eight sessions. Of these patients, two indicated that they had forgotten the appointments and one patient said she was too busy. One patient declined to comment on the reasons for terminating the course.

Patient characteristics

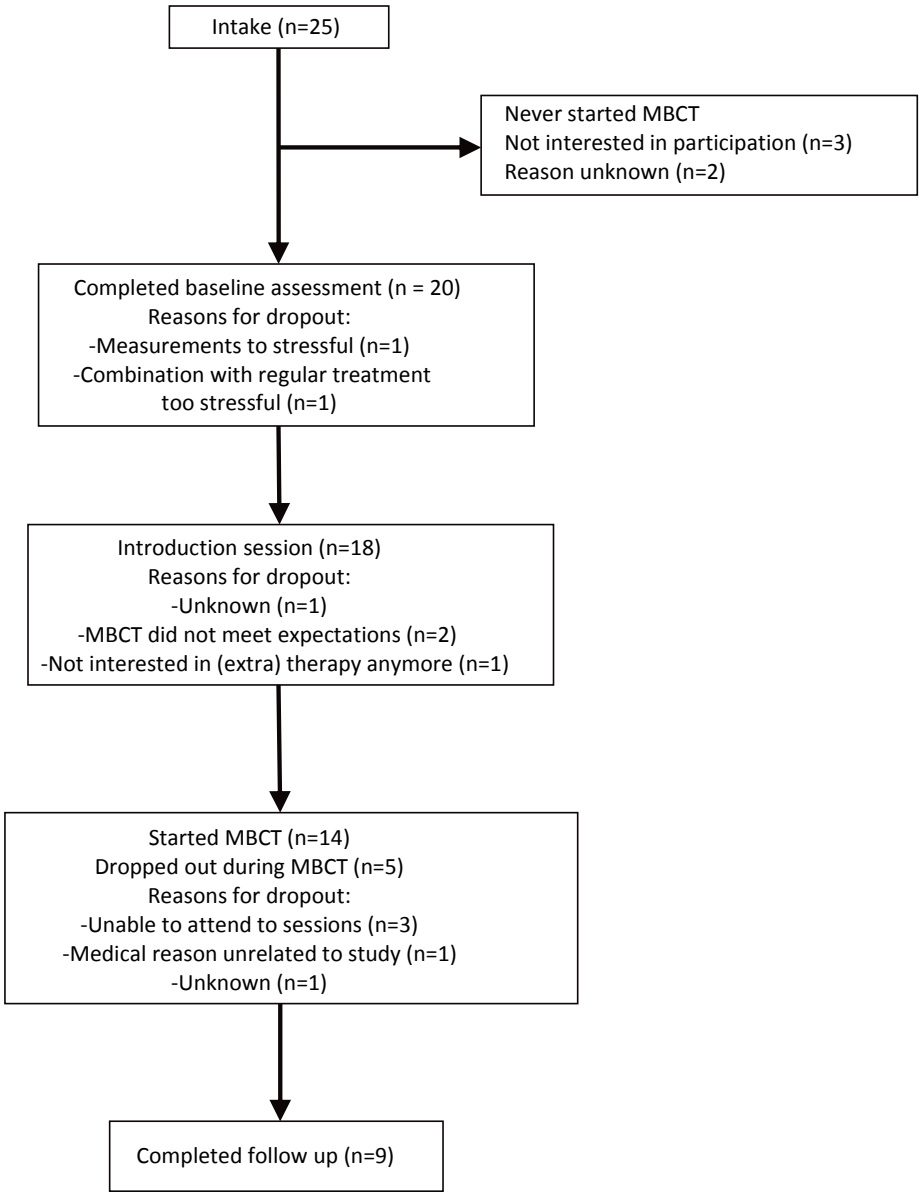
Six female and three male patients finished the training and the post-treatment and follow up assessments. Patient's age ranged from 31 to 54. Participants represented a rather chronically ill subsample of our population. On average, patients had been in prior treatments for 40 months (range 18-120 months) at the start of MBCT.

All patients had a diagnosis of PTSD at baseline. At pre-treatment, eight participants still fulfilled the criteria of PTSD according to the MINI Plus and six according to the CAPS.

Seven scored above the cut-off for PTSD on the SRIP. The mean CAPS score was M = 79.7 (*SD* = 12.5, range 58-94). Three patients also had a current major depressive disorder and four patients had experienced a depressive episode in the past. Two patients were diagnosed with comorbid panic disorder, one with social anxiety disorder and one with somatization disorder. None of the patients fulfilled the criteria of alcohol- or drug dependence or abuse or psychosis.

All patients had experienced multiple traumas and six patients had been traumatized in childhood (under the age of 12). Traumatic events most mentioned were physical and sexual violence; physical violence was experienced by all patients and sexual violence by six patients. Other events mentioned were war experiences, imprisonment and torture, the sudden unexpected death of a loved one, being attacked with a gun and non-consensual, unpleasant or violent sexual experiences.

Figure 1. Flowchart of MBCT participants



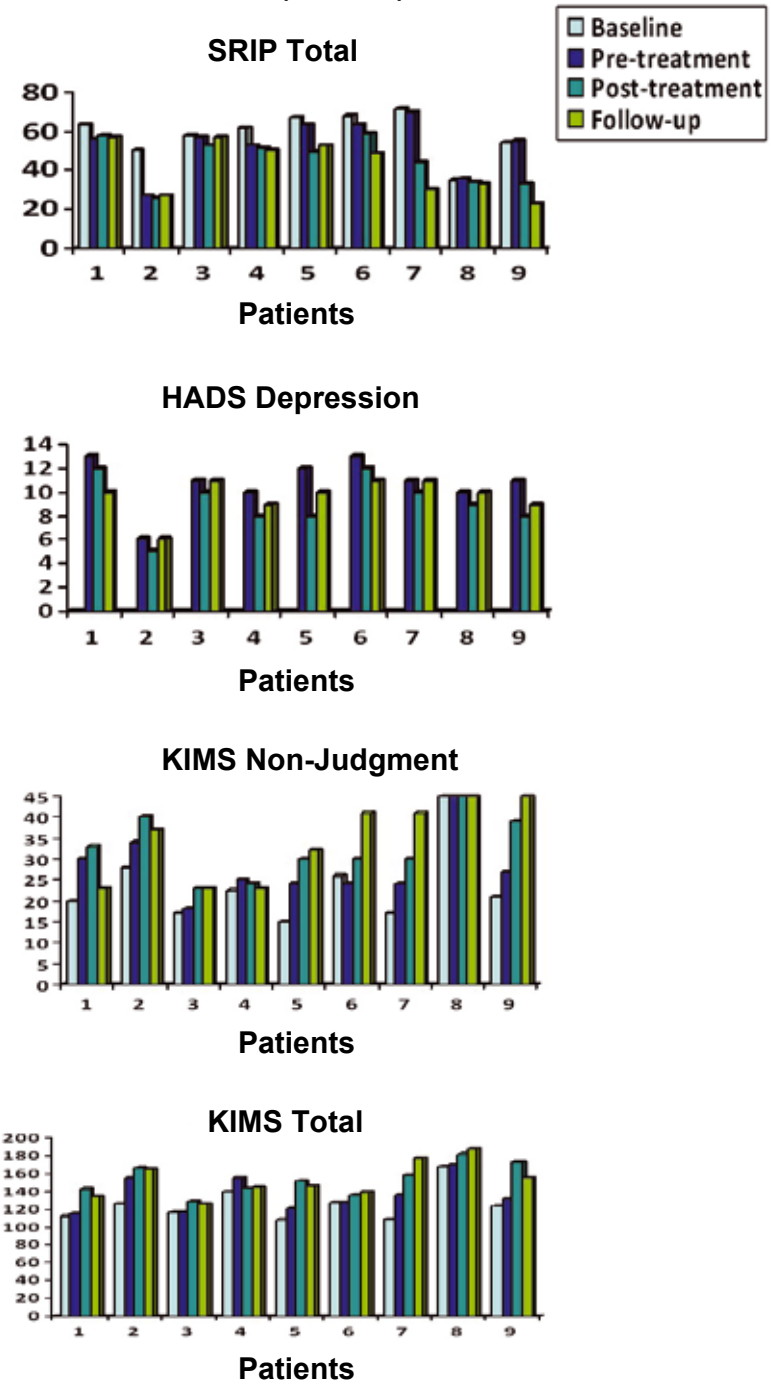
Analysis

When available, we used cut-off scores to determine whether patients no longer fulfilled the DSM-IV criteria at post-treatment (SRIP and CAPS). Results of the structured clinical interview (CAPS) are discussed only when deviant from scores on the self-report questionnaires.
Furthermore, we used the Jacobson & Truax (1991) formula to compute criteria for clinical meaningful improvement. For the HADS, we used norms of both a functional and a dysfunctional population (Spinhoven et al., 1997); the clinical meaningful cut-off point was set at 6.4 for the Depression subscale. For the KIMS-E, we calculated cut-off points for subscale non-judgment using data of the original study of Baer & Smith (2004) for a functional population (sample 2), and data from a representative sample of a dysfunctional population (Schoorl, van Mil-Klinkenberg, & van der Does, 2013). Since the KIMS-E was recently extended with the subscale non-reactivity, we used data for a functional population from the study of Raes et al. (2009) and data from a representative sample of a dysfunctional population (Schoorl, et al., 2013) to determine the clinical meaningful cut-off point for the KIMS-E total scale. This resulted in the following cut-off points; 27.5 (non-judgment) and 136.5 (KIMS-E Total).

