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Using Neurobiological Measures to Predict and Assess Treatment Outcome of Psychotherapy in Posttraumatic Stress Disorder: Systematic Review

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Key Words

Posttraumatic stress disorder · Cognitive behavioral therapy · Eye movement desensitization and reprocessing · Psychotherapy

Abstract

Background: Trauma-focused cognitive-behavioral therapy (TF-CBT) and eye movement desensitization and reprocessing (EMDR) are effective treatments for posttraumatic stress disorder. However, little is known about their neurobiological effects. The usefulness of neurobiological measures to predict the treatment outcome of psychotherapy also has yet to be determined. ***Methods:*** Systematic review of randomized controlled trials (RCTs) focused on neurobiological treatment effects of TF-CBT or EMDR and trials with neurobiological measures as predictors of treatment response. ***Results:*** We included 23 publications reporting on 16 separate trials. TF-CBT was compared with a waitlist in most trials. TF-CBT was associated with a decrease in heart rate and blood pressure and changes in activity but not in volume of frontal brain structures and the amygdala. Neurobiological changes correlated with changes in symptom severity. EMDR was only tested against other active treatments in included trials. We did not find a difference in neurobiological treatment effects between EMDR and other treatments. Publications on neurobiological predictors of treatment response showed ambiguous results. ***Conclusion:*** TF-CBT was associated with a reduction of physiological reactivity. There is some preliminary evidence that TF-CBT influences brain regions involved in fear conditioning, extinction learning and possibly working memory and attention regulation; however, these effects could be nonspecific psychotherapeutic effects. Future trials should use paradigms aimed specifically at these brain regions and physiological reactivity. There are concerns regarding the risk of bias in some of the RCTs, indicating that methodologically more rigorous trials are required. Trials with neurobiological measures as predictors of treatment outcome render insufficient results to be useful in clinical practice.

Introduction

Posttraumatic stress disorder (PTSD) is a common, disabling and often chronic anxiety disorder [1, 2], which can develop after exposure to a traumatic event. It is characterized by symptoms of re-experiencing, avoidance and hyperarousal [3]. In recent decades, accurate and

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minimally invasive genotyping, neuroimaging, physiological and endocrinological techniques have emerged, and studies using these together with preclinical studies have facilitated a better understanding of the underlying mechanisms of PTSD [4]. Four cardinal findings have emerged: (1) PTSD is associated with changes in the neural circuitry involving the prefrontal and limbic structures [5, 6], (2) changes in the neural circuitry correlate with changes in the autonomous nervous system (ANS) [7] and hypothalamus pituitary adrenal (HPA) axis activity [8, 9], (3) changes in the neural circuitry, ANS and HPA axis arise from an interaction between environmental factors and a genetic profile [4, 10] and (4) these changes play a crucial role in the development and maintenance of PTSD [7].

Persistent PTSD leads to considerable suffering and disturbances of social and work-related functioning [1], which underlines how important effective treatments can be. Several psychological treatments for PTSD have been developed [11]. Of these, trauma-focused cognitive-behavioral therapy (TF-CBT) and eye movement desensitization and reprocessing (EMDR) have been shown to be effective in reducing symptoms [12]. Studies measuring the effects of these psychotherapies on the neural circuitry, ANS and HPA axis activity are underrepresented in comparison to analogous studies of pharmacotherapy [13]. Biological measures, however, render important insights into the working mechanisms of psychotherapy, although it is not yet sure if these insights can indeed improve treatment strategies [14]. Biological measures may be useful to predict treatment outcome [15] and may contribute to psychoeducation through outcome feedback [16]. Given this background, we conducted a systematic review following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [17] with the following objectives: (1) to examine the effects of TF-CBT and EMDR on the (re)activity of the limbic and frontal structures, ANS and HPA axis, (2) to examine if neurobiological changes correlate with changes in PTSD severity and (3) to examine if pretreatment neurobiological measures can predict treatment outcome.

Methods

Search Strategy

We conducted searches in MEDLINE, Embase, PsycINFO, PILOTS and the Cochrane register of controlled trials and database of systematic reviews. Each database was searched from inception to the second week of February 2012. A clinical librarian experienced in conducting systemic reviews assisted us with the formation of appropriate search terms for each of the databases. The following terms were used: posttraumatic stress disorder and eye movement desensitization and reprocessing OR cognitive behavioral therapy OR processing therapy OR exposure therapy OR brief psychotherapy OR short-term psychotherapy (for a complete list of search terms for each individual database, see www.karger.com/doi/10.1159/000343258). Given the broad range of possible outcome measures, including the search terms for each outcome is undesirable because it would narrow our search and risk omitting relevant studies. The reference lists of selected articles were also monitored for relevant studies.

Retrieved studies were imported into Reference Manager (version 12, for Windows, Thomson Reuters, New York, N.Y., USA). Duplicates were identified and eliminated. Thereafter, the first 2 authors reviewed all titles and abstracts independently. Articles were selected for full-text review if based upon the title and abstract, inclusion criteria were met or uncertainty regarding eligibility persisted. Disagreements were discussed and resolved after the title abstract review and after full text reviews. Final agreement was reached in all cases.

Quality Assessment

In accordance with the PRISMA statement and the Cochrane handbook [18], included randomized controlled trials (RCTs) were assessed for potential risk of bias on the following 5 domains: whether or not (1) the study used a randomized sequence of assignments, (2) the allocation sequence was concealed from those involved in the enrolment and assignment of participants, (3) people who determined the outcome measurements were aware of intervention assignments (blinding of outcome assessment), (4) outcome data were missing due to attrition during the study or exclusion from analysis and (5) selective reporting of outcomes occurred (for the detailed assessment criteria for each individual domain, see the Cochrane handbook, chapter 8 [18]). All RCTs were assessed separately on these 5 domains by both reviewers. Disagreements were discussed in order to reach one final judgment. We did not address the blinding of participants or therapists, given the obvious difficulties regarding blinding during psychotherapy.

