A Systematic Review Evaluating PTSD Treatment Effects on Intermediate Phenotypes of PTSD

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Objective: Although the efficacy of evidence-based treatments for posttraumatic stress disorder (PTSD) has been well established, high rates of treatment dropout and/or nonresponse or under-response to treatment suggest a need to explore novel treatment approaches. Most current research has focused on DSM-based categorical outcomes as primary indicators of treatment response, which may obscure the phenotypic heterogeneity of PTSD and limit the ability to map symptoms to underlying neurobiology. This systematic review aimed to identify intermediate phenotypes (IPs) of PTSD and evaluate IP sensitivity to PTSD treatments.

Method: Five databases were searched for empirical studies published in English between January 1, 2010 and August 1, 2022 examining behavioral and pharmacological PTSD treatment effects on biobehavioral PTSD outcomes. Results: Twenty-two studies met the inclusion criteria. Most studies evaluated behavioral treatment outcomes (n = 20), while only two studies evaluated pharmacological interventions. Five PTSD IPs were identified, including “impairments in working memory,” “alterations in cognitive control,” “unstable threat processing,” “heightened fear or startle response,” and “disturbances in sleep and wakefulness.” This review offers preliminary support to suggest the utility of IP measures in assessing treatment efficacy; however, risk of bias and methodological limitations constrain the validity and generalizability of the results. Conclusions: The paucity of research combined with the heterogeneity of study methodologies and significant study limitations makes it difficult to draw strong conclusions regarding IP sensitivity to treatment. However, the existing body of research incorporating this framework shows potential for the IP approach to improve the translation of treatment efficacy from clinical trials to clinical settings.

Clinical Impact Statement
This review highlights the paucity of literature examining posttraumatic stress disorder (PTSD) treatment efficacy on intermediate phenotypes (IPs) of PTSD. However, the existing body of research using the IP approach suggests that IPs allow for replicable, multidimensional analysis of treatment effects on basic domains of functioning, and present new ways of advancing treatment development.

Keywords: posttraumatic stress disorder, intermediate phenotypes, evidence-based treatment

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Posttraumatic stress disorder (PTSD) is a chronic condition that occurs following a traumatic event and is characterized by trauma-related symptoms of intrusions, avoidance, negative alterations in cognition and mood, and altered arousal or reactivity (American Psychiatric Association, 2013). Clinical practice guidelines (CPGs) recommend trauma-focused psychotherapies as first-line treatments for PTSD (Department of Veterans Affairs and Department of Defense [VA/DoD], 2017; Foa et al., 2010; National Institute for Health and Care Excellence, 2018). Pharmacotherapy or individual nontrauma-focused psychotherapy are recommended when trauma-focused psychotherapy is not readily available or not preferred (Hamblen et al., 2019). While CPGs are supported by empirical evidence indicating treatment efficacy (Cusack et al., 2016; Jonas et al., 2013), many individuals fail to improve (Koek et al., 2016; Larsen, Bellmore, et al., 2019). For instance, psychological treatments for PTSD report nonresponse
rates as high as 50% (Larsen, Fleming, & Resick, 2019; Schottenbauer et al., 2008; Steenkamp et al., 2020), and only 30% of participants achieve full clinical remission following pharmacotherapy, while 20% show little or no improvement (Alexander, 2012; Berger et al., 2009; Krystal et al., 2017). Therefore, there is an urgent need to explore novel approaches in treating PTSD.

The limited efficacy of existing treatments may be partly explained by the gold-standard use of a total PTSD symptom severity score as the primary outcome measure of treatment response in definitive clinical trials (Krystal et al., 2017; Varker et al., 2020). Total symptom severity scores are typically derived from self-report measures (i.e., the Posttraumatic Stress Disorder Checklist (PCL; Blevins et al., 2015) and structured clinical interviews (i.e., the Clinician-Administered PTSD Scale (CAPS; Weathers et al., 2018), which correspond with categorical criteria defined by the Diagnostic and Statistical Manual of Mental Health Disorders (DSM; American Psychiatric Association, 2013). While the categorical classification system of the DSM has improved the reliability of psychiatric diagnoses, some argue that this nosology obscures the phenotypic and genetic heterogeneity that underlies the disorder. There are 636,120 ways to meet diagnostic criteria for PTSD using the DSM-5 (Galatzer-Levy & Bryant, 2013); thus, individuals with differing symptom presentations may receive the same diagnosis, total symptom severity score, and treatment recommendations without regard to genomics, brain structure or function, gene–environment interactions, or other physiologic or psychosocial factors. To complement the categorical, symptom-based approach to measuring treatment efficacy, biologically based, homogeneous phenotypic subgroups may help narrow the search for mechanism-based treatment targets and improve clinical outcomes.

There is increasing interest in the use of intermediate phenotypes as potentially more sensitive indicators of treatment efficacy than standard diagnostic categories (Clementz et al., 2020; Norrholm et al., 2015; Reilly & Sweeney, 2014; van Rooij & Jovanovic, 2019). An intermediate phenotype (IP) is a genetically determined neurobiological process with a causal role in the disease pathway, which attempts to capture an essential aspect of the pathological entity rather than the entire DSM diagnosis (Liberson, 2018). Characterized in aggregate by quantifiable biomarkers (i.e., neuroendocrine, neuroimaging), physiological responses (i.e., heart rate, skin conductance, electromyography), and observable behaviors (i.e., sleep, cognitive outcomes; Michopoulos et al., 2015; Stout et al., 2022), IPs denote specific dimensions of functioning driven by independent cellular and molecular processes within dedicated brain circuits (Flint et al., 2014; Rasetti & Weinberger, 2011).

For example, the Bipolar and Schizophrenia Network for Intermediate Phenotypes (BSNIP) consortium, a large, collaborative study that aims to develop biologically derived classifications of psychotic and mood disorders, recently identified three neurobiologically distinct psychosis IPs with diametrically opposed deviations in intrinsic electroencephalography activity (Clementz et al., 2016, 2020). Notably, the clinical features associated with these IPs were distinct from those associated with DSM diagnoses, suggesting that IPs and categorical syndromes may yield different treatment outcomes. In fact, extending the results of the aforementioned study, a second study showed that clozapine, an antipsychotic drug for psychosis, normalized the intrinsic neural activity of individuals with an IP of neurocognitive deficits but exacerbated the intrinsic activity of those with a neuroaffective dysregulation IP (Clementz et al., 2020; Hudgens-Haney et al., 2021). Thus, the IP approach may mitigate sources of heterogeneity within a disorder and help to predict treatment response by identifying subgroups of individuals who would most benefit from specific mechanism-based treatments.

Given the complexity of psychiatric diagnoses like PTSD, in which causal relations between genes, symptoms, and treatment outcomes are poorly understood, identifying intermediary subprocesses along the genome diagnosis continuum may be beneficial in identifying therapeutic outcomes by reducing heterogeneity. Furthermore, treatment studies employing this dimensional IP approach may help guide the development of novel, more personalized treatments while improving the translation of treatment efficacy from clinical trials to clinical settings (Liberson, 2018). This review aims to systematically identify the IPs of PTSD that have been used in PTSD treatment studies and to assess the IP response to treatment. By critically reviewing studies that have evaluated PTSD treatment efficacy using biobehavioral indices of treatment response, this review will (a) identify IPs of PTSD, (b) synthesize findings regarding IP sensitivity to pharmacological and behavioral treatment, (c) examine concordance between PTSD symptom severity score and IP treatment outcomes, and (d) discuss the benefits and limitations of IP constructs in contributing to PTSD treatment advancement.