Results

At post-treatment, three patients (# 5, 7 and 9) scored below the cut-off score for PTSD on to the SRIP. Patient 5 scored just above this cut-off at follow-up. Patient 6' score dropped beneath the cut-off point at follow-up. The results on the CAPS confirmed these results. These four patients also demonstrated significant improvement in mindfulness skill non-judgment and total mindfulness skills at post-treatment and follow-up. There were no improvements of depressive symptoms. Figure 2 shows the symptom and skills scores of each participant who completed the course.
Patient 1 demonstrates no significant change at post-treatment, except for total mindfulness skills. There were no significant improvements for patient 3 either on any of the self-report questionnaires at post-treatment or follow-up. Clinical meaningful change was observed in PTSD-symptoms according to the CAPS at post-treatment, but these gains were lost at follow-up (for a detailed description of patient 3, see below).
At pre-treatment, patient 4 was diagnosed with PTSD according to the SRIP. Self-report scores for posttraumatic symptoms were just beneath cut-off at follow-up (cut-off SRIP Total ≥ 52, patient 4 scored 51 at follow-up). However, SRIP scores at pre-treatment were 53; indicating that the improvement was not substantial. On total mindfulness skills patient 4 scored above a clinical meaningful cut-off at all four measuring times.

Figure 2. Scores on self-report measurements at baseline, pre-treatment, post-treatment and follow up for each patient



According to both the SRIP and the CAPS, symptom levels of patient 2 and 8 were below cut-off scores for PTSD at the start of MBCT. At post-treatment and follow up no significant change in symptoms or mindfulness skills was observed in these patients; both patients scored beyond cut-off scores in the direction of functionality on all measures at baseline, except for the HADS Depression subscale (patient 8 scored above cut-off at all assessment moments).

Home practice

Participants were advised to practice six days a week for 20 minutes per day or longer. Patients reported spending an average of 21 minutes per day on home practice from week 2-9.

Exit interviews

During the exit interviews all patients indicated that they experienced a decrease in symptoms (both PTSD and depressive symptoms). Patients mentioned that they experienced fewer flashbacks, intrusions and/or nightmares, less avoidance (cognitive and/or behavioral), were better able to think about the future, had an improved ability to concentrate, felt less irritable and less anxious. Patients also felt less depressed, more optimistic, less worrisome and more active.

All patients reported an increase in at least one of the facets of mindfulness; awareness (six patients), mildness (seven patients) and feelings of rest and relaxation (seven patients). All but one patient mentioned that they were more acceptant (of self or others or of the experienced events) after MBCT. All patients would recommend MBCT to other patients, but also to other (healthy) people.

Homework was difficult for most patients, but gradually this became less challenging. One patient mentioned explicitly that it was the first time in his life that he was able to do homework.

Safety

No exarcebation of symptoms was reported according to the measurements and the exit-interview. None of the patients who dropped out mentioned side effects as a reason. During the program, we did not observe patients who were overwhelmed during meditations.

Case studies

Patient 3

Ella is a 37-year-old single mom of a ten year old son. She was born in Spain. As a child she witnessed domestic violence since her father was very abusive of her mother. At the age of eight years old, Ella was raped twice by a friend of the family. When she was fifteen years old, she had other unpleasant and unwanted sexual experiences. Around this time she became addicted to hard drugs (heroine). Despite

her addiction, Ella finished high school at the age of sixteen and worked as a sales person in a clothing shop.
After she stopped using heroine, Ella met her Dutch husband at the age of 22. She immigrated to the Netherlands where her son was born a few years later. She never had a job in the Netherlands. After her divorce nine years ago, she gradually developed severe PTSD and depressive symptoms. Ella had been in treatment since then. She took antidepressant medication for the last five years and tried EMDR and counseling group therapy, but treatment had not lead to substantial improvement. She was recently referred to a new therapist, who recommended MBCT to her.

Results
At the time of the pre-treatment assessment, Ella was diagnosed with current depressive disorder (episode lasting the last nine years), panic disorder and PTSD. Scores on the self-report symptom questionnaires indicated high depressive and posttraumatic symptom levels at baseline and pre-treatment (see figure 2). Depressive symptoms increased during this 4-week period.
Ella expressed her doubts about group therapy before she started MBCT, since her experience with group treatment was quite negative. After information about the specific training character of MBCT, she decided to participate anyway. During the sessions, Ella was engaged, and actively supported other participants. She had difficulties planning her homework, but this improved as the training proceeded. During the sixth session, Ella reported feeling happy for the first time in years. She was more able to enjoy time with her son and could correct herself when she was harsh and judgmental to herself. She called this increased mildness ''revolutionary''. In the exit-interview, Ella indicated that she felt less shameful and guilty about the traumatic events that she experienced. She felt this had a large beneficial effect on her symptoms, even through the follow-up period, but she expressed the need for more sessions of MBCT.
According to the self-report measurements, her level of PTSD symptoms did not decline substantially after MBCT, and at follow-up Ella was at the pre-treatment symptom level again. Her scores on the clinical interview indicated that she improved significantly in PTSD symptoms at post-treatment (CAPS Total pre-treatment 94 points to 67 points at post-treatment). But at follow-up, she was back on her pre-treatment scores again. No change in depressive symptoms was observed nor were meaningful changes in mindfulness skills.
In this case, the experiences of the participant, the results of the interview and the self-reported scores on the questionnaires seem to diverge. When asked about this difference in symptom scores in the exit interview, Ella indicated that she experienced language problems when filling in the self-report questionnaires. When she was asked about this at baseline, she did not want to admit this, but now she felt less judgmental towards herself. She therefore indicated that the results on the structured interview were more valid.

Patient 9

Bob is a 49-year-old married man, who had been sexually abused by a pedophile at the age of thirteen. This abuse continued for several years and he was also forced into prostitution until he was eighteen years old. When he was around 30 years old, his first partner committed suicide and Bob found his body. After this traumatic experience, he developed severe PTSD and depressive symptoms. He once attempted suicide.

Bob worked as a teacher with children with learning problems. He started treatment about eighteen months before he started MBCT (supportive counseling), but this did not lead to any symptom change. Bob asked his therapist for a referral to MBCT after he received information about the training.

Results

Bob was diagnosed with depressive disorder (recurrent), social phobia and PTSD and he showed high symptom scores on the self-report measurements and CAPS at both baseline and pre-treatment. At the start of the program, Bob seemed detached; he did not participate in group discussions and never had any questions about the meditations, other exercises or homework, although his homework attendance seemed high (which he confirmed in the exit interview). He only mentioned twice that he experienced an increase in intrusions and nightmares.

After four weeks, Bob started to participate more actively. He said that meditating changed his life; it changed his attitude towards the traumatic memories. Since he stopped avoiding, he experienced a major decrease in anxiety. During the following sessions, Bob became more and more enthusiastic about MBCT. The intrusions and nightmares became less frequent, but not less vivid. However, Bob declared that he thought he no longer fulfilled the criteria of PTSD.

This was confirmed in his scores on the self-report questionnaires and the structured clinical interview. PTSD symptoms declined after treatment and his scores were more than halved at follow-up (SRIP Total scores pre-treatment 55 to 23 at follow-up). Also, Bob's mindfulness skills increased significantly from pre-treatment to post-treatment, as did mindfulness facet non-judgment.

The scores on the depression self-report measure did not change. In the exit interview Bob stated that MBCT also helped him with his depressive symptoms. He said he had learned to recognize the symptoms and take action at an early stage to prevent further mood deterioration.

Discussion

In the exit interviews, all patients who completed MBCT described positive therapeutic effects of the program. However, results on the outcome measures showed that of the six patients diagnosed with PTSD at pre-treatment, in only four patients clinical meaningful improvement in PTSD symptoms was observed at post-treatment and/or follow-up. Also, positive effects on total mindfulness skills were observed in these patients, but no meaningful clinical decrease in depressive symptoms.

The present outcomes are open to several explanations. The participating patients were diagnosed with chronic PTSD and all of them were in treatment for a long time at the start of MBCT. This sample was quite representative for a relatively large amount of patients treated in our clinic, but also for the clinical reality in the treatment of PTSD patients; 25 to 45% of patients who improved after treatment continue to meet the criteria for PTSD at the end of treatment (Van Minnen & Hagenaars, 2002). Treatment resistance in patients with PTSD is even more common than in other anxiety disorders (Foa et al., 2004).

Six patients had high levels of symptoms at the start of the training, indicating that they were non-responders to regular treatment. The finding that four of these patients no longer fulfilled the criteria of PTSD at post-treatment and/or follow-up, has to be seen in this light; meaningful therapeutic effects on symptoms in chronic, treatment resistant patients is of clinical interest. A fifth patient improved temporarily, suggesting that MBCT had the hypothesized effect although not abiding. Our observations seem broadly in line with results of a clinical audit of treatment-resistant depressed patients (N = 50, effect-size 1.04) (Kenny & Williams, 2007), although obviously sample size and design of the studies are not comparable.

No effect of MBCT on depression symptoms was reported in our sample. Possibly some of the working elements of MBCT on depression symptoms were lost during the process of adjusting the protocol to a PTSD population. Another explanation might be that MBCT is only effective in relapse prevention, and not in reducing current depressive symptomatology. However, recently, preliminary positive effects of MBCT on current depressive symptoms are reported (Geschwind, Peeters, Huibers, Van Os, & Wichers, 2012; Chiesa, Mandelli, & Serreti, 2012). Furthermore, when MBSR was applied to patients with PTSD, a reduction in depressive symptoms was also observed, although partly lost at follow up (Kimbrough et al., 2010).

The decrease in posttraumatic stress symptoms coincided with an increase in mindfulness skills and specifically non-judgment, in the improved patients. Since evidence is accumulating that mindfulness can be an effective psychological treatment for a range of psychiatric disorders, results supporting the rationale of MBCT is encouraging.

All patients reported beneficial effects of MBCT in the exit interviews, but only about half of the patients improved according to our questionnaires. Possibly, our choice of measurements was too restricted (symptoms), or improvements take more time

than our follow-up period lasted. From the results of our exit interviews, we suggest the use of more general symptom measures (e.g., SCL-90) or quality of life-questionnaires to measure short term improvements. In a study comparing CBT with MBSR in patients with generalized social phobia, CBT led to a greater reduction of social anxiety symptoms, but both methods were equally efficacious in improving mood, functioning and subjective well-being (Koszycki, Benger, Shlik, & Bradwejn, 2007).