Inclusion Criteria

Design

In order to differentiate neurobiological treatment effects from time effects, the studies used for objectives (1) and (2) had to be randomized and controlled. For objective (3), the studies did not have to meet these conditions in order to be included. Considering the difficulties of blinding participants and practitioners during psychotherapy, studies did not have to be blinded to be included. Single-case studies were excluded, and only studies published in English were included.

Participants

Participants had to fulfil the criteria for PTSD or partial PTSD at the beginning of treatment. People with partial PTSD are somewhat less impaired than individuals with (full) PTSD; however, symptoms also cause clinical meaningful levels of functional impairment in these individuals [19]. To fulfil the diagnosis of partial PTSD, individuals needed to meet the A, E and F DSM-IV criteria for PTSD in combination with one or more symptoms in each of the 3 symptom groups (criteria B, C and D) or meeting 2 of 3 symptom clusters for criteria B, C or D. There was no restric-

tion on the basis of the type of traumatic event. Since comorbidity is common in PTSD [2], studies involving individuals with comorbid psychiatric disorders besides PTSD were not excluded; the primary diagnosis for participants had to be PTSD, however.

Interventions

We included studies if participants had been treated with either EMDR or TF-CBT. EMDR had to involve bilateral stimulation by means of eye movements, beeps or taps whilst patients focused on a traumatic image, thought, emotion or bodily sensation. TF-CBT was defined as each treatment which involved both (1) deliberate systematic confrontation with trauma-related stimuli through imaginal or in vivo exposure and (2) therapists assisted identification and disconfirmation of distorted thought patterns and beliefs regarding oneself, traumatic events and the world. In line with the most recent Cochrane review on psychological interventions in PTSD [12], this group also included (prolonged and narrative) exposure [20] and brief eclectic psychotherapy (which also includes psychodynamic treatment elements) [21].

Comparison

For treatment outcome studies, the following comparisons were included: comparison to a waitlist condition, delayed-treatment conditions, routine clinical care or other active treatments.

Outcome Measures

Studies were included if one or more of the following measures were performed: hormonal levels, brain activity or volume(s), activity of the ANS or if genotyping was performed. For the correlation analysis – objective (2) – the severity of a posttraumatic stress symptom had to be either rated by a clinician using a standardized measure or by a standardized self-report measure.

Data Analysis

Because of the large clinical heterogeneity between studies, calculation of the standardized mean difference was judged unreasonable by our consulting statistician.

Outcome data were extracted independently by the first two authors. Reported measures only included continuous neurobiological outcomes. To minimize the heterogeneity of outcomes, we translated continued measures to a standardized effect size (i.e. posttreatment mean of intervention group minus posttreatment mean of control group, divided by the pooled standard deviation). Calculations were performed on a PC in Microsoft Office Excel 2007.

Results

Search Findings

We included a total of 23 publications from 16 separate trials (fig. 1). Sixteen concerned 11 RCTs and were used for objectives (1) and (2) [22–37]. The remaining 7 publications reported on 5 trials which were used for objective (3) [38–44]. All studies applied DSM-IV criteria except Renfrey and Spates [35] and Rogers et al. [33], who applied DSM-III criteria. Studies included both people with full PTSD and partial PTSD. The age of participants ranged from 18 to 71 years. Most studies included both males and females and were conducted on an outpatient basis. The most common traumatic events were combat-related events, accidents and interpersonal violence. Participants were recruited through advertisement, (self-)referrals and inpatient programs. Baseline PTSD severity ranged from moderate to severe with most participants suffering from chronic PTSD (symptoms lasting 3 months or more). The most common exclusion criteria were substance-use disorder, personality disorder and psychotic disorders. Figure 2 summarizes the risk of bias of the included RCTs.

In the 11 included RCTs, 321 patients were analyzed. Different types of outcome data of a portion of these patients were reported in separate publications [22, 28, 29] and [24–26, 30]. The number of people randomized in trials ranged from 12 to 78.

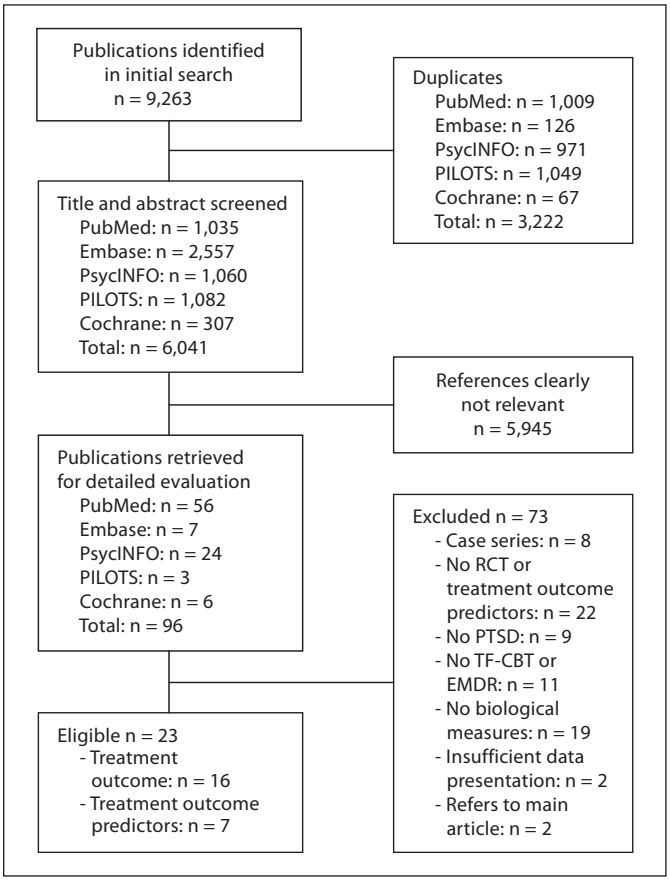

Fig. 1. Flow diagram of trials included and excluded in systematic review.