Method

Protocol Registration and Selection Criteria

A systematic search process was conducted following the guidelines described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009). Before undertaking the review, the systematic review protocol was registered in PROSPERO (Registration Number: CRD42021231277).

Selection Criteria

Studies were selected following a search for original research articles published, unpublished, or ongoing in English between January 1, 2010 and August 1, 2022. Studies were included if the sample was comprised of human subjects at least 18 years of age with a primary diagnosis of PTSD provided by a validated measure of diagnosis (Wilson & Keane, 2004). Types of studies included were randomized trials, nonrandomized trials, interrupted time series studies, repeated measures studies, and before–after studies. Review articles and case studies were excluded.

Outcomes

Studies were required to report at least one objective, quantifiable behavioral, neurocognitive, and/or physiological index of treatment response. Studies reporting only subjective self-report, clinical, neuroendocrine, event-related potential, or neuroimaging outcomes were excluded (for reviews, see Pagani et al., 2021; Thomaes et al., 2014). Comparators included pretreatment assessment, use of placebo or waitlist control, or use of another active drug or therapy.

Treatments

Studies were included if they evaluated a behavioral and/or pharmacological treatment for adults with PTSD defined in line with
CPGs published by the American Psychological Association (2017), the International Society for Traumatic Stress (Bisson et al., 2019), and/or Veterans Affairs/Department of Defense (VA/DoD, 2017). Only treatments that were given strong or moderate recommendations by one or more guidelines were included. This review excluded treatments with insufficient evidence to demonstrate PTSD treatment efficacy at this time (i.e., Behavioral: Acceptance and Commitment Therapy, Seeking Safety; Pharmacological: alprazolam, d-cycloserine risperidone, topiramate, quetiapine).

Pharmacological treatments included in the search were fluoxetine, paroxetine, sertraline, venlafaxine, nefazodone, imipramine, and phenelzine. Behavioral treatments included in the search were trauma-focused cognitive behavioral therapy (TF-CBT), cognitive behavioral therapy for insomnia (CBT-I), prolonged exposure (PE), cognitive processing therapy (CPT), cognitive therapy, brief eclectic psychotherapy (BEP), eye movement desensitization and reprocessing (EMDR), narrative exposure therapy (NET), written exposure therapy (WET), and present-centered therapy (PCT). Behavioral treatments had to be implemented at the level of individual patients, rather than group, family, or couple therapy. Only in-person treatment modalities were included, as virtually delivered therapy has not been provided a formal recommendation by CPGs and has been reviewed elsewhere (Deng et al., 2019). A list of recurring abbreviations is presented in Table 1 in the online supplemental materials.

Information Sources and Search Strategy

A systematic search of the PubMed and APA PsycInfo databases was conducted by the first author (AP) with each of the clinician-recommended pharmacotherapies and psychotherapies in combination with any of the following keywords: “PTSD,” “posttraumatic stress disorder,” “heart rate,” “skin conductance,” “SCR,” “galvanic skin response,” “GSR,” “autonomic reactivity,” “physiological reactivity,” “startle,” “eyelink,” “facial electromyography,” “EMG,” “fear conditioning,” “conditioned fear,” “eye tracking,” “attention bias,” “memory,” “sleep,” “neurocognitive,” and “behavioral paradigm.” The “related words” expander was applied to all searches. No limiters were applied to maximize search results and to identify unpublished and ongoing studies. Additionally, the ClinicalTrials.gov, Cochrane Central Register of Controlled Trials (CENTRAL), and PTSDpubs (an extensive PTSD resource produced by the U.S. Department of Veteran Affairs) databases were searched using the same keywords. Manual searches were also performed on the reference lists of the retrieved papers and previous reviews and meta-analyses.

Study Selection and Data Collection Process

Duplicates were removed with the aid of the EndNote™ Reference Manager. Titles and study abstracts were screened by the first author (AP) using the selection criteria outlined and were submitted to full-text analysis. Any uncertainties about the inclusion or exclusion of studies were resolved by discussion with an independent reviewer (SMC). Full texts of the remaining articles were independently screened by two reviewers (AP and SMC) and those that did not satisfy the eligibility criteria were excluded. Discrepancies were resolved by a discussion between the two reviewers (Figure 1).

The search strategy resulted in 4,795 records from databases with five additional records through reference lists of retrieved papers and previous systematic reviews. After the removal of duplicates (N = 2,627), exclusions based on titles and abstracts (N = 2,493), and exclusions following full-text analyses (N = 115), N = 22 studies were included in this review (see Figure 1 for a flow diagram of study selection).

The following information was extracted from each study: (a) PTSD IP examined (b) treatment implemented, (c) measure(s) used, (d) population characteristics, and (e) comparator used (Table 1). Data were extracted by the first author (AP) and checked for accuracy by an independent reviewer (SMC) with any disagreement resolved by discussion. A qualitative synthesis was undertaken to review research evaluating treatment effects on IPs of PTSD using common empirical themes identified by the study authors.

Risk of Bias in Individual Studies

The methodological quality of the included studies was independently assessed by two reviewers (AP and SMC) using the NIH Quality Assessment Tool for (a) Controlled Intervention Studies, (b) Observational Cohort and Cross-Sectional Studies, and (c) Before–After (Pre–Post) Studies with No Control Group depending on the study type. All criteria were answered as “yes,” “no,” “cannot determine,” “not applicable,” or “not reported.” The quality score was calculated by dividing the number of criteria that were present (yes) by the total number of applicable criteria. Studies were considered “high quality” with low risk of bias if ≥70% of the criteria were present. Studies were considered to be “average quality” if 51%–69% of the criteria were present, and poor quality with “high risk” of bias if ≤50% of the criteria were present (Tables 1–3 in the online supplemental materials; Maass et al., 2015). Discrepancies between reviewers were resolved by discussion.

Results

Search Findings

Twenty-two studies that used behavioral, neurocognitive, and/or physiological measures to evaluate pharmacological or behavioral PTSD treatment effects were included in this review (see Table 1 for study characteristics). Samples ranged in size from n = 6 to n = 189 (M = 58.2 ± 46.6; Min = 40.5) with an average age of 38.9 (SD = 6.62). Samples generally included more males (58.2%) than females (41.8%). Half (11/22) of the included studies reported race, and non-White samples were more greatly represented (53.9%) than White samples (46.1%) among studies in which race was reported. Included studies were mainly of community samples (n = 11) or samples of active or veteran members of the military (n = 10). The most common exclusion criteria were substance use disorder, unmanaged psychotic disorder, unmanaged bipolar disorder, current suicidality, and the use of certain psychotropic medications.