Exacerbation of symptoms is a common side-effect of PTSD treatment (Schottenbauer, Glass, Arnkhoff, Tendick, & Hafter Gray, 2008). Beforehand, possible negative effects of meditation on patients with PTSD could be expected (Dobkin et al., 2012). But none of the patients in this study reported negative effects of MBCT, and neither did any of the participating patients in two earlier test groups. Most patients indicated in the exit interviews that flashbacks or intrusions during mediations were quite common and that MBCT sometimes led to a temporary increase in symptoms. However, patients did not seem to experience this as overwhelming and/or a reason for drop-out. Possibly, we informed our patients adequately about what to expect during exercises and homework (Crane & Williams, 2010). It might have been helpful also that we encouraged patients continuously to take responsibility for their own wellbeing, both during the course and while practicing at home (see also Dobkin et al., 2012).

Nevertheless, when evaluating feasibility, it is of importance that only nine patients of the fourteen that started MBCT also finished the program. It is very well possible that specifically patients with PTSD that do not get better tend to drop out (Bradley, Green, Russ, Dutra, & Westen, 2005). Moreover, another four patients did not start with the program after the introductory session, and might have been drop outs when we had not scheduled this first session.

Drop out and treatment refusal is a known problem in PTSD research and treatment (Foa et al., 2004, Schottenbauer et al., 2008). Our drop-out rate is comparable to rates in traditional treatment for PTSD (Imel, Laska, Jakupcak, & Simpson, 2013); for example drop-out rates from 0 to 50% are reported for Cognitive Behavioral Therapy (CBT) (Schottenbauer et al., 2008). In line with this, the reason for drop out most reported in this study seemed not linked to MBCT specifically; e.g., patients indicated that they forgot the weekly training. The timing of the drop out however, does seem typical for mindfulness-based interventions; when participants drop out, they do early on in the program (Crane & Williams, 2010).

Recommendations for clinical utility of the MBCT-protocol in patients with PTSD are as follows. When combining the results of our previous study (Schoorl, Van Mil-Klinkenberg, & Van Der Does), the results of the present study and earlier studies (Wahbeh, Lu, & Oken, 2011, Thompson & Waltz, 2010), it seems that when providing MBCT to PTSD patients, specific attention should be given to mindfulness facet non-judgment. Our augmented protocol might have tackled some of the specific demands of a PTSD population, since the improved patients also demonstrated increased mindfulness skills and specifically non-judgment. Considering the

suggestions of the patients in the exit-interview, another recommendation could be to add more sessions to the program. This might lead to further improvement, more reductions in depressive symptomatology and more sustainable therapeutic effects.
There are several limitations to this pilot study. Most importantly, the small sample size only leaves room for a qualitative analysis of results and no mediation analyses could be done to further investigate the associations between change in mindfulness skills and symptoms. Also, we investigated MBCT a chronic, possibly treatment resistant patient group. Comparing our results with the aforementioned study on MBSR in PTSD (Kimbrough et al., 2010) is therefore limited considering the differences in study design. Since pharmacotherapy and social counseling also continued during MBCT, established improvements might not be solely due to MBCT. However, since all of these patients were in treatment for a long time at the start of MBCT, it does seem plausible that MBCT was responsible for the positive changes in symptoms.
In conclusion, results from the present pilot study suggest that MBCT can be effective in reducing PTSD symptoms in some, but not all, chronic treatment-resistant patients. The treatment gains coincided with improved mindfulness skills, but no meaningful clinical effect on depressive symptoms was observed. Furthermore, the safety and feasibility of MBCT in PTSD seem satisfactory, although possibly biased by the drop out rate.

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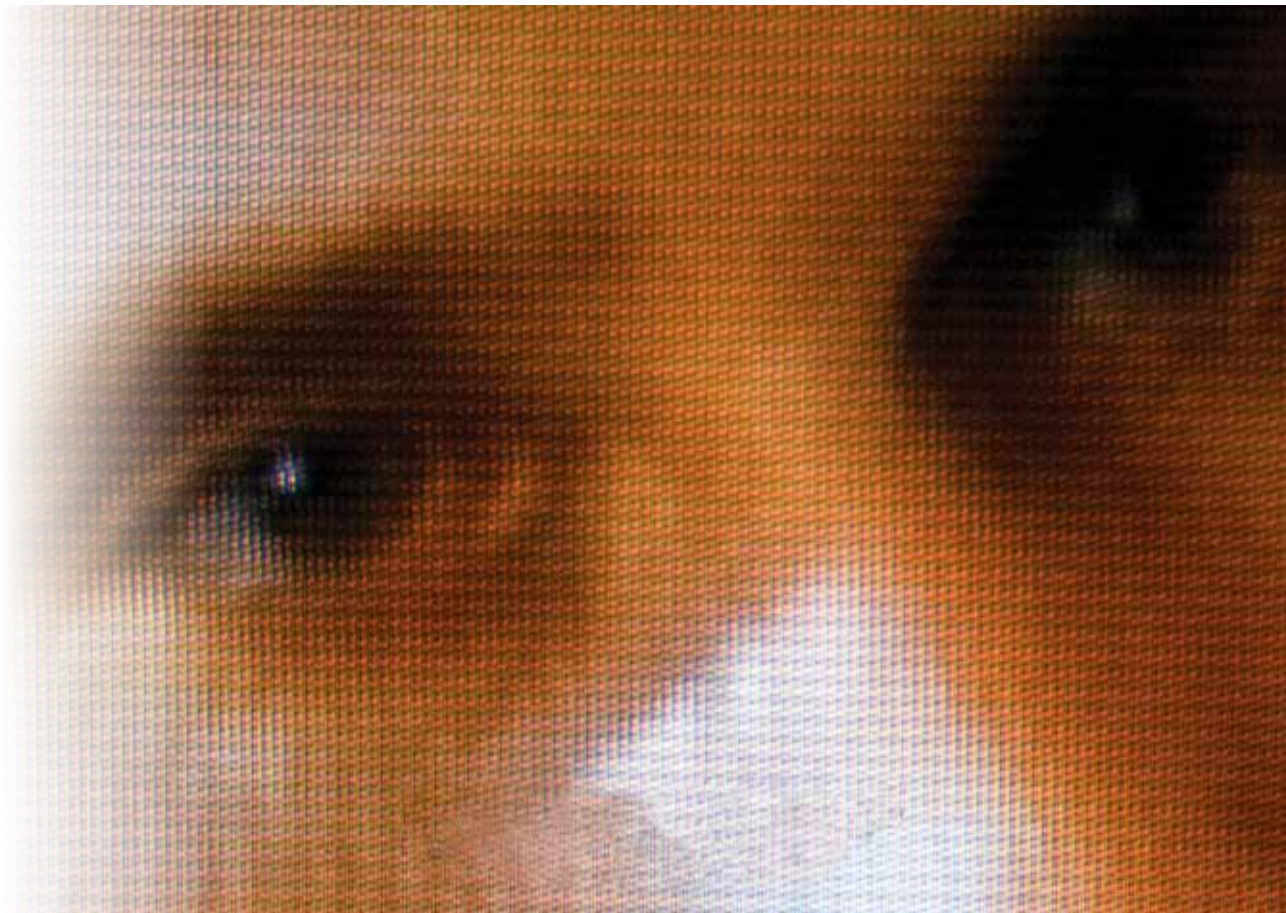
7

General discussion



General Discussion

Effect of ABM: RCT and case series

We tested the therapeutic effect of ABM in a large RCT in patients with PTSD. The effect of ABM on symptoms or on AB was not significantly larger than the effect in the control condition, which led us to conclude that the presently tested version of ABM is not effective in PTSD. One could argue that both conditions were effective, since the control condition may not have been neutral. The control condition – in fact an extended version of the assessment version of the Dot-probe test – is equivalent to training people at a 50/50 contingency. For individuals who have an attentional bias towards threat, this might work as a low-dose treatment. But in fact the effect sizes of the improvement in both conditions were even somewhat smaller than the effect sizes of pill-placebo in pharmacotherapy trials of chronic PTSD (Marshall, Beebe, Oldham, & Zaninelli, 2001; Davidson, Rothbaum, van der Kolk, Sikes, & Farfel, 2001; Brady et al., 2000).

Our findings are disappointing, since positive effects of ABM had been shown in GAD and SAD (Amir, Beard, Burns, & Bomyea, 2009a; Amir et al., 2009b; Schmidt, Richey, Buckner, & Timpano, 2009) and attentional bias to threat is also a feature of PTSD (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & Van IJzendoorn, 2007). Several explanations could account for these negative results, and will be discussed in detail further below.

However, just after we first analyzed the results of our RCT, Amir (2010) reported on two studies with positive effects of ABM in PTSD patients (male veterans) in a conference presentation. The preliminary outcomes of an open trial with 13 patients were presented, together with the results of another 13 patients participating in an RCT. ABM was individualized (self-selected stimuli) and verbal stimuli were used. On a PTSD self-report questionnaire, patients in the ABM condition demonstrated significant effects of the training, and patients in the control condition showed no response. In addition, a recent meta-analysis (Hakamata et al., 2010) suggested that ABM with verbal stimuli might outperform ABM with pictorial stimuli. We then decided to further investigate the hypothesis that individualized, verbal ABM would generate more positive clinical results in patients with PTSD (also male combat veterans). We tried to replicate the study of Amir in a case series design (N = 6). But again, we found no effect of ABM on any of the outcome measures (symptoms or AB).

The second research aim of our RCT was to investigate the tolerability and acceptability of ABM. Since 13.4% declined participation, we concluded that the acceptability of ABM was moderate. Regarding tolerability, the mean drop-out rate (25.2%) was comparable to drop-out rates in traditional treatments for PTSD (i.e. Cognitive Behavioral Therapy, CBT) (Schottenbauer et al., 2008). We had expected lower drop-out rates, since ABM is short and could be carried out at home. Also, the

attrition rates in the three reported clinical trials (Amir et al., 2009a; Amir et al., 2009b; Schmidt et al., 2009) ranged from 0-8%. However, in only one of these studies, a flowchart according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines was presented (Amir et al., 2009b). Moreover, in all three studies participants were paid for their participation (Beard, 2011). It is therefore likely that attrition in our study is a realistic representation of the acceptability of ABM in the 'real world', when patients do not receive a financial incentive.