In addition, 143 unique nonrandomized participants were included for objective (3). Sample sizes varied between 13 and 45. Again, different outcome data of a portion of participants were presented in separate publications ([40, 41] and [26, 44]).

Effects of TF-CBT and EMDR on the (Re)Activity of the Limbic and Frontal Structures, the ANS and the HPA Axis (1)

TF-CBT versus Waitlist or Support

Twelve publications out of 7 trials described a comparison between TF-CBT and a waitlist condition or supportive psychotherapy (table 1) [22–31, 36, 37]. In 6 of these publications, TF-CBT was compared to waitlist or support using psychophysiological measures as a treatment outcome (table 1) [22–27]. One of these described effect sizes but did not report sufficient data for effect-size recalculation [25]. In the other 6 publications, TF-CBT was compared to waitlist using brain activity and brain volume as an outcome measure (table 1) [28–31, 36, 37].

EMDR versus Active Treatment or Routine Clinical Care

In 3 trials, EMDR was either compared with active treatment(s) or routine clinical care (table 1) [33–35]. All 3 used psychophysiological measures as a treatment outcome. One publication did not report sufficient data to calculate effect sizes [34].

EMDR versus Prolonged Exposure

One trial compared the treatment effects of EMDR with prolonged exposure on HPA-axis activity (table 1) [32].

Correlation between Biological Treatment Outcome and Change in Symptom Severity (2)

In a total of 7 publications out of 4 trials, change in biological variables was correlated with change in PTSD symptoms (table 2) [22, 24, 26, 29–31, 36]. Correlations between a change in neurobiological variables and a change in symptom severity scores were obtained using the Pearson product-moment correlation coefficient in all the publications. In 4, outcome data from the intervention group and the control group(s) were combined to calculate correlations [22, 24, 26, 30]; in the remaining 3, only outcome data from the intervention group were used [29, 31, 36]. Symptom severity was measured with either the Clinician-Administered PTSD scale (CAPS) or the Structured Interview for PTSD (SI-PTSD) [45, 46]. In 3 publications, a change in psychophysiological variables was correlated with a change in symptom severity [22, 24, 26] and in 4, a change in brain activity was correlated with a change in symptom severity [29–31, 36].

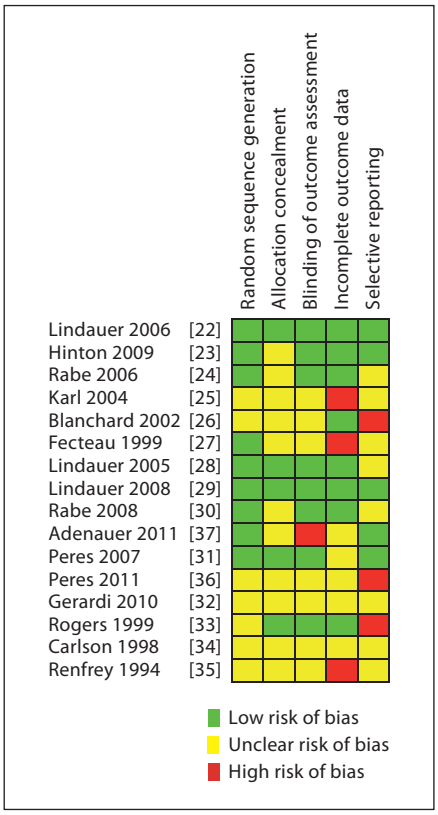

Fig. 2. Risk of bias of included RCTs.

Pretreatment Neurobiological Measures to Predict Treatment Outcome (3)

Seven publications on 5 studies assessed if pretreatment biological and genetic variables could predict treatment outcome (table 3) [38–44]. One reported that genotyping was used [39], 3 reported neuroimaging [40–42], 1 reported endocrine measures [38] and 2 reported the use of psychophysiological measures [43, 44].

Discussion

This is the first systematic review assessing both the biological treatment outcome of psychotherapy and biological predictors of treatment outcome in PTSD. We identified 6 controlled neuroimaging trials of TF-CBT,

Table 1. Summary of findings: neurobiological treatment effects of TF-CBT and EMDR in PTSD