The majority of included studies evaluated behavioral treatment outcomes, including PE (n = 11), EMDR (n = 4), TF-CBT (n = 3), CBT-I (n = 3), PCT (n = 1), and BEP (n = 1). Only two studies evaluated pharmacological interventions, one assessing paroxetine and the other assessing sertraline. Descriptions of the behavioral and pharmacological treatments evaluated by studies in this review are presented in Table 2 in the online supplemental materials.
Five IPs of PTSD were identified from the included studies: “impairments in working memory” (n = 3), “alterations in cognitive control” (n = 4), “unstable threat processing” (n = 5), “heightened fear or startle response” (n = 10), and “disturbances in sleep and wakefulness” (n = 4).

Impairments in Working Memory

Individuals with PTSD often report impaired executive functioning, including difficulties with memory and concentration. Influential cognitive models theorize that these difficulties arise when considerable amounts of information processing resources are allocated toward task-irrelevant trauma-related thoughts, feelings, and behaviors at the expense of other emotion-neutral cognitive operations (Brewin & Holmes, 2003). Working memory capacity is one cognitive resource typically implicated in PTSD. Working memory involves actively maintaining and manipulating information relevant to ongoing tasks and goals. Impairments in concentration and working memory have been hypothesized to contribute to PTSD symptoms of intrusions (Brewin & Smart, 2005).

Three included studies assessed the PTSD IP of “impairments in working memory.” Two studies evaluated TF-CBT (Schindler et al., 2020; Szabó et al., 2014), and one study compared EMDR and BEP (Nijdam et al., 2018). The summarized study results are presented in Table 1. Descriptions of the measures used to assess the IP of “impairments in working memory and concentration,” as well as detailed descriptions of the individual studies, are presented in the supplemental materials.

One of the two studies using TF-CBT found that those with PTSD had poorer pretreatment working memory than trauma-exposed controls as measured by the Wechsler Memory Scale (WMS; Wechsler, 1987, 2009) and Paired Associates Learning Test (PAL; Robbins & Sahakian, 2002). However, significant improvements over the course of treatment were observed, such that no group differences were observed posttreatment (Szabó et al., 2014). This study also reported a reduction in total PTSD symptom severity over time. While improved PTSD symptom severity over time was also found in the second TF-CBT study (Schindler et al., 2020), no differences in working memory were observed over time or between groups using the Digit Span subtest of the WMS.

In the only study comparing EMDR and BEP, both treatments were equally efficacious in reducing PTSD symptom severity and improving verbal working memory performance over time as measured by both the California Verbal Learning Test (CVLT; Delis et al., 1987–2000) and the Paragraph Recall Test (PRT; Nijdam et al., 2018). Moreover, improved scores on both measures were associated with reductions in global PTSD symptom severity (Table 2).

Alterations in Cognitive Control

Research suggests deficits in the functional domains of inhibitory control and cognitive flexibility in those with PTSD (for
### Table 1

**Study Characteristics**

<table>
<thead>
<tr>
<th>PTSD IP</th>
<th>Intervention</th>
<th>Measure</th>
<th>Participants (n = total enrolled)</th>
<th>Study retention (% dropout)</th>
<th>Comparator</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Impairments in working memory</td>
<td>Trauma-focused cognitive behavioral therapy</td>
<td>Digit span subtest of Wechsler Memory Scale (WMS) in Autobiographical memory test Simons task</td>
<td>German community sample (n = 103) Msex = 36.6 (88.8% female)</td>
<td>59/103 (42.7%)</td>
<td>Trauma-exposed healthy controls</td>
<td>Schindler et al. (2020)</td>
</tr>
<tr>
<td>• Alterations in cognitive control</td>
<td>Trauma-focused cognitive behavioral therapy</td>
<td>WMS Paired Associates Learning Test (PAL)</td>
<td>Newly PTSD-assigned Hungarian community sample (n = 20) Msex = 44.3 (65% female)</td>
<td>40/40 (0%)</td>
<td>Trauma-exposed healthy controls</td>
<td>Szabó et al. (2014)</td>
</tr>
<tr>
<td>• Unstable threat processing</td>
<td>Eye movement desensitization and reprocessing</td>
<td>California Verbal Learning Test (CVLT) Trail Making Test (TMT) Stroop Color-Word Task</td>
<td>Netherlands community sample (n = 140) Msex = 40.3 (55.7% female)</td>
<td>88/140 (37.1%)</td>
<td>Brief eclectic psychotherapy (~14.7, 45 min weekly sessions)</td>
<td>Nijdam et al. (2018)</td>
</tr>
<tr>
<td>• Alterations in cognitive control</td>
<td>Prolonged exposure</td>
<td>Attentional blink task</td>
<td>U.S. veterans (n = 20) Msex = 32.0 (0% female; 60% non-White)</td>
<td>20/20 (0%)</td>
<td>Pretreatment</td>
<td>Harlé et al. (2020)</td>
</tr>
<tr>
<td>• Alterations in cognitive control</td>
<td>Sertraline</td>
<td>Affective anticipation task</td>
<td>OEF/OIF U.S. veterans (n = 31) Msex = 31.6 (0% female; 58.1% non-White)</td>
<td>24/31 (22.6%)</td>
<td>Pretreatment</td>
<td>Simmons et al. (2013)</td>
</tr>
<tr>
<td>• Unstable threat processing</td>
<td>Prolonged exposure</td>
<td>Emotional reactivity task</td>
<td>U.S. community sample (n = 66) Msex = 36.7 (65% female)</td>
<td>51/66 (22.8%)</td>
<td>Waild list control</td>
<td>Fonzo et al. (2017)</td>
</tr>
<tr>
<td>• Unstable threat processing</td>
<td>Prolonged exposure</td>
<td>Emotional Stroop task DOT probe task</td>
<td>French community sample (n = 42) Msex = 41.5 (57.8% female)</td>
<td>38/42 (9.6%)</td>
<td>Healthy controls</td>
<td>El Khoury-Malhame et al. (2011)</td>
</tr>
<tr>
<td>• Heightened fear or startle response</td>
<td>Potentiated startle</td>
<td>Potentiated startle</td>
<td>OEF/OIF U.S. veterans (n = 36) Msex = 32.8 (5.9% female; 36% non-White)</td>
<td>26/30 (13.3%)</td>
<td>High treatment responders; Low treatment responders</td>
<td>Robison-Andrew et al. (2014)</td>
</tr>
<tr>
<td>• Heightened fear or startle response</td>
<td>Prolonged exposure</td>
<td>Active or veteran members of the U.S. military (n = 189) Msex = 42.3 (30.8% female; 43.8% non-White)</td>
<td>189/189 (0%)</td>
<td>High treatment responders; Low treatment responders</td>
<td>Maples-Keller et al. (2019)</td>
<td></td>
</tr>
<tr>
<td>• Heightened fear or startle response</td>
<td>Prolonged exposure</td>
<td>Active or veteran members of the U.S. military (n = 123) Msex = 32.4 (41.2% female; 44.8% non-White)</td>
<td>123/123 (0%)</td>
<td>High treatment responders; Low treatment responders</td>
<td>Maples-Keller et al. (2022)</td>
<td></td>
</tr>
<tr>
<td>• Heightened fear or startle response</td>
<td>Prolonged exposure</td>
<td>Fear conditioning</td>
<td>U.S. community sample (n = 85) Msex = 35.5 (72.3% female; 67.2% non-White)</td>
<td>58/85 (31.8%)</td>
<td>Trauma-exposed healthy controls</td>
<td>Helpman et al. (2016)</td>
</tr>
<tr>
<td>• Heightened fear or startle response</td>
<td>Prolonged exposure</td>
<td>Imaginal recall</td>
<td>Active members of the U.S. military (n = 90) Msex = 31.0 (5.5% female)</td>
<td>73/90 (19%)</td>
<td>Waild list control</td>
<td>Katz et al., 2020</td>
</tr>
<tr>
<td>• Heightened fear or startle response</td>
<td>Prolonged exposure</td>
<td>Script-driven imagery</td>
<td>OEF/OIF U.S. veterans (n = 35) Msex = 32.0 (0% female; 43.3% non-White)</td>
<td>18/35 (48.6%)</td>
<td>Pretreatment</td>
<td>Wangelin and Tuerk (2015)</td>
</tr>
<tr>
<td>• Heightened fear or startle response</td>
<td>Prolonged exposure</td>
<td>English community sample (n = 32) Msex = 41.2 (37.5% female)</td>
<td>30/32 (6.3%)</td>
<td>Waild list control</td>
<td>Wells et al. (2015)</td>
<td></td>
</tr>
<tr>
<td>• Heightened fear or startle response</td>
<td>Prolonged exposure</td>
<td>Script-driven imagery</td>
<td>Australian motor vehicle accident survivors (n = 26) Msex = 32.5 (50% female)</td>
<td>23/26 (11.6%)</td>
<td>Waild list control</td>
<td>Dunne et al. (2012)</td>
</tr>
<tr>
<td>• Heightened fear or startle response</td>
<td>Eye movement desensitization and reprocessing</td>
<td>Imaginal recall</td>
<td>Italian community sample (n = 6) Msex = 45.8 (50% female)</td>
<td>6/6 (0%)</td>
<td>Pretreatment</td>
<td>Furina et al. (2015)</td>
</tr>
<tr>
<td>• Heightened fear or startle response</td>
<td>Eye movement desensitization and reprocessing</td>
<td>Fear conditioning</td>
<td>French community sample (n = 41) Msex = 40.5 (58.5% female)</td>
<td>35/41 (14.7%)</td>
<td>Healthy controls</td>
<td>Wurtz et al. (2016)</td>
</tr>
<tr>
<td>• Disturbances in sleep and wakefulness</td>
<td>Paroxetine</td>
<td>Polysomnography Multiple Sleep Latency Test (MSLT)</td>
<td>Chinese community sample affected by Wenchuan earthquake (n = 23) Msex = 47.2 (82.6% female)</td>
<td>8/23 (65.3%)</td>
<td>Pretreatment</td>
<td>Zhang et al. (2017)</td>
</tr>
<tr>
<td>• Disturbances in sleep and wakefulness</td>
<td>Cognitive behavioral therapy for insomnia</td>
<td>Actigraphy</td>
<td>U.S. veterans (n = 11) Msex = 58.6 (0% female; 87.5% non-White)</td>
<td>8/11 (27.3%)</td>
<td>Pretreatment</td>
<td>Gellis and Gehrman (2011)</td>
</tr>
</tbody>
</table>