Possible explanations for the lack of effect of ABM

The large difference in outcomes is difficult to explain. In the three mentioned clinical trials on SAD and GAD effect sizes as large as 1.4 are reported, compared to an effect size of 0.4 for the placebo condition, a difference of 1.0. Our effect sizes were 0.66 (ABM) and 0.46 (control condition), a difference of only 0.2.

Methodological issues

The role of attentional bias in ABM

Our sample size is considerably larger than most studies, so lack of power is not a likely explanation. In our study, no overall AB at pre-treatment was observed. Reviewers of our paper indicated that this absence of AB explains the disappointing clinical results; when no attentional vigilance is present, ABM seems redundant.

Of course, we had expected to find AB in our sample. However, we aimed at evaluating the treatment as it is being advocated - for *any* patient with PTSD, not just for 'patients with PTSD who also have attentional bias'. For this reason, AB was not an inclusion criterion. Serotonergic dysfunction for example, is also never used as a criterion to start treatment with selective serotonin reuptake inhibitors (SSRIs). Furthermore, since we did not test our version of the DPT in a control group, we can not compare our results to healthy controls. Possibly a control group might have demonstrated AB towards neutral stimuli, which would indicate that AB in patients with PTSD is characterized by automatic avoidance of neutral stimuli.

Attentional bias modification is based on three assumptions; 1. particular patient groups have specific biases in their attention; 2. this bias can be modified by training; and 3. changing this bias will have an effect on symptoms. Each of these assumptions has been tested in previous research, including the assumption that patients with PTSD have an attentional bias to threat. Yet, since AB is always reported on group level (patients vs. controls), it cannot be concluded that every individual patient has a positive bias score to threat.

In addition, in only one of the previous clinical ABM studies, AB data at the start of the treatment were reported (Amir et al., 2009b) and the positive clinical results were reached despite the demonstrated lack of AB on group level. Furthermore, we performed a post-hoc analysis with patients with positive AB (> 5 ms, n = 46), but no effect of ABM was demonstrated in this subgroup.

Although extensive research has linked AB towards threat (vigilance) to anxiety and anxiety disorders (Williams, Mathews, & MacLeod, 1996; Bar-Haim et al., 2007), attentional *avoidance* is also reported in several studies, associated with specific time-intervals of the presented stimuli (Cisler & Koster, 2010). In line with the vigilance-avoidance theory (Mogg, Bradley, Miles, & Dixon, 2004), anxious individuals are thought to have a specific pattern of fast vigilance of threatening stimuli (i.e., within < 500 ms), followed by avoidance of threatening stimuli. However, several studies observed threat avoidance in anxiety with the same time-interval (500 ms) as used in our studies (e.g. Mansell, Clark, Ehlers, & Chen, 1999; Musa, Lepine, Clark, Mansell, & Ehlers, 2003; Chen, Ehlers, Clark, & Mansell, 2002; Pine et al., 2005, Monk et al., 2006, Putman, 2011).

Attentional bias in PTSD

Although the preponderance of evidence shows that PTSD is associated with automatic attention to threat (vigilance) (Williams et al., 1996, Bar-Haim et al., 2007), attentional avoidance has also been observed, for instance in maltreated children (Pine et al., 2005). Avoidance of angry and threatening faces was found to be related to a history of physical abuse and to PTSD symptoms. Moreover, experiential avoidance is one of the diagnostic criteria of PTSD (APA, 2000); PTSD is typically associated with attentional tendencies away from threatening stimuli.

Two studies used the DPT with pictorial stimuli in trauma victims (Elsesser, Sartory, & Tackenberg, 2004; Elsesser, Sartory, & Tackenberg, 2005). Although not all participants had PTSD, the mixed results (respectively avoidance and absence of AB) seem in line with our findings. Another study demonstrated that AB towards *positive* stimuli (i.e. happy faces) mediated the relationship between traumatic experiences and PTSD symptoms (avoidance) in adult survivors of childhood maltreatment with and without PTSD (Fani, Bradley-Davino, Ressler, & McClure-Tone, 2011).

However, a recent longitudinal study on risk factors associated with the development of PTSD, again identified attentional vigilance to threat during combat employment as a risk factor for PTSD development (Wald et al., 2013). The results also indicated that AB interacts with other risk factors, and that AB is differentially related to different phases in the development of PTSD.

Taken together, it seems that the direction of attentional bias depends strongly on various methodological variables (e.g., stimulus-type, cue-target delay) but the separate influence of these parameters has not been sufficiently investigated. In addition, it is very likely that AB interacts with other cognitive biases and risk factors. The relationship between AB and PTSD clearly is more complicated than formerly thought.

This seems in line with the results of a close inspection of the phenomenon of AB in PTSD as measured by the emotional Stroop task (EST) (Kimble, 2009). In 92% of the reviewed dissertations and in 56% of the publications in peer reviewed journals, the effect is not demonstrated, despite general consensus. It has been suggested that these results are due to the Stroop task and illustrate that more appropriate

experimental tasks (e.g., the Dot-probe Test) should be used to assess the relationship between PTSD and AB (Bardeen & Orcutt, 2011). However, it cannot be ruled out that publication bias is as strong for research with the DPT. A review on AB in PTSD as measured with the DPT including dissertation abstracts and peer reviewed journals is needed to clarify this issue.

Reliability of the Dot-probe Test

Another problem in ABM research is the lack of validated cognitive measures. For example; concerns have been raised on the reliability of the DPT (Schmuckle, 2005; Staugaard, 2009). In our case series (Schoorl, Putman, Mooren, Van Der Werff, & Van Der Does, 2013) the pattern of intra-individual change in AB as measured with the DPT also indicates problems with the test-retest validity. Improving reliability of widely used cognitive measures or developing new cognitive tasks that are first validated before dissemination seems mandatory (Mauer & Borkenau, 2007). Without such reliable measurements, any positive clinical outcomes of ABM can not be attributed to a change in AB.

ABM and the nature of anxiety disorders

The absence of therapeutic effects might fit with theoretical considerations that positive effects of ABM depend on the 'specifity' of the anxiety disorder (Reese, Mc Nally, Najmi, & Amir, 2010). Some anxiety disorders are more stimulus-driven (e.g., phobias, PTSD) than others (e.g., GAD, SAD). ABM might have more effect in 'general' anxiety disorders, characterized by ruminative symptoms, and not in 'specific' anxiety disorders, like phobias. In (non-clinical) spider-fearful individuals ABM reduced attentional bias only temporarily and anxiety was not reduced (Reese et al., 2010). However, rumination and worry are also important features of PTSD and function as a cognitive avoidance strategy (Ehlers & Steil, 1995; Bomyea, Risbrough, & Lang, 2012). Furthermore, posttraumatic anxiety is also strongly related to abstract ''general'' themes (e.g., 'anything bad can happen to me anytime'), in contrast with specific phobias.

About 70% of our PTSD patients also suffered from a depressive episode. This depression comorbidity is very common, but might account for the lack of positive results of ABM in PTSD. Studies in this area reported mixed results. AB in mood disorders has been demonstrated at later stages of information processing (e.g., 1500 ms) (see Mogg & Bradley, 2005, for a review). Recent outcomes of a study using a spatial cueing task found no difference in AB between trauma-exposed participants with and without PTSD and healthy controls, but a group effect was evident between depressed and non-depressed individuals (Hauschildt, Wittekind, Moritz, Kellner, & Jelinek, 2013). Moreover, null results of ABM in a small sample of patients with major depressive disorder (MDD) have been reported, and post-hoc analysis suggested that ABM can even be counterproductive in patients with severe depressive symptoms (Baert, De Raedt, Schacht, & Koster, 2010). Six different

versions of ABM for dysphoria were tested in a case series design and none of these versions had any consistent effect on AB (Kruijt, Putman, & Van Der Does, 2013).
However, in an influential meta-analysis, (Bar-Haim et al., 2007), it was concluded that ''whether or not participants with depression were included in the anxious group did not modulate the attentional bias effect''. In addition, in the ABM-study on GAD (Amir et al., 2009a) the positive effects of ABM treatment were not limited to anxiety but extended to depressive symptoms, implying that these symptoms might also be sensitive to attentional bias manipulation. Furthermore, comorbid MDD is not necessarily a reason for other PTSD therapies to fail; for example, no difference in effect of PTSD treatment (CBT) in patients with or without comorbid depression was observed (Tarrier, Sommerfield, Pilgrim, & Faragher, 2000).
New data may be available soon that hopefully clarify these matters. At clinicaltrials.gov, the main register where clinical trials are recorded before the onset to objectively evaluate the outcomes; two RCTs investigating ABM in combat veterans with PTSD were announced by Dr. Amir in 2008. Since preliminary findings were reportedly positive (Amir, 2010), we look forward to compare the designs and outcomes with our results.

Progression in ABM research

Another potential explanation for our null results can be that ABM only targets AB, whereas other forms of cognitive bias (e.g., interpretation bias) might also play a role in the development and maintenance of anxiety disorders (Hallion & Ruscio, 2011; Beard, 2011). This would be in line with research (Hirsch, Clark, & Mathews, 2006-Hallion) and theoretical models (e.g., Ouimet, Gawronski, & Dozois, 2009; Eysenck, Santos, Derakshan, & Calvo, 2007) that indicate that mood and anxiety disorders are characterized by a broad range of cognitive biases. Future research could focus on changing multiple cognitive biases to generate more positive effect on symptoms.
Thus, at this point, it seems too early to identify the active factors of ABM and other cognitive bias modification research (Beard, 2011). Moreover, the acceptability of CBM might not be sufficient. In our trial, we observed that patients found the treatment boring and tiring. Although we excluded one patient who literally fell asleep during ABM, we have doubts about some other participants' level of compliance. We did not observe patients who ostensibly malperformed on the DPT – the DPT RT data did not show unusual patterns either – and without doubt all patients hoped to benefit. However, subtle ways to avoid looking at the pictures, fatigue, dissociative phenomena and the severity of PTSD symptoms could have had an impact on the efficacy of ABM. Explicit instructions have been suggested to enhance performance, but might not solve the involuntary problems with task performance (Beard, 2011; Hallion & Ruscio, 2011).