Study, first author	Number of participants, treatments, controls (sessions)	Measures/provocation	Results
Lindauer 2006 [22]	20 PTSD, 9 BEP, 11 WL (16)	HR and BP/baseline, SDI and recovery	↓ HRR score in BEP >* WL (d = 1.02); ↓ SBP baseline and DSBP recovery in BEP >* WL
Hinton 2009 [23]	24 PTSD with orthostatic panic attacks, 12 TF-CBT, 12 delayed TF-CBT (12)	HR and BP/standing up provoking orthostatic panic attack	↓ SBP in immediate TF- CBT >** delayed TF-CBT at 2nd assessment (end immediate TF-CBT) (d = 1.38); DSBP and HR = between groups at 2nd assessment; SBP, DSBP and HR = between groups at end delayed TF-CBT
Rabe 2006 [24]	35 (partial) PTSD, 17 TF-CBT, 18 WL (8–12)	HR/baseline, positive, negative and trauma-related pictures	↓ HRR trauma-related pictures in TF-CBT >* WL (d = 0.78); HRR positive and negative pictures = between groups
Karl 2004 [25]	9 (partial) PTSD, 6 TF-CBT/ST, 3 WL (8–12)	EMG musculus orbicularis oculli/ neutral, startle and trauma sounds	↓ EMG reactivity to startle and trauma sounds in TF-CBT/ ST group >** WL (d = 2.89/2.8); ↓ EMG reactivity to neutral sounds TF-CBT/ST group >* WL (d = 1.67)
Blanchard 2002 [26]	73 (partial) PTSD, 25 TF-CBT and 26 ST, 22 WL (8–12)	HR, BP, SCL/baseline, mental arithmetic, SDI and relaxation	↓ HRR in TF-CBT group >*** both ST (d = 0.77) and WL (d = 0.51); BP and SCL reactivity = between groups
Fecteau 1999 [27]	20 PTSD, 10 TF-CBT, 10 WL (4)	HR/baseline and trauma script	Trend towards ↓ HRR in TF-CBT group > WL ($p < 0.1$, d = 0.75)
Lindauer 2005 [28]	18 PTSD, 9 BEP, 9 WL (16)	MRI	= in VOIs: amygdala, hippocampus and parahippocampal gyrus in both groups
Lindauer 2008 [29]	20 PTSD, 10 BEP, 10 WL (16)	[99mTc]HMPAO SPECT/trauma SDI	↓ rCBF in right middle frontal gyrus (dorsolateral prefrontal cortex) and right uncus in BEP >** WL
Peres 2007 [31]	27 partial PTSD, 16 TF-CBT, 11 WL (8)	[99mTc]HMPAO SPECT/trauma SDI	↑ rCBF in left anterior cingulate cortex, left prefrontal cortex, thalamus, left parietal lobe, left hippocampus and left Broca's area in TF-CBT >*** WL; ↓ rCBF in left amygdala in TF-CBT >*** WL
Peres 2011 [36]	24 (partial) PTSD, 12 TF-CBT, 12 WL (8)	fMRI/cued recall during positive, negative and trauma sounds	↑ BOLD in mid-prefrontal cortex and ↓ BOLD in left amygdala in TF-CBT >*** WL; = between groups in ROIs (anterior cingulate cortex, orbito frontal cortex, thalamus, insula, parietal lobe, hippocampus) or whole-brain analysis
Rabe 2008 [30]	35 (partial) PTSD, 17 TF-CBT, 18 WL (8–12)	EEG/baseline, positive, negative and trauma pictures	Trend towards ↓ reactivity in right anterior region in TF-CBT group > WL ($p = 0.07$); = reactivity in posterior region in TF-CBT compared to WL
Adenauer 2011 [37]	19 PTSD, 11 NET, 8 WL (12)	MEG/steady state visually evoked fields during trauma and aversive pictures	↑ activity in superior parietal cortex and left occipital brain regions in NET >(* and **) WL
Gerardi 2010 [32]	50 PTSD, 25 EMDR, 25 PE (9)	salivary cortisol/baseline and postexposure	= salivary cortisol level between groups
Rogers 1999 [33]	12 PTSD, 6 EMDR, 6 exposure (1)	HR/baseline and trauma imagery	= in HR(R) between groups
Carlson 1998 [34]	27 PTSD, 8 EMDR and 12 biofeedback, 7 RCC (12)	HR, SCL, EMG and skin temperature/baseline and SDI	= in EMG (bilateral frontalis, trapezius, left sternomastoid and left forearm flexor), HR, SCL and skin temperature between groups between pretreatment and posttreatment and between posttreatment and follow-up
Renfrey 1994 [35]	23 (partial) PTSD, 8 EMD and 8 EMD with automated EMs, 7 with visual fixation (6)	HR(R)/baseline, positive and negative imagery	= in HR(R) between groups between pretreatment and posttreatment and between posttreatment and follow-up

BEP = Brief eclectic psychotherapy; BOLD = blood oxygen level dependence; BP = blood pressure; DSBP/SBP = diastolic/systolic blood pressure; EEG = electroencephalogram; EMG = electromyogram; HR(R) = heart rate (reactivity); MEG = magnetoencephalography; NET = narrative exposure therapy; PE = prolonged exposure; rCBF = regional cerebral blood flow; RCC = routine clinical care; ROI/VOI = region/volume of interest; SCL = skin conductance level; SDI = script-driven imagery; SPECT = single-photon emission computed tomography; ST = supportive therapy; WL = waitlist.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 2. Summary of findings: correlation between change in neurobiological variables and change in symptom severity scores

Study, first author	Sample	Pre-/post-change in biological variable	Δ on psychometric scale	Correlation
Lindauer 2008 [29]	9 BEP	rCBF left superior temporal gyrus, left + right superior/middle frontal gyrus	SI-PTSD total	+ left superior temporal gyrus z(9) = 3.1*; + left + right superior/middle frontal gyrus: left z = 3.36***, right z = 3.52*
Lindauer 2006 [22]	9 BEP + 11 WL	HRR to neutral, stressful and trauma scripts	SI-PTSD total	+ HRR trauma script: r(20) = 0.56**; = HRR neutral and stressful scripts
Peres 2011 [36]	12 TF-CBT	BOLD left amygdala, mid-prefrontal cortex cued recall trauma sounds	CAPS	+ mid prefrontal cortex r(12) = 0.82*; – left amygdala r(12) = 0.86*
Peres 2007 [31]	16 TF-CBT	rCBF left prefrontal cortex, left amygdala and other brain regions	CAPS	+ left prefrontal cortex z = 3.79**; – left amygdala z = 3.12**; = other brain areas
Rabe 2006 [24]	17 TF-CBT + 18 WL	HRR to positive, negative and trauma-related pictures	CAPS	+ HRR trauma pictures r(35) = 0.30* = HRR positive/negative pictures
Rabe 2008 [30]	17 TF-CBT + 18 WL	Activity within left/right hemisphere and activation asymmetry	CAPS	+ right anterior activation r(35) = 0.39* = left hemisphere activation, posterior or anterior asymmetry
Blanchard 2002 [26]	25 TF-CBT + 26 ST + 22 WL	HRR to trauma imagery	CAPS	+ HRR: r(73) = 0.29**