*(table continues)
meta-analyses, see Scott et al., 2015; Woon et al., 2017). Inhibitory control reflects the ability to suppress attention toward goal-unrelated stimuli and to resist the execution of prepotent but unwanted responses, while cognitive flexibility represents the ability to switch between tasks or strategies (Diamond, 2013). Impairments in these executive function domains have been hypothesized to contribute to PTSD symptoms of intrusions, problems with concentration, hypervigilance, and hyperarousal (Aupperle et al., 2012; Buckley, 2000; Vasterling & Arditte Hall, 2018). Notably, PTSD is associated with altered cognitive processing of both threat-relevant and trauma-neutral information, suggesting both content-dependent and generalized cognitive dysfunction. The present section will focus on altered cognitive control for neutral information, while the “Heightened Fear or Startle Response” section will review studies examining altered cognitive processing for emotionally salient stimuli.

Four included studies assessed the PTSD IP of “alterations in cognitive control.” One study evaluated TF-CBT (Schindler et al., 2020), one study evaluated PE (Harlé et al., 2020), one study compared PE and sertraline (Echiverri-Cohen, 2013), and one study compared EMDR and BEP (Nijdam et al., 2018). The summarized study results are presented in Table 1. Descriptions of the measures used to assess the IP of “alterations in cognitive control,” as well as detailed descriptions of the individual studies, are presented in the supplemental materials.

In the study using TF-CBT, individuals with PTSD exhibited poorer pretreatment cognitive flexibility in response to conflict during the Simon task (Simon, 1990; see Table 3 in the online supplemental materials for task description) than nontraumatized controls; however, no improvements were observed over the course of TF-CBT treatment (Schindler et al., 2020). The Simon task further revealed no significant effects of group or time on inhibitory control. In one study using PE (Harlé et al., 2020), inhibitory control on a stop-signal task (SST) improved over time; further, less impulsive posttreatment performance was associated with pre- to posttreatment PTSD symptom reductions. Similarly, in a study comparing PE and sertraline, inhibitory control measured by the Attentional Blink task improved across treatments over time. Individuals with greater PTSD symptom reductions from PE showed increased inhibitory control over the course of treatment than those treated with sertraline (Echiverri-Cohen, 2013). Combined, these studies highlight the potential role of PE in treating PTSD-related impairments in inhibitory control.

In the only study using EMDR and BEP, both treatments were associated with pre- to posttreatment improvements in inhibitory control and cognitive flexibility as, respectively, measured by the Stroop Color-Word task (Stoop, 1935) and the Trail Making Test (TMT; Nijdam et al., 2018; Reitan, 1955). No main effects of treatment modality or interaction effects between treatment and time were found for either measure, suggesting that EMDR and BEP may be equally efficacious in treating PTSD-related impairments in inhibitory control and cognitive flexibility. Improvements on the TMT, but not the Stroop task, were associated with decreased PTSD symptom severity.

### Unstable Threat Processing

Previous research has shown that those with PTSD demonstrate impaired cognitive processing for emotionally salient information relative to those without PTSD (Iacoviello et al., 2014; Naim et al., 2015). Some research suggests a processing bias toward threat-related cues, facilitated detection of threatening stimuli, and difficulty disengaging from threat stimuli (Ehlers & Clark, 2000). Heightened threat perception is consistent with PTSD symptoms of hypervigilance and increased arousal and may contribute to intrusions (Shechmer & Bar-Haim, 2016). Conversely, consistent with the PTSD avoidance symptom cluster, other studies have found a processing bias away from threat in which perceptual focus is averted from threatening stimuli and the specificity of autobiographical trauma memory is reduced (Wald et al., 2011).