Comparison with recent ABM results

As mentioned above, only one of the three successful clinical trials was reported in accordance with the CONSORT guidelines. None was pre-registered at a clinical trial

database. This means that the primary outcome measures were also not preregistered, making it possible that the researchers have capitalized on chance. For example, close examination of the ABM trial in GAD that is generally presented as a positive trial (Amir et al., 2009a) reveals that there were no improvements on a worry scale that is generally used as primary outcome measure (Emmelkamp, 2012). Furthermore, other unregistered studies probably exist, with either positive or negative results (Beard, 2011; Emmelkamp, 2012).

The present RCT is the first study carried out with a clinical PTSD sample representative of most mental health care settings ('real world' setting). Previous studies in GAD and SAD were pilot studies and included younger and more highly educated patients. The sample size of these studies was also notably smaller. Our results therefore seem of clinical relevance.

Other negative results of ABM in SAD have been reported recently (Boetcher, Berger, & Renneberg, 2012; Carlbring et al., 2012; Neubauer et al., 2012). These negative findings are primarily discussed as problems attributed to the internet delivery of ABM, as opposed to the laboratory setting used in the studies with positive clinical findings (Amir et al., 2009a; Amir et al., 2009b; Schmidt et al., 2009). Technical problems, disturbances during the training or a different stress level (e.g. AB ''not activated'') in the home setting are suggested to have lead to the different outcomes.

These explanations seem at least insufficient, since earlier positive results of internet-delivered ABM have also been reported (Malcolm 2003, reported in MacLeod & Rutherford, 2004; MacLeod, Soong, Rutherford, & Campbell, 2007; See, MacLeod, & Bridle, 2009). Furthermore, it does not resolve another failure to replicate positive effects on AB and anxious reactivity of a single session of ABM delivered in the laboratory (Julian, Beard, Schmidt, Powers, & Smits, 2012, in an attempt to replicate Amir et al., 2008).

Our study was not a direct replication, but a conceptual replication of the Amir and Schmidt studies. As with other conceptual replications, the chances of publication of these null results in a journal are much smaller then when positive effects are found. As described by Pashler & Harris (2012), failing conceptual replications seem to generate a typical reaction; the researchers are prone to attribute null results to deviations from the original method (e.g., internet-delivered, see above). Although our results might not directly contradict the positive results originally reported, the outcomes at least question the robustness of the underlying effect.

In this light, it is not surprising that the possibility that ABM is an ineffective treatment for SAD is not even suggested in the recent RCTs. This brought Emmelkamp (2012) to write a commentary with the sole purpose ''to discuss other potential reasons for these negative results'', advising against further investigating (internet-delivered) ABM. The theoretical background for a lack of robust evidence for ABM is also discussed, since the author found no evidence that other effective treatments coincide with a reduction in AB. His conclusion is that if the working mechanism of ABM is not clear, it is premature to apply ABM clinically.

The tendency to diminish the impact of null results is also mirrored in the conclusions of one of the two meta-analyses on ABM (Hallion & Ruscio, 2011), in which the authors found strong evidence for publication bias in the field of ABM research.

One can only speculate on the background of this bias in the field of Cognitive Bias research. Since ABM treatment stems from experimental research, researchers might not have much experience with clinical standards in research (e.g., CONSORT guidelines). Also, as Emmelkamp (2012) points out, the field of experimental psychology might be in need for clinical applications to valorize their research area.

Whatever the reasons for the problems with ABM research, disseminating ABM to clinical patients is not yet appropriate. More importantly, based on our results and results of the recent studies on SAD, the commercial exploitation of (internet-delivered) ABM in this phase seems premature if not unethical. A website like www.managingyouranxiety.com (accessed March 7th, 2013) where patients can buy time-limited access to DPT training programs is very premature.

Limitations and recommendations for further research

In our RCT, the patients with PTSD formed a rather heterogeneous sample; some patients suffered from childhood traumas and others were traumatized later in life. It is often theorized that there is a difference in attentional bias between those with versus those without childhood trauma, since these subgroups also present different symptoms (McCauly et al., 2003). However, we analyzed the data of the first 71 patients of our sample (35 with childhood trauma) and found no significantly different AB in these subgroups (Tjaarda, 2011). As mentioned above, one study investigated AB in adult survivors of childhood maltreatment with and without PTSD (Fani et al., 2011). Only AB towards positive stimuli (i.e., happy faces) was found to mediate the relationship between the traumatic events and PTSD symptoms.

We aimed to test a representative clinical sample, and we therefore did not exclude patients based on the nature of the traumatic event they experienced. The stimuli material consisted of various threatening scenes (e.g., a man holding a gun, a car accident), and have not been equally relevant for all patients. However, in our case series, we specifically tested the effect of personalized ABM in a homogeneous sample of male veterans (Chapter 4), leading to similar disappointing outcomes.

Attentional control and attentional bias

In our large clinical PTSD sample, AC was found to moderate the relationship between PTSD symptoms and AB (Chapter 3). Patients high in PTSD and low in AC showed attentional avoidance and no association between AB and PTSD was observed in patients with medium or high levels of AC. These outcomes may have important implications: high AC might buffer against the development of AB in PTSD, and low or medium levels of AC are a potential risk factor for AB in PTSD.

Theoretical implications

Our results seem to validate theoretical considerations on the interplay between AC and AB (Eysenck et al., 2007); in our study, AC was indeed found to play a crucial role in the relation between bottom-up information processing and (PTSD-related) anxiety. PTSD patients with greater AC seem able to inhibit reflexive attentional processes, and this is in line with earlier empirical evidence that validated these relationships (Derryberry & Reed, 2002; Bardeen & Orcutt, 2011; Putman, Arias-Garcia, Pantazi, & Van Schie, 2012). Thus, our outcomes extend earlier results to a patient population, thereby forming the first step in closing the gap between experimental research and clinical studies.

Interesting in this light are the results of an analogue study investigating three different forms of ABM (training towards or away from threatening stimuli and a control condition) in socially anxious students. Compared to the controls, participants in both training conditions experienced less anxiety in response to a subsequent social stress task (Klumpp & Amir, 2010). It was suggested that ABM, regardless of the direction of the training, primarily affects AC; ABM might have facilitated AC, thereby enabling disengagement from the task-irrelevant stimuli and limiting the impact of threatening information in anxiety.

In any case, when considering AB as a dysfunctional attentional reaction related to anxiety, high AC is hypothesized to play a correcting or inhibiting role in AB. It seems mandatory that the specific relationship between the protective function of attentional control, attentional bias and anxiety should be further examined in clinical samples to elaborate on the relationships and relevance. With more evidence for a moderating effect of AC, a comprehensive rationale that can account for different bias effects (e.g., inhibiting vigilance or avoidance) could be developed and tested.

Furthermore, AC is measured through self report only (mostly ACS) in the abovementioned studies. At this point, extending AC studies with more behavioral measures is recommended, to strengthen both theory and empirical evidence.

Developmental impact of AC

The capacity to use attentional resources likely originates in prefrontal cortical regions (Bishop, Jenkins, & Lawrence, 2007). AC is considered to both regulate posterior attentional systems and to underlie subsequent behavioral output.

Individual differences in effortful control have been found to affect the development of specific areas of cognitive functioning (Heim & Keil, 2012) and self-regulating capacities (Derryberry & Rothbart, 1997). AC is regarded as a regulating trait or temperament factor (Rothbart, Ahadi, & Evans, 2000). One study indicated that by the age of 45 months, the ability to control attention was already highly stable (Kochanska & Knaack, 2003). Reactive temperament (e.g., emotional arousibility) then can be regulated by effortful control, buffering against pathological mood and anxiety disturbances. These positive effects on self-regulation can lead to better adjustment in adulthood and enhanced psychological wellbeing (Compton, 2000; Eisenberg, Fabes, Guthrie, & Reiser, 2000).

Negative consequences of low AC can lead to diminished self-regulating of reactions on fear. This relationship, between non-emotional AC and self reported anxiety, is confirmed in children from 5-18 years old (see for a summary, Sportel, Nauta, De Hullu, De Jong, & Hartman, 2011). Children with low AC seem more susceptible to development of anxiety disorders, specifically when high in Behavioral Inhibition (BI, i.e. internalizing behavior) since AC was found to moderate the relationship between BI and a range of affective disorders in children (Sportel et al., 2011).

In individuals with low AC, poor adaptation after trauma can also be expected. One analogue study explored the associations between AC, PTSD and affective responding in trauma exposed students (Bardeen & Read, 2010). AC was found to predict recovery from trauma retelling, independent from PTSD symptoms, with greater recovery in participants high in AC.

In children, few studies also found a moderating effect of AC on the relationship between attentional reactivity and anxiety (Helzer, Connor-Smith, & Reed, 2009; Susa, Pitică, Benga, & Miclea, 2012). In the study of Susa and colleagues (2012) a stronger relationship was found between attentional focus and anxiety, than between shifting and anxiety, suggesting that specifically the ability to remain concentrated on a task buffers against AB.

Lonigan, Vasey, Phillips, & Hazen (2004) theorized that the relationship between AB and anxiety in children can be better understood when taking moderating factors into account. They suggested that high AC as a personality dimension enables high anxious children to constrain threat-related bias. The impact of AB therefore seems to depend on individual attentional control ability. When children are not able to acquire the ability to inhibit AB in childhood through AC, they might be prone to develop affective disorders (Kindt & van der Hout, 2001).

Taken together, it seems that ''cold'' cognitive factors (AC) are of crucial importance to understand the development of the relationship between "hot'' emotionally driven attentional processing of threatening information and anxiety (state or trait).

Clinical Implications

ABM

Hypothetically, AC could even explain the abovementioned mixed results reported in AB studies (e.g., great variance, difficulty to replicate results). In a review on ABM in anxiety disorders, it is also suggested that attentional control is the mechanism of change in ABM (Bar-Haim, 2010).

We performed a post-hoc analysis with high and low AC as between-subjects factor. Based on the median score in our sample, low AC was defined as below 39 points, and high AC as 39 points or more. Again, we found no effect of ABM on symptoms. To date, we are not familiar with any other study that evaluated directly the effect of AC on the effect of ABM.