For abbreviations, see table 1.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

but none of EMDR. Overall, these trials did not yield unambiguous findings. Two showed that after TF-CBT, activity in the mid-prefrontal cortex increased while activity in the amygdala decreased [31, 36]. Both structures are involved in fear conditioning and extinction learning and show disturbed activity in people with PTSD [47]. Lindauer et al. [29] demonstrated that after TF-CBT, activity had decreased in the dorsolateral prefrontal cortex, which is part of the neural circuitry underlying working memory function. Disturbances in this neural circuitry seem to be involved the development and maintenance of PTSD [48, 49]. However, in the single-photon emission computed tomography trial of Peres et al. [31], no changes in activity of the dorsolateral prefrontal cortex were found. Contrasting findings were also found regarding the role of the anterior cingulate cortex, orbitofrontal cortex, thalamus, insula, Broca's area, parietal lobe and hippocampus in TF-CBT treatment response. These areas are all implicated in the processing and integration of (sensory) information and the formation of structured memories and narratives. Deviations in both structure and function of these areas have been found in people with PTSD [50–53]. In their single-photon emission computed tomography study, Peres et al. [31] found that after treatment, activity in these regions increased, while in their functional magnetic resonance imaging (fMRI) study [36] activity did not change. In a magnetoencephalography study, Adenauer et al. [37] demonstrated that after TF-CBT treatment, activity increased in the parietal and occipital brain regions which are involved in attention regulation towards aversive stimuli. However, a substantial amount of magnetoencephalography outcome data was lost during this trial. Given the relatively small number of neuroimaging trials and mostly divergent findings in these trials, no conclusion can yet be drawn on the effects of TF-CBT (or EMDR) on neural activity in PTSD. Furthermore, because TF-CBT was compared to a waitlist condition and not to an active treatment in all trials, results may be regarded as nonspecific (psychotherapeutic) effects rather than specific effects of TF-CBT.

In contrast to the included neuroimaging trials, physiological-treatment outcome trials showed less ambiguous results. Regarding TF-CBT, all included publications showed a reduction of posttreatment physiological reactivity compared to waitlist conditions. PTSD is associated with a heightened physiological reactivity [54]. A height-

Table 3. Summary of findings: biological predictors of treatment outcome

Study, first author	Biological measure	Treatment	Responders/ nonresponders	Outcome
Bryant 2010 [39]	5-HTTLPR genotype	TF-CBT	45 PTSD CAPS scores	↑ CAPS scores at follow-up in low-expression 5-HTTLPR expression group than in high-expression group (F = 1.38**)
Bryant 2008 [41]	MRI VOI ACC	TF-CBT	7 R/6 NR	Pretreatment rACC in NR < R (z = 4.42***)
Bryant 2008 [40]	fMRI neutral emotional faces ROI: amygdala, ACC	TF-CBT	7 R/7 NR	Pretreatment bilateral amygdala in NR > R (right z = 1.85*, left z = 2.13*); pretreatment right ventral ACC in NR > R (z = 2.23*); pretreatment bilateral dorsal ACC R > NR (z = 3.1**)
Nardo 2010 [42]	MRI gray matter density	EMDR	10 R/5 NR	Pretreatment gray matter density in frontal and limbic structures R > NR (z score range = 3.0–4.54***)
Yehuda 2009 [38]	5α-THF, total glucocorticoids, 5α-reductase activity	PE	14 R/14 NR	Pretreatment 5α-reductase activity NR < R (F = 6.43*); = R, NR in pretreatment 5α-THF and total glucocorticoids
Blanchard 2003 [44]	Baseline HR and HR during SDI	TF-CBT/ support	57 PTSD, correlation CAPS scores	= correlation between pretreatment HR and posttreatment CAPS scores in support
Tarrier 2002 [43]	SCL neutral, startle and trauma scripts	Exposure/ CT	42 PTSD, correlation CAPS scores	= correlation between pretreatment SCL and posttreatment CAPS scores

ACC = Anterior cingulate cortex; 5α-THF = 5α-tetrahydrocortisol; NR = nonresponder; R = responder. For other abbreviations, see table 1.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

ened physiological reactivity to traumatic cues seems to reflect an elevated sensitivity to unconditioned aversive stimuli [55]. We found that after TF-CBT, heart rate reactivity, systolic blood pressure and electromyogram (EMG) reactivity decreased. These findings indicate that successful treatment reduces physiological reactivity to traumatic cues and thus decreases sensitivity to aversive unconditioned stimuli. Again, since in almost all trials TF-CBT was compared to waitlist, this might be a nonspecific psychotherapeutic effect. We did not identify trials in which EMDR was compared to a waitlist condition. Our review showed no differences in the physiological treatment effects of EMDR compared to other active treatments [32–35]. People treated with EMDR or other active treatments had both a reduction of heart rate and EMG reactivity. These findings show that active treatment (or time) reduces physiological reactivity but that the reduction is not specific for EMDR.