Four included studies assessed the PTSD IP of “unstable threat processing.” Two studies examined the effects of PE (Fonzo et al., 2017; Simmons et al., 2013), one study examined the effects of EMDR (Al Khoury-Malhame et al., 2011), and one study assessed the effect of TF-CBT (Schindler et al., 2020). The summarized study results are presented in Table 1. Descriptions of the measures used to assess the IP of “unstable threat processing,” as well as detailed descriptions of the individual studies, are presented in the supplemental materials.

In the two studies using PE, no improvements in anticipatory threat processing were found over time as measured by an affective anticipation task (Simmons et al., 2013), nor were time or group differences observed in threat reactivity or threat regulation using the respective Emotional Reactivity and Emotional Regulation tasks (Fonzo et al., 2017).

In a study using EMDR, the Emotional Stroop task revealed that those with PTSD had greater pretreatment bias toward emotionally salient words than healthy controls. However, this threat processing bias improved over the course of treatment with no posttreatment...
Table 2  
Summary of Outcomes

<table>
<thead>
<tr>
<th>Sample size (after dropout)</th>
<th>IP improvement</th>
<th>PTSD improvement</th>
<th>IP findings</th>
<th>PTSD findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>59</td>
<td>N</td>
<td>Y</td>
<td>NC in working memory, autobiographical memory, inhibitory control, or conflict adaptation over time or between groups (ps &gt; .05)</td>
<td>↓ PTSD symptom severity over time (p &lt; .001, d = 1.12)</td>
<td>Schindler et al. (2020)</td>
</tr>
<tr>
<td>40</td>
<td>Y</td>
<td>Y</td>
<td>↑ working memory in the PTSD group over time (PAL: p &lt; .005, d = 0.92; WMS: p &lt; .005, d = 0.88); no posttreatment difference between the PTSD and control groups (p = .70)</td>
<td>↓ PTSD symptom severity over time (p &lt; .005)</td>
<td>Szabó et al. (2014)</td>
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<tr>
<td>88</td>
<td>Y</td>
<td>Y</td>
<td>↑ working memory over time (CVLT: p = .001, d = 0.30; PRT: p &lt; .001, d = 0.68); ↑ cognitive flexibility over time (p &lt; .001, d = 0.38); ↑ inhibitory control over time (p = .02; d = 0.19); No difference between BEP and EMDR for any measure (ps &gt; .05)</td>
<td>↓ PTSD symptom severity over time (ps &lt; .001; BEP: d = 1.55; EMDR: d = 1.73); no difference between EMDR and BEP (p = .48)</td>
<td>Nijdam et al. (2018)</td>
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<tr>
<td>20</td>
<td>Y</td>
<td>Y</td>
<td>↑ inhibitory control over time (p &lt; .001)</td>
<td>↓ PTSD symptom severity over time (p &lt; .001)</td>
<td>Harlé et al. (2020)</td>
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<td>38</td>
<td>Y</td>
<td>NR</td>
<td>↑ inhibitory control in those with greater PTSD symptom reduction from PE than in those that responded with sertraline (p = .01, d = 0.80)</td>
<td>↓ PTSD symptom severity associated with ↑ inhibitory control (p &lt; .001)</td>
<td>Echiverri-Cohen (2013)</td>
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<td>24</td>
<td>N</td>
<td>NR</td>
<td>NC in anticipatory threat processing over time (p &gt; .10)</td>
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<td>Simmons et al. (2013)</td>
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<tr>
<td>51</td>
<td>N</td>
<td>NR</td>
<td>NC in threat reactivity or threat regulation over time or between groups (ps &gt; .05)</td>
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<td>Fonzo et al. (2017)</td>
</tr>
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<td>38</td>
<td>Y</td>
<td>NR</td>
<td>↓ threat bias in the PTSD group over time (p &lt; .05); no posttreatment difference between the PTSD and control groups (p &lt; .05); ↑ threat disengagement in the PTSD group over time (p &lt; .05); no posttreatment difference between the PTSD and control groups (p &lt; .05); NC in threat vigilance over time or between groups (ps &gt; .05)</td>
<td></td>
<td>El Khoury-Malhame et al. (2011)</td>
</tr>
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<td>26</td>
<td>Y</td>
<td>NR</td>
<td>↑ startle from pre- to mid-treatment (p &lt; .05) and ↑ startle from mid- to posttreatment (p &lt; .05) for high responders</td>
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<td>Robison-Andrew et al. (2014)</td>
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<td>189</td>
<td>Y</td>
<td>NR</td>
<td>NC in startle for low responders over time</td>
<td></td>
<td>Maples-Keller et al. (2019)</td>
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*table continues*
Table 2 (continued)