In an interesting but conceptually opposite study of McEvoy and Perini (2009), CBT augmented with either attention training (ATT; Wells, 1990; 2000) or relaxation was considered equally effective in treating patients with social phobia. In ATT, the goal is on teaching patients in three phases to stay focused, learn to shift attention more flexibly and to divide attention. The authors were specifically interested in the effect of treatment on AC and hypothesized that CBT with ATT would have a larger impact on AC. This prediction was not supported, but changes in AC were associated with greater symptom improvement at post-treatment in both conditions (McEvoy & Perini, 2009).

It could also be the case that anxious participants high in AC are less likely to benefit from ABM, since they are already capable of ''correcting'' their automatic attentional tendencies (AB). In addition, particularly patients low in AC might show more pronounced treatment effects (Verwoerd, Wessel, & De Jong, 2012). Therefore, pre-treatment selection based on individual AC could be investigated as a potential valuable addition to the ABM protocol. However, clearly this assumption needs to be further investigated first. Another implication of the recent findings can be that in traditional therapies, attentional differences might indicate different treatment approaches. For example, in individuals low in AC emotionally overwhelming effects of therapy can be expected since AC affects self-regulatory capacities. Thus, a pre-treatment phase in which self-regulating skills are targeted might be of benefit for these patients.

In any case, based on theory and empirical findings so far, including measures of AC in research in both cognitive bias modification and other more traditional treatments seems valuable.

Training AC

Effortful strategies to control attention also seem more accessible for change through training (Hallion & Ruscio, 2011; Bardeen & Read, 2010). Since AC can be an early developmental protective factor, training attentional control in childhood might be of specific importance. One study indicated positive effects of AC training on cognitive functioning in children (Wass, Scerif, & Johnson, 2012).

Training AC might be beneficial throughout the life span, as one study suggests (Bherer, 2008); training attentional shifting was found to enhance executive task performance in both younger and older adults, suggesting cognitive plasticity in AC. Considering that AC is conceptualized as a temperament factor, this might be an interesting line of research.

Diverse forms of cognitive control training are designed and investigated so far. An example is the abovementioned ATT (Wells, 2000). Effects of ATT are mainly investigated in small pilot studies (e.g., Wells & Papageorgiou, 2001). Mindfulness-based interventions (first introduced as attentional control training, Teasdale et al, 1995) are even more widely applied in clinical settings. Although the positive effect of mindfulness-based therapy on attentional control is often theorized (Bishop et al., 2007, Teasdale et al., 1995), this relationship is by our knowledge not directly examined so far. We found one study exploring the effects of MBSR on performance on the Attention Network Test (ANT; Fan, McCandliss, Sommer, Raz, & Posner, 2002). This test is designed to measure three overlapping attentional subsystems: alerting, orienting and conflict monitoring. Compared to controls, participants in the MBSR condition demonstrated significantly improved orienting after the intervention, (Jha, Krompinger, & Baume, 2007). One other study reported positive effects on sustained attention (using cognitive tasks) in healthy meditators (Chambers, Lo, & Allen, 2008). In an interesting study with schoolchildren aged 7-9 years, a mindfulness practice program added to the regular school program resulted in better executive functioning in children that were less well regulated according to their teachers and parents (Flook et al., 2010).

Mindfulness and PTSD

Metacognitions: mindfulness skills and reactivity in PTSD

As hypothesized, symptoms of PTSD, mindfulness skills and reactivity were found to correlate in a large sample of clinical patients with PTSD. Moreover, mindful non-judgment was associated with anxiety sensitivity even when controlled for PTSD and depressive symptoms. Our study extended earlier results on the relationship between PTSD symptoms and an attitude of acceptance in a clinical sample (Wahbeh, Lu, & Oken, 2011; Thompson & Waltz, 2010). The sample was also heterogeneous regarding the nature of the trauma, which implies that the findings are generalizable.

Our outcomes suggest that negative metacognitions may indeed play a role in the development and maintenance of PTSD. Simply stated, the more an individual 'passes judgment' on his or her physical, emotional or cognitive reactions to a traumatic event, the higher his or her risk of developing PTSD becomes. This risk might be reduced if an accepting attitude can be developed, or is already present when a traumatic event occurs.

Our clinical results confirmed the relationship between facets of mindfulness and anxiety sensitivity that had been demonstrated in a community sample (Vujanovic,

Zvolensky, Bernstein, Feldner, & McLeish, 2007). Mindfulness is hypothesized to ''dampen'' the negative effects of anxiety sensitivity (AS) as a risk factor for psychological disturbance. High AS can lead to an automatically enrolling pattern of anxiety-driven reactions (such as catastrophyzing or panic-related arousal symptoms) when encountering a threatening situation. High mindfulness skills on the other hand might facilitate allocating attention to the here-and-now, thereby preventing these automatic patterns and creating room for disconfirmation of negative beliefs (Vujanovic et al., 2007).

Several influential theories (Brewin, Dalgleish, & Joseph, 1996; Ehlers & Clark, 2000; Foa, Steketee, & Rothbaum, 1989) have already pointed out that in traditional treatments (e.g., CBT or EMDR) negative metacognitions are not explicitly addressed. The Self-Regulatory Executive Functioning model (S-REF model; Wells & Matthews, 1996) is an attempt to combine advances in cognitive theory with treatment implications. Specifically, according to this transdiagnostic model, stimulus-driven and effortful cognitive control mechanisms, metacognitive beliefs and the interaction between these factors contribute importantly to the development of emotional disorders. The S-REF model proposes that dysfunctional cognitive processing prevent the disconfirmation of negative metacognitions (e.g., anxiety sensitivity), or inhibit positive beliefs (e.g., non-judgment). The negative beliefs in its turn are fueling maladaptive cognitive strategies. These strategies are; inflexible self-focused attention, perseverative thinking (worry, rumination), threat monitoring and inadequate coping strategies.
The clinical implications of the S-REF model are that treatments should also be focused on enhancing attentional control and targeting negative metacognitions, as is integrated in ATT (see above) and in MBCT. The results of our cross-sectional design seem to validate components of the model, since we found that a non-judgmental attitude ('belief') is independently associated with another negative metacognitive construct (AS). The interaction between mindfulness, AS and PTSD might be further evaluated in the laboratory, while experimentally manipulating mindfulness. For example, in patients with PTSD, the effect of trauma reminders on AS can be measured after a single session of mindfulness meditation, compared with controls who did not receive the intervention. Even more interestingly, in accordance with the S-REF model, investigating the relationships between AC and AS and non-judgment could add to further understanding the working mechanism of MBCT.

Results case series
Although several theoretical reports suggest that mindfulness-based interventions might be particularly suitable for PTSD treatment (Follete, Palm, & Pearson, 2006; Vujanovic, Niles, Pietrefesa, Schmertz, & Potter, 2011), only one open label trial investigating MBSR in PTSD patients was published so far (Kimbrough, Magyari,

Langenberg, Chesney, & Berman, 2010). The goal of our case series was to explore the feasibility and clinical effects of MBCT.
Regarding feasibility, our conclusion was two-sided. On the one hand, in the exit interviews, patients stated that they would recommend MBCT to others. In addition, potential side-effects (e.g., overwhelming emotional experiences during meditation, symptom exacerbation) were not observed in the participating patients. But on the other hand, the early drop-out rate was high. Several explanations can account for this effect, either related to mindfulness interventions specifically (e.g., early drop out; Crane & Williams, 2010) or to PTSD (e.g., patients that do not improve during treatment tend to drop out; Bradley, Green, Russ, Dutra, & Westen, 2005) or to the sample involved in the case series (chronic, possibly treatment resistant patients). These questions need to be further investigated in a next study.

The therapeutic effects of MBCT in our study were mixed. Less than half of the patients reached clinically meaningful improvements, coinciding with enhanced mindfulness skills. In the exit-interviews however, all patients reported (large) beneficial effects of MBCT. Again, this might be due to different factors (e.g., placebo effect).
Possibly, as some patients suggested, more sessions of MBCT might have resulted in a larger therapeutic effect. Other (symptom) measures might have better tapped the reported changes. But it can also not be ruled out that MBCT is not appropriate for the treatment of PTSD. We recommend further examination of MBCT first in a less chronic population.
Furthermore, as mentioned before, in addition to the outcomes of our cross-sectional study, an interesting line of research is to study the effects of MBCT on attentional control and reactivity. These constructs seem to tap underlying mechanism of change related to mindfulness interventions and might target the therapeutic effect patients reported better.

Overall conclusion

Our studies are an example of research into the potential clinical applications of cognitive science. Given the unexpected outcomes of our RCT (chapter 2), the necessity of such research in real world clinical settings cannot be made clearer. The aim of clinical research is to bridge the gap between science and practice and we hope that our studies contribute to that goal.
Although there is a distinct need for more effective treatments for PTSD, designing and testing effective novel therapies is a long and complicated process. Derived from experimental cognitive psychology, ABM seemed promising and ready for clinical dissemination. However, outside the laboratory the therapeutic effects were limited, at least for the treatment of PTSD. Even augmenting existing treatments for PTSD with ABM seems therefore redundant.

Our outcomes in the MBCT case series are mixed and the generalizibility of our results is limited because of the study design. However, the findings connecting mindfulness skills to vulnerability factors of PTSD (reactivity) indicate that some facets of mindfulness may be particularly relevant for the development and maintenance of PTSD. These outcomes provide some theoretical underpinning for the application of MBCT in the treatment of PTSD. Our case-series in chronic, possibly treatment resistant PTSD patients also formed preliminary evidence that MBCT might be effective in PTSD. Yet, its acceptability (both in patients and therapists) needs to be enhanced.

Both research in ABM and MBCT suffer from methodological problems (e.g., no pre-treatment trial registration, small sample size). At the same time, these interventions are already disseminated and advocated for diverse clinical populations. Considering the disappointing therapeutic effect of ABM in PTSD, it seems essential that researchers and clinicians first focus on well-conducted scientific research before clinical application of new treatments.
The working mechanisms of MBCT should be further validated first, to be followed with ''real world'' RCTs with valid control conditions. The clinical acceptability of MBCT in PTSD needs to be investigated in more detail and this might lead to further adjustments of the classic MBCT protocol. Also, independent measures of cognitive changes should be added to research protocols.