We included 7 trials which use pretreatment biological measurements to predict treatment outcome. Bryant et al. [40, 41] found that decreased rostral anterior cingulate cortex volumes and increased amygdala/ventral anterior cingulate cortex activity were associated with a poor response to TF-CBT. The findings of Nardo et al. [42] stand in contrast to this. They found that reduced amygdala gray matter volume predicted a poor response to EMDR. However, it would be premature to draw conclusions based on these differential findings because both studies had small sample sizes and used different paradigms. The 2 included trials which used physiological measures to predict treatment outcome had a relatively large sample size; nevertheless, no association was found between pretreatment physiological measures and treatment outcome [43, 44]. We included only 2 trials which used either genetic measurements (5-HT receptor gene variants) or pretreatment endocrinological measurements as predictors of treatment outcome; this makes it too early to make general conclusions about both measurements. There is only a limited number of trials in which biological measures are used to predict treatment outcome. Trials using somewhat comparable measurements yield negative or partially contrasting findings, making the use of biologi-

cal predictors of treatment outcome not (yet) suitable for clinical practice.

Taken together, these findings indicate that more high-quality research is necessary before we can infer any firm conclusions on the neurobiological working mechanisms of psychotherapy in PTSD or start to think of implementing neurobiological measures in clinical practice. Against this background, there is a great need for biological-treatment outcome studies of psychotherapies, especially EMDR, and RCTs comparing multiple active treatments, as well as studies assessing predictors of treatment response to different treatments using neuroimaging, endocrinological or genetic measurements or combinations of multiple measures [12].

Seven of the 16 included publications on RCT outcome data had a high risk of bias on one of the five domains (fig. 2). The remaining publications of RCTs almost all had a certain degree of uncertainty regarding risk of bias due to the inadequate reporting of data and the methodologies used. These findings stress the need for methodologically more rigorous trials and improvement of reporting, for instance, by using intent-to-treat analysis, by not omitting reports of negative findings and by using Cochrane criteria for reporting on RCTs [18]. The large heterogeneity between studies made it not reasonable to pool the study results. To enhance the comparability of studies, future research should make use of standardized treatment and measurement protocols. Measurement protocols should include standardized paradigms which directly assess systems involved in PTSD. Paradigms aimed at fear conditioning [56], extinction learning, attention regulation and working memory [57] might be profitable.

Finally, we did not find any study that assessed biological-treatment effects of psychotherapy in children with PTSD. This group deserves special attention because early disruptions of the biological fear systems increase the risk of PTSD and other anxiety disorders in later life [58]. The brain's fear circuitry contains a high rate of plasticity during childhood and adolescence [59]. Long-term treatment benefits in this group could thus be very substantial.

The populations included in our review varied considerably with regard to types of trauma and PTSD severity. Included trials also had a wide variety of measurement procedures, number of treatment sessions, comparison conditions and trial durations. Including trials which recruited individuals with partial PTSD made sure that results related to a wide range of individuals suffering from posttraumatic stress symptoms but added to the heterogeneity. This heterogeneity meant it was not reasonable to perform a meta-analysis. Most publications reported sufficient data to calculate effect sizes, but this was not possible in all of them.

We chose to follow the example of the most recent Cochrane review on psychological interventions in PTSD and present prolonged exposure, narrative exposure therapy and brief eclectic psychotherapy in the TF-CBT group instead of presenting them independently of one another. These and other trauma-focused cognitive behavioral therapies share certain treatment modules but also have distinct treatment components. As we did not differentiate between different TF-CBT components, it is not yet possible to attribute neurobiological effects to specific treatment components.

Seven of the included publications on RCT outcome data had a high risk of bias, mainly regarding incomplete outcome data or selective reporting (fig. 2). Incomplete outcome data raise the risk of attrition bias and an exaggeration of the effect size [18]. Selective reporting can lead to an imbalance of negative and positive findings.

The total number of people included in this review was relatively small. If noncontrolled trials were included, it would increase this number, but would make it impossible to differentiate between treatment effects and time effects, which is an important concern, given the considerable time effects observed in the waitlist groups of the RCTs that were included.

Our review did not account for the possibility of a publication bias and we included only studies that were published in English.

However, the strength of this systematic review lies in the fact that it follows the PRISMA statement for systematic reviews and meta-analyses and has a robust and comprehensive search strategy, an extensive assessment of risk of bias and is of an innovative character.