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<tr>
<th>IP</th>
<th>Intervention</th>
<th>Sample size (after dropout)</th>
<th>IP improvement</th>
<th>PTSD improvement</th>
<th>IP findings</th>
<th>PTSD findings</th>
<th>Reference</th>
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<tr>
<td>• Heightened fear or startle response</td>
<td>• Prolonged exposure</td>
<td>123 Y</td>
<td>Y</td>
<td>Y</td>
<td>↓ fear heart rate over time ($p = .04$), but no difference between responder groups ($p = .46$)</td>
<td>↓ fear heart rate over time ($p = .04$), but no difference between responder groups ($p = .46$)</td>
<td>Roy et al. (2015)</td>
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<td>↓ startle over time in high responders ($p = .02$, $\eta^2 = 0.30$), but not low responders ($p = .06$, $\eta^2 = 0.19$)</td>
<td>↓ startle over time in high responders ($p = .02$, $\eta^2 = 0.30$), but not low responders ($p = .06$, $\eta^2 = 0.19$)</td>
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<td>↓ startle in high responders compared to low responders posttreatment ($p = .04$, $\eta^2 = 0.12$)</td>
<td>↓ startle in high responders compared to low responders ($p = .03$, $\eta^2 = 0.13$)</td>
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<td></td>
<td>↓ return of fear during recall in high responders compared to low responders ($p = .03$, $\eta^2 = 0.13$)</td>
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<td>Maples-Keller et al. (2022)</td>
</tr>
<tr>
<td>• Heightened fear or startle response</td>
<td>• Prolonged exposure</td>
<td>58 N</td>
<td>Y</td>
<td>Y</td>
<td>↓ PTSD symptom severity over time for the PTSD group ($p &lt; .001$); NC in trauma-exposed controls ($p = .96$)</td>
<td>↓ PTSD symptom severity over time for the PTSD group ($p &lt; .001$); NC in trauma-exposed controls ($p = .96$)</td>
<td>Helpman et al. (2016)</td>
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<td>↓ PTSD symptom severity associated with ↓ fear SCR over time ($p = .02$)</td>
<td>↓ PTSD symptom severity associated with ↓ fear SCR over time ($p = .02$)</td>
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<td>↓ PTSD symptom severity associated with ↓ fear SCR over time ($p = .05$)</td>
<td>↓ PTSD symptom severity associated with ↓ fear SCR over time ($p = .05$)</td>
<td>Katz et al. (2020)</td>
</tr>
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<td>• Heightened fear or startle response</td>
<td>• Prolonged exposure</td>
<td>73 N</td>
<td>Y</td>
<td>Y</td>
<td>↓ startle over time across groups over time ($p &lt; .001$); no difference in change in fear SCR over time between treatment and control groups ($p &gt; .05$)</td>
<td>↓ startle over time across groups over time ($p &lt; .001$); no difference in change in fear SCR over time between treatment and control groups ($p &gt; .05$)</td>
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<td>↓ fear heart rate over time ($p = .002$, $\eta^2 = .35$)</td>
<td>↓ fear heart rate over time ($p = .002$, $\eta^2 = .35$)</td>
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<td>↓ fear SCR over time ($p = .008$, $\eta^2 = .30$)</td>
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<td>• Heightened fear or startle response</td>
<td>• Prolonged exposure</td>
<td>18 Y</td>
<td>Y</td>
<td>Y</td>
<td>↓ PTSD symptom severity over time ($p &lt; .001, d = 2.09$)</td>
<td>↓ PTSD symptom severity over time ($p &lt; .001, d = 2.09$)</td>
<td>Wangelin and Tuerk (2015)</td>
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<td>↓ PTSD symptom severity associated with ↓ pretreatment fear heart rate ($p = .008, R^2 = .37$)</td>
<td>↓ PTSD symptom severity associated with ↓ pretreatment fear heart rate ($p = .008, R^2 = .37$)</td>
<td></td>
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<td>• Heightened fear or startle response</td>
<td>• Prolonged exposure</td>
<td>30 Y</td>
<td>Y</td>
<td>Y</td>
<td>↓ PTSD symptom severity over time for PE ($p &lt; .001$, $d = 1.34$) and MCT ($p &lt; .0005$); NC in waitlist controls ($p &gt; .05$)</td>
<td>↓ PTSD symptom severity over time for PE ($p &lt; .001$, $d = 1.34$) and MCT ($p &lt; .0005$, $g = 1.34$); NC in waitlist controls ($p &gt; .05$)</td>
<td>Wells et al. (2015)</td>
</tr>
<tr>
<td></td>
<td>• Metacognitive therapy*</td>
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<td>↓ fear heart rate in MCT compared to controls ($p &lt; .0005$); no difference between PE and controls ($p &gt; .05$)</td>
<td>↓ fear heart rate in MCT compared to controls ($p &lt; .0005$); no difference between PE and controls ($p &gt; .05$)</td>
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<td></td>
<td>No difference in fear heart rate between MCT and PE ($p = .652$)</td>
<td>No difference in fear heart rate between MCT and PE ($p = .652$)</td>
<td></td>
</tr>
<tr>
<td>• Heightened fear or startle response</td>
<td>• Trauma-focused cognitive behavioral therapy</td>
<td>23 Y</td>
<td>Y</td>
<td>Y</td>
<td>↓ PTSD symptom severity over time ($p &lt; .001$)</td>
<td>↓ PTSD symptom severity over time ($p &lt; .001$)</td>
<td>Dunne et al. (2012)</td>
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<td></td>
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<td></td>
<td>Fewer participants in the treatment group met diagnostic criteria for PTSD than waitlist at posttreatment ($p = .004$, $\eta^2 = 0.57$)</td>
<td>Fewer participants in the treatment group met diagnostic criteria for PTSD than waitlist at posttreatment ($p = .004$, $\eta^2 = 0.57$)</td>
<td></td>
</tr>
</tbody>
</table>
| Disturbances in sleep and wakefulness | Cognitive behavioral therapy for insomnia | 8 | N | N | • NC in any sleep measure over time (p > .05) | Gellis and Gehrman (2011)

| Disturbances in sleep and wakefulness | Cognitive behavioral therapy for insomnia | 73 | N | Y | • NC in sleep efficiency over time for those with PTSD (p = .07) or without PTSD (p = .16) | Carlson et al. (2021)

| Disturbances in sleep and wakefulness | Cognitive behavioral therapy for insomnia with adjunctive imagery rehearsal | 18 | Y | Y | • ↓ wake after sleep onset over time (p < .05, η² = 0.13) | Margolies et al. (2013)

| Heightened fear or startle response | Eye movement desensitization and reprocessing | 6 | Y | NR | • ↑ high-frequency heart rate variability over time (p = .03) | Farina et al. (2015)

| Heightened fear or startle response | Eye movement desensitization and reprocessing | 35 | Y | Y | • ↓ fear SCR over time for the PTSD group (p < .05), no posttreatment difference between the PTSD and control groups (p > .05) | Wurtz et al. (2016)

| Disturbances in sleep and wakefulness | Paroxetine | 8 | Y | Y | • ↓ mean sleep onset latency over time (p = .03) | Zhang et al. (2017)

| Disturbances in sleep and wakefulness | Disturbances in sleep and wakefulness | 18 | Y | Y | • ↓ wake after sleep onset over time (p < .05, η² = 0.04) | Margolies et al. (2013)

Note. BEP = brief eclectic psychotherapy; CVLT = California Verbal Learning Test; EMDR = eye movement desensitization and reprocessing; IP = intermediate phenotype; MCT = metacognitive therapy; NC = no change; NR = not reported; PAL = Paired Associates Learning Test; PE = prolonged exposure; PRT = Paragraph Recall Test; PTSD = posttraumatic stress disorder; SCR = skin conductance response; WMS = Wechsler Memory Scale.

* Metacognitive therapy currently receives insufficient recommendation by clinical practice guidelines for PTSD treatment.
group differences observed (El Khoury-Malhame et al., 2011). While this study found no evidence of enhanced vigilance toward threat in those with PTSD relative to controls using the Detection of Target (DOT) probe task, results showed that the PTSD group had greater difficulty orienting their attention away from threatening words pretreatment. This impairment in threat disengagement was ameliorated with EMDR treatment. Finally, in the only study to use TF-CBT, no improvements in autobiographical memory specificity were found over time or between the PTSD and control groups, despite pre- to posttreatment improvements in total PTSD symptom severity (Schindler et al., 2020).

**Heightened Fear or Startle Response**

Studies show heightened physiological fear response (i.e., skin conductance response [SCR], heart rate) and exaggerated startle response (i.e., electromyogram) to trauma-related stimuli in those with PTSD relative to those without (Norrholm et al., 2011; Orr et al., 2004; Orr & Roth, 2000; Pole, 2007). These phenotypic responses are consistent with PTSD diagnostic criteria of intrusions and marked alterations in arousal and reactivity (American Psychiatric Association, 2013).

Ten included studies assessed the PTSD IP of “heightened fear or startle response.” Five studies examined the effects of PE (Helpman et al., 2016; Katz et al., 2020; Maples-Keller et al., 2019, 2022; Wangelin & Tuerk, 2015), one study examined PE and PCT (Robison-Andrew et al., 2014), and one study compared PE with metacognitive therapy (MCT), which currently receives insufficient recommendation by CPGs to treat PTSD (Wells et al., 2015). One study examined the effects of TF-CBT (Dunne et al., 2012), and two studies assessed the effects of EMDR (Farina et al., 2015; Wurtz et al., 2016). The summarized study results are presented in Table 1. Descriptions of the measures used to assess the IP of “heightened fear or startle response,” as well as detailed descriptions of the individual studies, are presented in the supplemental materials.