Although attention problems are unmistakably part of PTSD, both theoretically as clinically, the relationships between the different cognitive components and PTSD symptoms is far more complicated than commonly stated. The importance of AB in PTSD as measured with the EST is already put in perspective (Kimble, 2009), and the measurement of AB in PTSD with other cognitive measurements (e.g., the DPT) might also be more complicated than formerly theorized.
Our results support recent theoretical notions on the influence of AC on automatic attentional processing in anxiety, including in PTSD. Therefore, an important future focus in cognitive research and clinical application should be on extending evidence about the interaction between ''lower'' and ''higher'' order information processing. This fundamental research should coincide with the investigation of the effects of existing PTSD therapies on AC and the introduction of new, validated, behavioral measures of AC.
The fact that attention research is more complicated than previously thought should of course not lead to abandoning this topic. Patients with PTSD suffer from (severe) attentional problems, which can be very disabling (e.g., not being able to concentrate on work, forget important tasks etc.). Moreover, patients often report that these problems are not tackled by existing treatments. Continuing this line of research is therefore of great interest and clinical importance.

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Samenvatting

PTSS is de enige psychiatrische stoornis waarbij een etiologische factor wordt genoemd in de DSM-IV-TR (APA, 2000). Het meemaken van een traumatische gebeurtenis of gebeurtenissen wordt gezien als de oorzaak van de klachten en symptomen. Dat de gebeurtenis(sen) traumatisch zijn geweest wordt gedefinieerd als volgt: er moet sprake zijn geweest van een directe ervaring met de dood, met de directe dreiging van de dood of ernstig letsel van jezelf of iemand anders. Voorbeelden van dergelijke gebeurtenissen zijn ernstige ongelukken, seksueel of fysiek misbruik, oorlogsituaties en natuurrampen.
In Nederland is de kans dat men op enig moment in het leven een traumatische gebeurtenis meemaakt 80%. Ongeveer 7% ontwikkelt vervolgens PTSS (De Vries & Olff, 2009). Het verloop van PTSS is vaak chronisch; bij 74% van de patiënten is de duur langer dan 6 maanden (Breslau, 2001). Daarnaast is er sprake van veel comorbiditeit; 92% van de patiënten voldoet aan de criteria van minstens één andere psychiatrische stoornis, bijvoorbeeld een depressieve episode (77%), gegeneraliseerde angststoornis (GAS, 38%), of alcohol afhankelijkheid/misbruik (31%; Friedman, Keane, & Resick, 2007). Daarnaast ervaren patiënten met PTSS vaak (ernstige) beperkingen op meerdere levensgebieden (zoals problemen in relaties, werk, financiële en/of somatische problemen).
Bewezen effectieve behandelingen voor PTSS zijn behandelingen waarbij blootstelling aan de herinneringen aan de meegemaakte gebeurtenis(sen) centraal staan, zoals in exposure behandeling (cognitieve gedragstherapie, CGT) of medicamenteuze behandeling. Helaas verbetert een significant deel van de patiënten niet of nauwelijks na een dergelijke standaard behandeling (Sherman, 1998; van Etten & Taylor, 1998). Ook zijn de drop out cijfers hoog: 21 (CGT) tot 32% (antidepressiva) van de patiënten beëindigt de behandeling voortijdig (Hembree et al., 2003). Het doel van dit proefschrift is dan ook om twee nieuwe behandelmogelijkheden te onderzoeken voor patiënten met posttraumatische stress stoornis (PTSS).

Attentional Bias Modification

Angststoornissen, waaronder PTSS, worden gekenmerkt door problemen met geheugen, aandacht en concentratie. De inleiding (hoofdstuk 1) is een overzicht van de diverse specifieke cognitieve problemen bij PTSS.
In ons onderzoek hebben we ons vooral gericht op aandachtsstoornissen bij PTSS, waarbij vaak een onderscheid wordt gemaakt tussen automatische en gecontroleerde aandacht. Attentional bias (AB) is een voorbeeld van een automatisch aandachtsproces; een vorm van aandacht die sterk gestuurd is door prikkels en die zonder bewuste beslissing plaatsvindt. Bij patiënten met PTSS wordt de aandacht vaak automatisch getrokken naar emotionele informatie, ten koste van taakgerelateerde aandacht (Bar-Haim et al., 2007). Ook automatische vermijding van dergelijke informatie bij PTSS is in experimenteel onderzoek enkele malen vastgesteld (zie bijvoorbeeld Pine et al., 2005) .

In hoofdstuk 2 bespreken we de resultaten van een grote gerandomiseerde gecontroleerde trial (RCT) naar de therapeutische effecten van Attentional Bias Modificatie (ABM) bij PTSS, vergeleken met een controle training. ABM is een gecomputeriseerde training gericht op het veranderen van AB, waardoor angstklachten kunnen afnemen. Uit de resultaten van drie eerdere RCT's blijkt dat ABM een effectieve behandeling is voor patiënten met sociale angststoornis (Amir et al., 2009a; Schmidt et al., 2009) en GAS (Amir et al., 2009b).

Voor ons onderzoek hebben we een versie ontwikkeld waarbij ABM thuis, via een beveiligde internetconnectie, kan worden gevolgd. Zowel de training als de controle conditie is gebaseerd op de Dot-probe Test (DPT). Iedere sessie is opgebouwd uit 200 trials. Een trial begint met een computerscherm waarop een fixatiekruis te zien is. Daarna verschijnen gedurende 500 ms twee plaatjes; een neutraal plaatje en een traumagerelateerd plaatje, boven en onder de locatie van het (verdwenen) fixatiekruis. Op het volgende scherm verschijnt vervolgens een letter op de hoogte van of het neutrale plaatje, of het traumagerelateerde plaatje. Deelnemers wordt gevraagd door middel van een druk op een toets aan te geven welke letter is verschenen (voor een voorbeeld van een trial, zie hoofdstuk 1, pag. 19). In de ABM conditie verschijnt de letter altijd op de hoogte van het neutrale plaatje, om deelnemers te leren de traumagerelateerde plaatjes te negeren. In de neutrale conditie verschijnt de letter in de helft van de gevallen op de locatie van het neutrale plaatje en in de andere helft op de locatie van het traumagerelateerde plaatje.

De DPT wordt ook gebruikt om AB te meten, waarbij het uitgangspunt is dat angst er toe leidt dat de aandacht automatisch gericht is op angstgerelateerde informatie, met andere woorden: deelnemers zullen sneller op een toets drukken als een letter op de locatie van de emotionele stimulus verschijnt omdat hun aandacht naar die locatie was getrokken.

Naast het effect op symptomen wilden we onderzoeken of ABM beter toepasbaar is in de klinische praktijk dan standaard behandelingen zoals CGT. Onze onderzoeksvragen waren: leidt ABM tot een verandering in attentional bias en tot verbetering van PTSS symptomen? En is ABM beter klinisch toepasbaar bij PTSS patiënten dan standaard behandelingen?

Op de afdeling psychotrauma van PsyQ Haaglanden is ABM vergeleken met een controleconditie in een grote RCT (n = 102). Gedurende drie weken volgden patiënten acht (20-minuten) sessies ABM of controletraining. Bij aanvang, na afloop en bij een follow up van drie weken werd een klinisch interview voor PTSS afgenomen (KIP), een vragenlijst naar depressieve symptomen (BDI) en een test voor attentional bias (DPT).

Zowel ABM als de controleconditie resulteerde in verbetering van de PTSS symptomen, maar ABM niet meer dan de controle conditie. Effectsizes van de klinische veranderingen in beide condities verschilden bovendien niet van placebocondities in farmacotherapeutische RCT's voor PTSS. Ook was er geen effect op AB. Het aantal drop outs verschilde niet van standaard behandelingen voor PTSS.

Hieruit concluderen wij dat de klinische toepasbaarheid van ABM niet beter was dan die van bestaande behandelingen.
Kortom, uit onze resultaten blijkt dat deze vorm van ABM geen effectieve behandeling is bij PTSS. Eén van de mogelijke verklaringen voor het gebrek aan therapeutisch effect kan zijn dat de gebruikte stimuli in de DPT nogal uiteenlopend van aard waren (bv. geweldsscènes, maar ook auto-ongelukken), terwijl voor patiënten waarschijnlijk maar één categorie plaatjes relevant was. Ook is er enige evidentie voor de grotere werkzaamheid van woorden in plaats van plaatjes als stimuli bij ABM (Hakamata et al., 2010).
In hoofdstuk 4 is een vervolgonderzoek (case series) beschreven waarbij de voornaamste onderzoeksvraag was of een geïndividualiseerde versie van ABM met verbale stimuli zou leiden tot positieve effecten op symptomen en aandachtsbias bij een relatief homogene groep veteranen. Zes patiënten van Centrum ’45 uit Oegstgeest participeerden in een single-case series met een A-B design (Barlow & Hersen, 1984) met een follow up van twee weken. Individuele baseline scores en controle training fungeerden als controle variabelen.
Uit de resultaten blijkt allereerst een grote variatie in intra- en inter-individuele AB scores van de patiënten. Daarnaast heeft ook deze versie van ABM geen effect op symptomen van PTSS of op AB.

Aandachtscontrole en attentional bias bij PTSS

Vervolgens hebben we de relatie tussen ‘‘hogere’’ en ‘‘lagere’’ informatie verwerkingsprocessen bij PTSS onderzocht (hoofdstuk 3). Uit eerder onderzoek was naar voren gekomen dat aandachtscontrole (AC) bij gezonde proefpersonen de relatie tussen automatische aandacht (attentional bias) en angst modereert (Derryberry & Reed, 2002). Om dit verband te exploreren bij patiënten met een angststoornis, hebben we bij de patiënten met PTSS die participeerden in bovengenoemde RCT naast de DPT een vragenlijst afgenomen om aandachtscontrole te meten (Aandachtscontrole Schaal, ACS, Derryberry & Reed, 2002).
Onze resultaten kwamen overeen met de resultaten bij gezonde proefpersonen. Bij patiënten met een gemiddelde of hoge aandachtscontrole bleek er geen verband te zijn tussen posttraumatische angst en AB. Patiënten met lage aandachtscontrole vertoonden wel automatische AB. Met andere woorden, het vermogen om aandacht bewust en strategisch te richten (AC) lijkt er voor te zorgen dat automatische aandachtsstoornissen niet optreden bij PTSS.