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References

1 Kessler RC: Posttraumatic stress disorder: the burden to the individual and to society. J Clin Psychiatry 2000;61(suppl 5):4–12.
2 Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE: Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:617–627.
3 American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, ed 4. Text revision (DSM-IV-TR). Washington, American Psychiatric Publishing, 2000.
4 Yehuda R, LeDoux J: Response variation following trauma: a translational neuroscience approach to understanding PTSD. Neuron 2007;56:19–32.
5 Francati V, Vermetten E, Bremner JD: Functional neuroimaging studies in posttraumatic stress disorder: review of current methods and findings. Depress Anxiety 2007;24:202–218.
6 Karl A, Schaefer M, Malta LS, Dorfel D, Rohleder N, Werner A: A meta-analysis of structural brain abnormalities in PTSD. Neurosci Biobehav Rev 2006;30:1004–1031.
7 Charney DS: Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. Am J Psychiatry 2004;161:195–216.
8 Carrion VG, Weems CF, Richert K, Hoffman BC, Reiss AL: Decreased prefrontal cortical volume associated with increased bedtime cortisol in traumatized youth. Biol Psychiatry 2010;68:491–493.
9 Rodrigues SM, LeDoux JE, Sapolsky RM: The influence of stress hormones on fear circuitry. Annu Rev Neurosci 2009;32:289–313.
10 Koenen KC, Amstadter AB, Nugent NR: Gene-environment interaction in posttraumatic stress disorder: an update. J Trauma Stress 2009;22:416–426.
11 Foa EB, Keane TM, Friedman MJ, Cohen JA: Effective treatments for PTSD: Practice Guidelines from the International Society for Traumatic Stress Studies. New York, The Guilford Press, 2008, p 139.
12 Bisson J, Andrew M: Psychological treatment of post-traumatic stress disorder (PTSD). Cochrane Database Syst Rev 2007;CD003388.
13 Roffman JL, Marci CD, Glick DM, Dougherty DD, Rauch SL: Neuroimaging and the functional neuroanatomy of psychotherapy. Psychol Med 2005;35:1385–1398.
14 Linden DE: How psychotherapy changes the brain – the contribution of functional neuroimaging. Mol Psychiatry 2006;11:528–538.
15 Siegle GJ, Carter CS, Thase ME: Use of fMRI to predict recovery from unipolar depression with cognitive behavior therapy. Am J Psychiatry 2006;163:735–738.
16 Knaup C, Koesters M, Schoefer D, Becker T, Puschner B: Effect of feedback of treatment outcome in specialist mental healthcare: meta-analysis. Br J Psychiatry 2009;195:15–22.
17 Moher D, Liberati A, Tetzlaff J, Altman DG: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
18 Higgins JPT, Green S: Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. The Cochrane Collaboration (available from www.cochrane-handbook.org, 2011).
19 Stein MB, Walker JR, Hazen AL, Forde DR: Full and partial posttraumatic stress disorder: findings from a community survey. Am J Psychiatry 1997;154:1114–1119.
20 Foa EB: Prolonged exposure therapy: past, present, and future. Depress Anxiety 2011;28:1043–1047.
21 Lindauer RJ, Gersons BP, van Meijel EP, Blom K, Carlier IV, Vrijlandt I, Olff M: Effects of brief eclectic psychotherapy in patients with posttraumatic stress disorder: randomized clinical trial. J Trauma Stress 2005;18:205–212.
22 Lindauer RT, van Meijel EP, Jalink M, Olff M, Carlier IV, Gersons BP: Heart rate responsivity to script-driven imagery in posttraumatic stress disorder: specificity of response and effects of psychotherapy. Psychosom Med 2006;68:33–40.
23 Hinton DE, Hofmann SG, Pollack MH, Otto MW: Mechanisms of efficacy of CBT for Cambodian refugees with PTSD: improvement in emotion regulation and orthostatic blood pressure response. CNS Neurosci Ther 2009;15:255–263.
24 Rabe S, Dorfel D, Zollner T, Maercker A, Karl A: Cardiovascular correlates of motor vehicle accident-related posttraumatic stress disorder and its successful treatment. Appl Psychophysiol Biofeedback 2006;31:315–330.
25 Karl A, Malta LS, Alexander J, Blanchard EB: Startle responses in motor vehicle accident survivors: a pilot study. Appl Psychophysiol Biofeedback 2004;29:223–231.
26 Blanchard EB, Hickling EJ, Veazey CH, Buckley TC, Freidenberg BM, Walsh JD, Keefer L: Treatment-related changes in cardiovascular reactivity to trauma cues in motor vehicle accident-related PTSD. Behav Ther 2002;33:417–426.
27 Fecteau G, Nicki R: Cognitive behavioural treatment of post traumatic stress disorder after motor vehicle accident. Behav Cogn Psychother 1999;27:201–214.
28 Lindauer RJ, Vlieger EJ, Jalink M, Olff M, Carlier IV, Majoie CB, den Heeten GJ, Gersons BP: Effects of psychotherapy on hippocampal volume in out-patients with posttraumatic stress disorder: a MRI investigation. Psychol Med 2005;35:1421–1431.
29 Lindauer RJ, Booij J, Habraken JB, van Meijel EP, Uylings HB, Olff M, Carlier IV, den Heeten GJ, van Eck-Smit BL, Gersons BP: Effects of psychotherapy on regional cerebral blood flow during trauma imagery in patients with post-traumatic stress disorder: a randomized clinical trial. Psychol Med 2008;38:543–554.
30 Rabe S, Zoellner T, Beauducel A, Maercker A, Karl A: Changes in brain electrical activity after cognitive behavioral therapy for posttraumatic stress disorder in patients injured in motor vehicle accidents. Psychosom Med 2008;70:13–19.
31 Peres JF, Newberg AB, Mercante JP, Simao M, Albuquerque VE, Peres MJ, Nasello AG: Cerebral blood flow changes during retrieval of traumatic memories before and after psychotherapy: a SPECT study. Psychol Med 2007;37:1481–1491.
32 Gerardi M, Rothbaum BO, Astin MC, Kelley M: Cortisol response following exposure treatment for PTSD in rape victims. J Aggression Maltreat Trauma 2010;19:349–356.
33 Rogers S, Silver SM, Goss J, Obenchain J, Willis A, Whitney RL: A single session, group study of exposure and eye movement desensitization and reprocessing in treating posttraumatic stress disorder among Vietnam War veterans: preliminary data. J Anxiety Disord 1999;13:119–130.
34 Carlson JG, Chemtob CM, Rusnak K, Hedlund NL, Muraoka MY: Eye movement desensitization and reprocessing (EDMR) treatment for combat-related posttraumatic stress disorder. J Trauma Stress 1998;11:3–24.
35 Renfrey G, Spates CR: Eye movement desensitization: a partial dismantling study. J Behav Ther Exp Psychiatry 1994;25:231–239.