Three studies used potentiated startle paradigms to investigate the effects of PE on physiological arousal. Participants in each of these studies were characterized as high responders (≥50% change in PTSD symptom severity) or low responders (<50% change in PTSD symptom severity) based on PTSD symptom reduction from pre- to posttreatment. One study found that high responders exhibited an increased startle response from pretreatment to mid-assessment and a decreased response from mid- to posttreatment. Low responders exhibited a flat startle profile over time (Robison-Andrew et al., 2014). Notably, this study collapsed analyses for participants that received either PE or PCT treatment; thus, additional work is needed to determine whether the treatments are differentially efficacious. A second study, which solely evaluated the effects of PE, similarly found that high PE responders demonstrated a significant decrease in trauma-potentiated startle over the course of treatment, while low treatment responders demonstrated a flat startle profile (Maples-Keller et al., 2019). While no change in SCR reactivity was found over time or between responder groups, pre- to posttreatment reduction in heart rate reactivity was observed across responder groups, with no difference between groups. A third study investigated the association between PE treatment response and extinction (new learning that a previously dangerous cue is now safe) and extinction retention (maintenance of extinction learning; Maples-Keller et al., 2022). High responders, but not low responders, showed a significant reduction in startle from pre- to posttreatment during extinction training. High responders also maintained fear extinction learning, whereas low responders showed a significant return of fear posttreatment. PTSD symptom severity scores improved during the course of treatment in the high responder group only; however, startle was not significantly correlated with PTSD symptom severity scores.

In a study using a traditional fear conditioning paradigm, no differences in fear SCR over the course of PE or between PTSD and trauma-exposed controls were observed; however, PE was associated with improved PTSD symptom severity over time, and reduced PTSD symptom severity was associated with reduced fear response (Helpman et al., 2016). Improvements in fear SCR were found over the course of PE in a study using an imaginal recall paradigm and reduced fear response was positively associated with PTSD symptom severity (Katz et al., 2020). However, no difference in fear SCR was observed between the PTSD and waitlist control groups, indicating equal improvement rates.

Improved fear SCR, heart rate, and reduced total PTSD symptom severity were also found over the course of PE in a study using a script-driven imagery task (Wangelin & Tuerk, 2015). Moreover, higher pretreatment fear heart rate was associated with greater PTSD symptom improvement over time, whereas lower pretreatment reactivity was associated with higher treatment dropout, suggesting that physiological reactivity may be an indicator of prognosis. Using a script-driven imagery task to compare PE and MCT with waitlist controls, pre- to posttreatment improvement in fear heart rate was observed for PE and MCT, with no change in the waitlist controls (Wells et al., 2015). Compared to controls, MCT was the only treatment resulting in lower posttreatment fear heart rate; there was no difference in heart rate between PE and waitlist, and no difference between MCT and PE. Both active treatments also resulted in significant reductions in PTSD symptom severity over time, and both active treatments differed from the waitlist at posttreatment. MCT resulted in lower posttreatment symptom severity scores than PE. However, no differences in fear response or symptom severity between PE and MCT were found at 3-month follow-up, suggesting that treatment effects may be more rapid with MCT compared with PE, but that both treatments may be equally efficacious long term.

The only TF-CBT study found no evidence of improved fear heart rate, systolic blood pressure, or diastolic blood pressure from pre- to posttreatment as measured by a script-driven imagery task (Dunne et al., 2012). However, reduced fear heart rate and systolic blood pressure were observed at 6-month follow-up. This study also reported posttreatment reduction in total PTSD symptom severity, which was maintained at 6-month follow-up.

In one of the two studies using EMDR, results from an imaginal recall task revealed increased high-frequency heart rate variability and decreased low-frequency/high-frequency ratio over time, indicating enhanced parasympathetic activation (Farina et al., 2015). The second study found higher pretreatment fear SCR to both shock and safe stimuli in the PTSD group than the control group during the conditioning phase of a fear conditioning paradigm; however, no difference between groups was observed post-EMDR treatment (Wurtz et al., 2016). Compared to controls, the PTSD group also demonstrated higher pretreatment fear SCR to the extinguished stimulus during the extinction phase, but no between-group difference was found posttreatment.
Disturbances in Sleep and Wakefulness

The DSM-5 diagnostic criteria for PTSD include disturbed sleep in both the intrusion and hyperarousal symptom clusters, respectively, referencing sleep disturbances as recurrent or distressing dreams and difficulty falling or staying (American Psychiatric Association, 2013). Clinical and epidemiological studies have found associations between subjective reports of sleep disturbances and exposure to traumatic events, with 70%–90% of those with PTSD reporting problems initiating or maintaining sleep (Maher et al., 2006; Ohayon & Shapiro, 2000).

Four studies assessed the PTSD IP of “disturbances in sleep and wakefulness.” One study assessed the effect of paroxetine (Zhang et al., 2017), and three studies assessed the effect of CBT-I (Carlson et al., 2021; Gellis & Gehrman, 2011; Margolies et al., 2013). The summarized study results are presented in Table 1. Descriptions of the measures used to assess the IP of “disturbances in sleep and wakefulness,” as well as detailed descriptions of the individual studies, are presented in the supplemental materials.

Paroxetine improved PTSD-related sleep disturbances as measured by polysomnography and the Multiple Sleep Latency Test (MSLT; Thorpy et al., 1992; Zhang et al., 2017). Improved daytime sleepiness as measured by the MSLT was associated with reductions in global PTSD symptom severity, reexperiencing symptom severity, and hyperarousal symptom severity.

The results of studies assessing CBT-I for sleep disturbances using actigraphy were inconsistent. One study found no significant changes in sleep or PTSD symptom severity from pre- to posttreatment (Gellis & Gehrman, 2011). Similarly, another study found no improvement in sleep over time for those with or without PTSD, and no differences between groups at posttreatment or 3-month follow-up; however, those with PTSD at baseline showed significant improvements in PTSD symptoms at posttreatment that were maintained at 3-month follow-up (Carlson et al., 2021). A third study reported improvements in both sleep and PTSD symptom severity over the course of CBT-I with adjunctive imagery rehearsal therapy (Margolies et al., 2013). This study also found improved posttreatment sleep efficiency in the treatment group relative to waitlist controls (Margolies et al., 2013).

Risk of Bias Assessment

Of the 22 studies included in this review, 10 received high-quality ratings, 10 received average-quality ratings, and 2 received low-quality ratings based on criteria established by the NIH Quality Assessment Tool for (a) Controlled Intervention Studies, (b) Observational Cohort and Cross-Sectional Studies, and (c) Before–After (Pre–Post) Studies with No Control Group depending on the study type. Detailed descriptions of the quality score calculations are presented in Tables 4a–4c in the online supplemental materials.