Mindfulness bij PTSS

De tweede behandelvorm die we hebben onderzocht bij patiënten met PTSS was mindfulness-based cognitieve therapie (MBCT). Uit twee meta-analyses is gebleken dat MBCT heeft geleid tot een verminderd risico op terugval bij patiënten met

terugkerende depressies (Piet & Hougaard, 2011) en tot klachtenverbetering bij patiënten met angststoornissen (GAS, paniekstoornis) (Fjorback et al., 2011).
In hoofdstuk 5 beschrijven we de resultaten van een cross-sectionele studie naar het verband tussen mindfulness vaardigheden, angstsensitiviteit (AS) en cognitieve reactiviteit (CR), en posttraumatische stress symptomen. Het doel van dit vragenlijstonderzoek was om meer zicht te krijgen op eventuele werkzame factoren van MBCT in de behandeling van PTSS. AS is gedefinieerd als ''angst voor angst'', met andere woorden, de neiging om te overreageren op angstsymptomen. AS is sterk gerelateerd aan de ontwikkeling van PTSS. CR is een kwetsbaarheidfactor voor het (opnieuw) ontwikkelen van depressieve klachten; herstelde patiënten met een depressie in de voorgeschiedenis vertonen vaker CR dan mensen zonder een dergelijke voorgeschiedenis. Bij verhoogde CR vertonen mensen bij een (lichte) stemmingsdaling sneller depressogene gedachtepatronen zoals hopeloze of suïcidale gedachten.
De therapeutische rationale van MBCT bestaat eruit patiënten te leren de (eerste) negatieve gedachtepatronen te accepteren, in plaats van te vermijden of bestrijden. Dat laatste vergroot vaak de impact van dergelijke gedachten, terwijl door een niet-oordelende houding geen metacognities ontstaan (gedachten over de gedachten), die zouden kunnen leiden tot psychische klachten.
Onze hypothesen werden bevestigd. Positieve correlaties tussen AS, CR en depressieve en posttraumatische symptomen werden aangetroffen en negatieve correlaties tussen mindfulness vaardigheden, AS and CR. Als we controleerden voor ernst van de symptomen, bleek dat vooral mindfulness aspect ''non-judgment'' (niet-oordelen) significant gerelateerd bleef aan AS en CR.
Onze conclusie is dat bij het toepassen van MBCT bij PTSS vooral aandacht moet worden besteed aan het ontwikkelen van een niet–oordelende, accepterende houding. Bovendien lijkt het op basis van onze resultaten zinvol het effect van MBCT te evalueren aan de hand van veranderingen in cognitieve reactiviteit.

In een pilot studie (hoofdstuk 6) onderzochten we vervolgens de therapeutische effecten van MBCT bij een kleine groep patiënten (n = 9) met PTSS. Ook hebben we de veiligheid en toepasbaarheid bekeken van het bestaande protocol (Segal et al., 2002), dat we hadden aangepast aan patiënten met PTSS. Negatieve bijwerkingen van therapie komen bij ongeveer 10% van de CGT-behandelingen voor (Schottenbauer et al., 2008). Bovendien zijn meditatieoefeningen een belangrijk onderdeel van MBCT, waarbij vanuit klinisch perspectief gedacht kan worden dat patiënten met PTSS emotioneel overweldigd raken door opgeroepen herinneringen of flashbacks.
Op vier momenten hebben we mindfulness vaardigheden en posttraumatische stress symptomen en depressieve symptomen gemeten: bij baseline, voor en na de behandeling en na een follow up van 10 weken.
De resultaten van de pilot studie waren niet eenduidig. Veertien patiënten zijn gestart met de training, en 9 patiënten hebben MBCT afgerond. Bij aanvang van

MBCT waren alle deelnemers gedurende lange tijd in behandeling (gemiddeld 40 maanden, range 18-120 maanden). In de exitinterviews waren patiënten zeer positief over de training, maar significante verbeteringen in symptomen werden bij 4 van de patiënten vastgesteld. Mindfulness vaardigheden namen toe, maar er was geen effect op depressieve symptomen. Negatieve effecten van MBCT werden niet vastgesteld.
Onze conclusie is dat MBCT door deze mogelijk therapieresistente groep als positief en veilig werd beoordeeld. In bijna de helft van de deelnemers werden daarnaast klinisch betekenisvolle verbeteringen geobserveerd, maar gezien het hoge aantal drop-outs, is de praktische toepasbaarheid van MBCT bij PTSS mogelijk beperkt. Dit zou nader onderzocht moeten worden in een minder chronische patiëntenpopulatie.
Andere aanbevelingen voor verder onderzoek zijn om de effecten van MBCT te evalueren in een RCT met een valide controle conditie. Daarbij kan ook worden onderzocht of verminderde cognitieve reactiviteit en/of verbeterde aandachtscontrole een mediërende rol spelen bij symptoomverbetering.

Conclusies en aanbevelingen
In de algemene discussie (hoofdstuk 7) gaan we eerst in op de mogelijke verklaringen voor het gebrek aan therapeutisch effect van ABM bij PTSS. Methodologische factoren komen aan bod, zoals de rol van AB bij PTSS en ABM. De (geringe) betrouwbaarheid van de DPT en andere testen voor AB worden besproken. Evenals de specifieke kenmerken van PTSS (bv. de hoge comorbiditeit met depressie) die de uitkomsten van onze RCT kunnen hebben beïnvloed. Recente uitkomsten van ABM bij sociale angststoornis worden vergeleken met onze resultaten en we bespreken theoretische afwegingen over het toepassen van ABM als toegevoegd element in behandeling, of als onderdeel van Cognitive Bias Modification (CBM).
Eén van onze voornaamste conclusies is daarbij dat het essentieel is positieve klinische effecten van een nieuwe behandelmethode eerst voldoende te repliceren in grote RCT's voordat verdere verspreiding (al dan niet commercieel) kan plaatsvinden.
Onze uitkomsten benadrukken het belang van aandachtscontrole; hogere executieve verwerkingscapaciteiten hebben mogelijk een beschermend effect op het ontwikkelen van angst gerelateerde automatische processen, zoals aandachtsbias. Recente informatieverwerkingstheorieën worden besproken, evenals de rol van aandachtscontrole in de cognitieve ontwikkeling. Onderzoek naar het vermogen om bewust en strategisch aandacht te richten en te behouden zal de komende jaren meer duidelijk moeten maken over de wisselwerking tussen automatische en niet-automatische cognitieve processen. Bovendien zou de mate van individuele aandachtscontrole meer onderzocht moeten worden in relatie tot therapie-effecten. Bij patiënten met hoge aandachtscontrole kan een ander soort behandeling zinvol zijn dan bij patiënten met lage aandachtscontrole. In dat kader bespreken we ook mindfulness-based cognitieve therapie (MBCT; Segal et al., 2002).

Tenslotte bespreken we de resultaten van de cross-sectionele studie naar cognitieve reactiviteit (CR en AS) met mindfulness vaardigheden bij PTSS met behulp van het Self-Regulatory Executive Functioning model (S-REF model; Wells & Mathews, 1996), waarin ook aandachtscontrole kan worden gevat. We sluiten het proefschrift af met suggesties voor verder (experimenteel) onderzoek naar de effecten van MBCT bij PTSS. Bij deze relatief nieuwe therapievorm is het van groot belang de werkingsmechanismen te valideren en therapie effecten te evalueren in grote RCT's om nieuwe toepassingen (zoals bij PTSS) met vertrouwen tegemoet te zien.

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Curriculum vitae

Maartje Schoorl werd op 9 juni 1972 geboren in Voorburg. In 1996 heeft zij de studie Nederlandse taal- en letterkunde afgerond aan de Universiteit Leiden. Vervolgens heeft zij de lerarenopleiding gevolgd en gewerkt als docent Nederlands. Na een baan als sociotherapeut in jeugdgevangenis Teylingereind, maakte zij in 1999 de overstap naar psychologie. De studie klinische en gezondheidspsychologie voltooide zij aan de Universiteit Leiden, waarna zij in 2001 startte als onderzoeker bij Centrum '45 in Oegstgeest. In 2002 is zij begonnen aan de opleiding tot gezondheidszorgpsycholoog, gecombineerd met voortzetting van onderzoeksactiviteiten binnen Centrum'45. Daarnaast was zij verbonden aan de Universiteit Leiden en heeft zij lesgegeven op de afdeling klinische en gezondheidspsychologie. In 2004 is zij bij Centrum '45 begonnen aan de opleiding tot klinisch psycholoog, die zij in 2008 heeft afgerond bij Rivierduinen op de afdeling persoonlijkheidsstoornissen. In november 2007 verwierf zij samen met haar begeleider prof. dr. A.J.W. van der Does een OOG (Opleiding Onderzoeker GGZ) subsidie van ZonMW, waarmee haar promotieonderzoek *Investigating new process-focused therapies in posttraumatic stress disorder: Attention bias modification and mindfulness-based cognitive therapy* grotendeels gefinancierd werd. Sinds januari 2008 werkt zij bij PsyQ Haaglanden, afdeling psychotrauma, als klinisch psycholoog en onderzoeker. In 2011 behaalde zij de registratie cognitief gedragstherapeut VGCT. In september 2013 is zij naast haar baan bij PsyQ Haaglanden gestart als klinisch docent op de afdeling klinische en gezondheidspsychologie van de Universiteit Leiden. Maartje is getrouwd met Mischa Wijffelman en samen hebben zij vier kinderen, Lucy (2005), Mia (2007), Yannick (2011) en Ruben (2013).

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