36 Peres JFP, Foerster B, Santana LG, Domingues Fereira M, Nasello AG, Savoia MN, Moreira-Almeida A, Lederman H: Police officers under attack: resilience implications of an fMRI study. J Psychiatric Res 2011;45: 727–734.
37 Adenauer H, Catani C, Gola H, Keil J, Ruf M, Schauer M, Neuner F: Narrative exposure therapy for PTSD increases top-down processing of aversive stimuli – evidence from a randomized controlled treatment trial. BMC Neurosci 2011;12:127.
38 Yehuda R, Bierer LM, Sarapas C, Makotkine I, Andrew R, Seckl JR: Cortisol metabolic predictors of response to psychotherapy for symptoms of PTSD in survivors of the World Trade Center attacks on September 11, 2001. Psychoneuroendocrinology 2009;34:1304–1313.
39 Bryant RA, Felmingham KL, Falconer EM, Pe BL, Dobson-Stone C, Pierce KD, Schofield PR: Preliminary evidence of the short allele of the serotonin transporter gene predicting poor response to cognitive behavior therapy in posttraumatic stress disorder. Biol Psychiatry 2010;67:1217–1219.
40 Bryant RA, Felmingham K, Kemp A, Das P, Hughes G, Peduto A, Williams L: Amygdala and ventral anterior cingulate activation predicts treatment response to cognitive behaviour therapy for post-traumatic stress disorder. Psychol Med 2008;38:555–561.
41 Bryant RA, Felmingham K, Whitford TJ, Kemp A, Hughes G, Peduto A, Williams LM: Rostral anterior cingulate volume predicts treatment response to cognitive-behavioural therapy for posttraumatic stress disorder. J Psychiatry Neurosci 2008;33:142–146.
42 Nardo D, Hogberg G, Looi JC, Larsson S, Hallstrom T, Pagani M: Gray matter density in limbic and paralimbic cortices is associated with trauma load and EMDR outcome in PTSD patients. J Psychiatr Res 2010;44: 477–485.
43 Tarrier N, Pilgrim H, Sommerfield C, Faragher B, Reynolds M, Graham E, Barrowclough C: A randomized trial of cognitive therapy and imaginal exposure in the treatment of chronic posttraumatic stress disorder. J Consult Clin Psychol 1999;67:13–18.
44 Blanchard EB, Hickling EJ, Malta LS, Jaccard J, Devineni T, Veazey CH, Galovski TE: Prediction of response to psychological treatment among motor vehicle accident survivors with PTSD. Behav Ther 2003;34:351–363.
45 Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, Keane TM: The development of a clinician-administered PTSD scale. J Trauma Stress 1995;8: 75–90.
46 Davidson JRT, Kudler HS, Smith RD: Assessment and pharmacotherapy of posttraumatic stress disorder; in Giller JEL (ed): Biological Assessment and Treatment of Posttraumatic Stress Disorder. Washington, American Psychiatric Press, 1990, pp 205–221.
47 LeDoux JE: Emotion circuits in the brain. Annu Rev Neurosci 2000;23:155–184.
48 Shaw ME, Moores KA, Clark RC, McFarlane AC, Strother SC, Bryant RA, Brown GC, Taylor JD: Functional connectivity reveals inefficient working memory systems in posttraumatic stress disorder. Psychiatry Res 2009;172:235–241.
49 Veltman DJ, Rombouts SA, Dolan RJ: Maintenance versus manipulation in verbal working memory revisited: an fMRI study. Neuroimage 2003;18:247–256.
50 Lanius RA, Williamson PC, Hopper J, Densmore M, Boksman K, Gupta MA, Neufeld RW, Gati JS, Menon RS: Recall of emotional states in posttraumatic stress disorder: an fMRI investigation. Biol Psychiatry 2003;53: 204–210.
51 Lanius RA, Williamson PC, Densmore M, Boksman K, Neufeld RW, Gati JS, Menon RS: The nature of traumatic memories: a 4-T fMRI functional connectivity analysis. Am J Psychiatry 2004;161:36–44.
52 Bremner JD, Vythilingam M, Vermetten E, Southwick SM, McGlashan T, Nazeer A, Khan S, Vaccarino LV, Soufer R, Garg PK, Ng CK, Staib LH, Duncan JS, Charney DS: MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. Am J Psychiatry 2003;160:924–932.
53 Lindauer RJ, Vlieger EJ, Jalink M, Olff M, Carlier IV, Majoie CB, den Heeten GJ, Gersons BP: Smaller hippocampal volume in Dutch police officers with posttraumatic stress disorder. Biol Psychiatry 2004;56:356–363.
54 Orr SP, Metzger LJ, Pitman RK: Psychophysiology of post-traumatic stress disorder. Psychiatr Clin North Am 2002;25:271–293.
55 Phelps EA, LeDoux JE: Contributions of the amygdala to emotion processing: from animal models to human behavior. Neuron 2005;48:175–187.
56 Wessa M, Flor H: Failure of extinction of fear responses in posttraumatic stress disorder: evidence from second-order conditioning. Am J Psychiatry 2007;164:1684–1692.
57 Oei NY, Tollenaar MS, Spinhoven P, Elzinga BM: Hydrocortisone reduces emotional distracter interference in working memory. Psychoneuroendocrinology 2009;34:1284–1293.
58 McLaughlin KA, Green JG, Gruber MJ, Sampson NA, Zaslavsky AM, Kessler RC: Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication II: associations with persistence of DSM-IV disorders. Arch Gen Psychiatry 2010;67:124–132.
59 Pynoos RS, Steinberg AM, Layne CM, Briggs EC, Ostrowski SA, Fairbank JA: DSM-V PTSD diagnostic criteria for children and adolescents: a developmental perspective and recommendations. J Trauma Stress 2009;22:391–398.