Discussion

This review aimed to identify PTSD IPs that have been used in PTSD treatment studies and to assess the responsivity of IPs to behavioral and pharmacological treatments. Using a rigorous and preregistered methodology with robust quality assessments, 22 studies met the criteria, and five IPs for PTSD were identified: (a) impairments in working memory, (b) alterations in cognitive control, (c) unstable threat processing, (d) heightened fear or startle response, and (e) disturbances in sleep and wakefulness. Approximately 90% of the included studies evaluated behavioral, rather than pharmacological, treatments for PTSD. Other limitations included small sample sizes and a lack of a control group. Despite these limitations, this review provides a foundation for identifying homogeneous, neurobiological constructs representing specified dimensions of functioning in PTSD, and emphasizes the need for future research to assess the utility of IPs in improving treatment outcomes for PTSD.

Several of the IPs identified here are consistent with those recently proposed by Liberzon (2018), based on a review of preclinical models for PTSD. These include impaired fear learning, exaggerated threat detection, diminished emotion regulation, and deficient context processing. Preclinical PTSD models and functional magnetic resonance imaging studies in humans have linked these functional impairments to dedicated neurobiological entities implicated in PTSD development and maintenance. For example, dysregulation of the basolateral amygdala has been implicated in abnormal conditioned fear acquisition, fear extinction, and fear generalization, which may contribute to exaggerated and persistent fear expression (Brown et al., 2014; Yang et al., 2008). Given its role in threat detection, hyperactivity in a network of regions including the insula, amygdala, and dorsal anterior cingulate cortex has been hypothesized to contribute to PTSD hypervigilance symptoms (Herringshaw et al., 2013; Seeley et al., 2007). Additionally, PTSD symptoms of heightened emotional response, irritability, impulsivity, and impaired memory have been linked to reduced activation of the lateral and medial prefrontal cortex (Andrewes & Jenkins, 2019; Nejati et al., 2021). Finally, dysfunction of the hippocampus and medial prefrontal cortex is associated with context processing deficits, including the inability to update schemas upon receipt of novel information, which may contribute to PTSD symptoms of intrusive memories, threat generalization, hypervigilance and hyperarousal, emotional numbing, and recklessness (Liberzon & Abelson, 2016).

Importantly, the identification of PTSD IPs and their relevant circuits may guide the creation of biologically coherent and homogeneous groups, which may better respond to targeted, mechanism-based treatments. However, the present review offers only preliminary support to suggest the utility of phenotype measures in assessing treatment efficacy to date. The majority of included studies evaluated outcomes for behavioral treatments, including PE (n = 11), EMDR (n = 4), TF-CBT (n = 3), CBT-I (n = 3), PCT (n = 1), and BEP (n = 1). Only two studies evaluated pharmacological interventions, with one study finding improved sleep and wakefulness following paroxetine (Zhang et al., 2017), and the other finding no improvements in inhibitory control following sertraline (Echiverri-Cohen, 2013). The unequal distribution of behavioral versus pharmacological treatment studies could be due to a paucity of FDA-approved medications for PTSD.

In contrast, a broad range of behavioral interventions show efficacy for PTSD. For example, working memory improvements were found following TF-CBT (Szabó et al., 2014; but see Schindler et al., 2020), as well as EMDR and BEP (Nijdam et al., 2018). EMDR and BEP were also shown to improve cognitive control (Nijdam et al., 2018), as did PE (Echiverri-Cohen, 2013; Harlé et al., 2020). Unstable threat processing was also improved with EMDR (El Khoury-Malhame et al., 2011), as was exaggerated fear and startle response (Farina et al., 2015; Wurtz et al., 2016).

Ordered by descending table number.
This review revealed several methodological issues that need to be considered in future research. First, very few randomized controlled trials (RCTs) evaluating treatment efficacy using IP outcomes exist (n = 6). Additionally, several existing RCTs failed to report adequate method of randomization or whether assessors were blind to treatment assignment. In the absence of RCTs, we also evaluated observational cohort studies (n = 6) and uncontrolled before-and-after studies (n = 7). These studies were limited by low treatment adherence, retrospective and poor-quality reporting, cross-sectional designs with short follow-up periods, and a lack of matched control groups. No studies compared different levels of treatment exposure (i.e., medication doses, categories of exposure, or exposure measured as a continuous variable), and only three studies assessed long-term follow-up to evaluate the maintenance of treatment effects.

Another major limitation of the present studies was small sample size coupled with a lack of sample size justification, power description, or effect estimates. Only 43% of studies that found significant effects of treatment on IP outcomes reported effect sizes, with sizes ranging from small to large. Given that samples ranged in size from n = 6 to n = 189 (M = 58.2 ± 46.6; Mdn = 40.5), replications of studies with larger samples are needed, and many of the existing findings should be considered only preliminary in nature. The applicability of the findings is also limited by the populations studied, which were largely comprised of young males. The overrepresentation of males is particularly notable given that females are at increased risk for PTSD (Blanco et al., 2018) and differentially express PTSD symptoms (Murphy et al., 2019) potentially due to the influence of gender roles, hormone levels, and sex-specific genotypes (Christiansen & Berke, 2020). However, the identification of PTSD IPs and their relevant brain-based mechanisms provide an attractive approach for exploring sex effects on PTSD treatment efficacy in future studies. Additionally, less than half of the included studies reported race/ethnicity (42%), an important limitation given the higher prevalence of PTSD and lower rates of treatment use among Black/African Americans compared with White Americans (McClendon et al., 2020). Studies also reported high rates of comorbidity, and no studies tested moderators of treatment response.

Conclusions

Future research is warranted to address the aforementioned limitations and to clarify the responsivity of IPs to behavioral and pharmacological treatments. First, only two pharmacological treatment studies using IP outcomes were published in the last 10 years. Additional investigations may elucidate the efficacy of pharmacological treatments on specific functional domains. Second, research concurrently examining multiple IP categories is needed to better clarify how IPs relate to each other. Third, while most symptom clusters seem to map on to IP outcomes, little progress has been made in experimentally modeling the avoidance, shame, guilt, and dissociation aspects of PTSD. Finally, this review was limited to evaluating IP sensitivity to treatments that currently receive strong or moderate recommendations by CPGs. Given that CPGs are based on reviews of the treatment literature, which largely use DSM-based symptom scores as primary outcome measures of treatment response, future reviews should aim to identify alternate PTSD treatment options by characterizing IP sensitivity to treatments that do not currently receive CPG recommendations.

The small number of studies included in this review illustrates that the literature examining PTSD treatment efficacy on IPs is sparse and underrepresented relative to analogous studies using clinical symptom-based outcomes. The scarcity of research combined with the heterogeneity of study methodologies and significant study limitations makes it difficult to draw strong conclusions regarding IP sensitivity to treatment. However, with these limitations in mind, the existing body of research incorporating this functional framework shows potential for the IP approach to improve the translation of treatment efficacy from clinical trials to clinical settings. Encompassing diverse neurobiological constructs, IPs allow for replicable, multidimensional analysis of treatment effects on basic domains of functioning and present new ways of advancing treatment development. For example, an IP measure of exaggerated fear response associated with elevated SCR could serve as a biologically informative diagnostic tool, potentially signaling later symptomatology, illness course, and functional outcomes. Moreover, biologically homogenous IP subgroups, like those who predominantly suffer from sleep disturbances, for example, will be rich targets for treatment studies where knowledge of brain–behavior relationship will move us toward a more personalized approach to medicine.

References

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