Review

Biological Psychiatry

Emerging Domain-Based Treatments for Pediatric Anxiety Disorders

Amit Lazarov and Yair Bar-Haim

ABSTRACT

Domain-specific cognitive training treatments for pediatric anxiety disorders rely on accurate and reliable identification of specific underlying deficits and biases in neurocognitive functions. Once identified, such biases can serve as specific targets for therapeutic intervention. Clinical translations typically reflect mechanized training protocols designed to rectify the identified biases. Here, we review and synthesize research on key neurocognitive processes that emerge as potential targets for specialized cognitive training interventions in pediatric anxiety disorders in the domains of attention, interpretation, error monitoring, working memory, and fear learning. For each domain, we describe the current status of target establishment (i.e., an association between pediatric anxiety and a specific neurocognitive process), and then review extant translational efforts regarding these targets and the evidence supporting their clinical utility in youths. We then localize each of the domains within the path leading to efficacious, evidence-supported treatments for pediatric anxiety, providing a roadmap for future research. The review indicates that specific cognitive targets in pediatric anxiety have been established in all the reviewed domains except for fear learning, where a clear target is yet to be elucidated. In contrast, evidence for clinical efficacy emerged only in the threat-related attention domain, with some preliminary findings in the domains of interpretation and working memory. The path to clinical translation in the domain of error monitoring is yet unclear. Implications and potential avenues for future research and translation are discussed.

https://doi.org/10.1016/j.biopsych.2020.08.030

The prevalence of anxiety disorders in children and adolescents (hereafter referred to as youth) is estimated at 10% to 32% (1). Left untreated, anxiety disorders often persist to adulthood, manifesting in additional comorbidity (2,3). Although the need for psychological services is vast, only a small portion of youth in need of treatment receive it (4). Moreover, despite effective treatments for pediatric anxiety (e.g., cognitive behavioral therapy [CBT] or selective serotonin reuptake inhibitors), many patients do not remit and others relapse (5–7). Hence, a pressing call for novel interventions for pediatric anxiety disorders had been voiced (1,8).

A vigorous response to such calls comes from research on anxiety-related cognitive biases and their modification via mechanized training protocols. Akin to the Research Domain Criteria approach (7,9,10), it has been suggested that targeting the well-defined neurocognitive mechanisms underlying pediatric anxiety may lead to specialized cognitive bias modification (CBM) treatments targeting dysfunctional domains associated with the disorder. As with any therapeutic approach, CBM has advantages and disadvantages. The advantages include the protocols' noninvasive nature, strong tie to cognitive-neuroscience, and strong dissemination potential. The disadvantages include small-to-medium effect sizes and difficulties establishing far-transfer effects. In this review, we describe progress in 1) identification of the specific underlying neurocognitive mechanisms of pediatric anxiety, 2) their establishment as viable targets for intervention, and 3) the translation and testing of their efficacy in clinical trials.

A mandatory first step in developing mechanistic treatments entails reliable identification of biases or deficits in basic neurocognitive functions related to the disorder (i.e., a group difference between disorder-positive and healthy participants or a correlation between a cognitive mechanism and symptoms). Achieving this mandatory step justifies clinical translation efforts designed to rectify the identified bias. Next, research must examine whether the devised translation indeed engages and modifies the targeted neurocognitive function. Proceeding to clinical efficacy studies with no clear target or without proof of target engagement hinders the ability to advance clinical translation (11–14). Finally, studies examining the effects of such mechanistic changes on symptomatic behavior can ensue; if they are successful, clinical utility may be established in randomized controlled trials (RCTs) (11).

Here, we review the extant research on key neurocognitive processes emerging as potential targets for specialized training interventions in pediatric anxiety. These include the domains of attention, interpretation, error monitoring, working memory, and fear learning. For each domain, we describe the current status of target establishment, and then we review the extant translational efforts concerning these targets and the evidence supporting their clinical utility. We also discuss age-related information on the developmental trajectory of these targets and their association with anxiety. Delineating the developmental trajectory of specific biases is important for the identification of the relevant time frames for intervention.

ISSN: 0006-3223

Unfortunately, knowledge about the developmental trajectories of cognitive biases is limited. Still, when such knowledge exists we refer to it in our discussion.

ATTENTION

Figure 1 illustrates key findings along the path from target establishment to clinical translation. Selective attentional processing of threat-related information has a key role in the etiology and maintenance of anxiety disorders (15–18). Despite concerns associated with the reliability of some of the attention bias scores derived from some of the applied measurement tasks (19), attention-related biases have been widely documented in anxious adults through the use of diverse reaction-time and eye-tracking tasks, suggesting a medium effect size for the association between threat-related attention and anxiety [for meta-analyses, see (20,21)]. Although less research has been conducted with youth, an international study of 1291 participants (22) and a meta-analysis of reaction-time–based measurements of threat-related attention bias (23) indicate the same threat vigilance pattern in anxious youth as in adults but with a smaller effect size. In contrast, a meta-analysis of eye-tracking studies (24) has indicated that anxious youth dwell less on threat versus neutral stimuli than nonanxious control youths, suggesting threat avoidance rather than threat vigilance in pediatric anxiety. Such discrepancies call for research into the specific mechanisms underlying the association between threat-related attention and anxiety in different modalities.

Although the link between attention bias and anxious behavior has been established in children as young as 2 to 5 years of age (25,26), research has also shown that the difference in threat bias between anxious and nonanxious youth increases with age (23). Three models of how threat-related attention biases may develop over time and link to anxiety have been proposed (27). One model posits that development plays no role in attentional threat biases and that individuals who are initially biased maintain that bias over time. An alternative model predicts that attention biases for threat are normative early in life, diminish across development, and persist only in those who develop anxiety disorders. A third model predicts that attentional biases are caused by specific events and therefore are the result of direct experiences. The developmental trajectory of threat-related attention biases bears consequences for the relevant time frame for intervention. Extant data provide minimal evidence of developmental

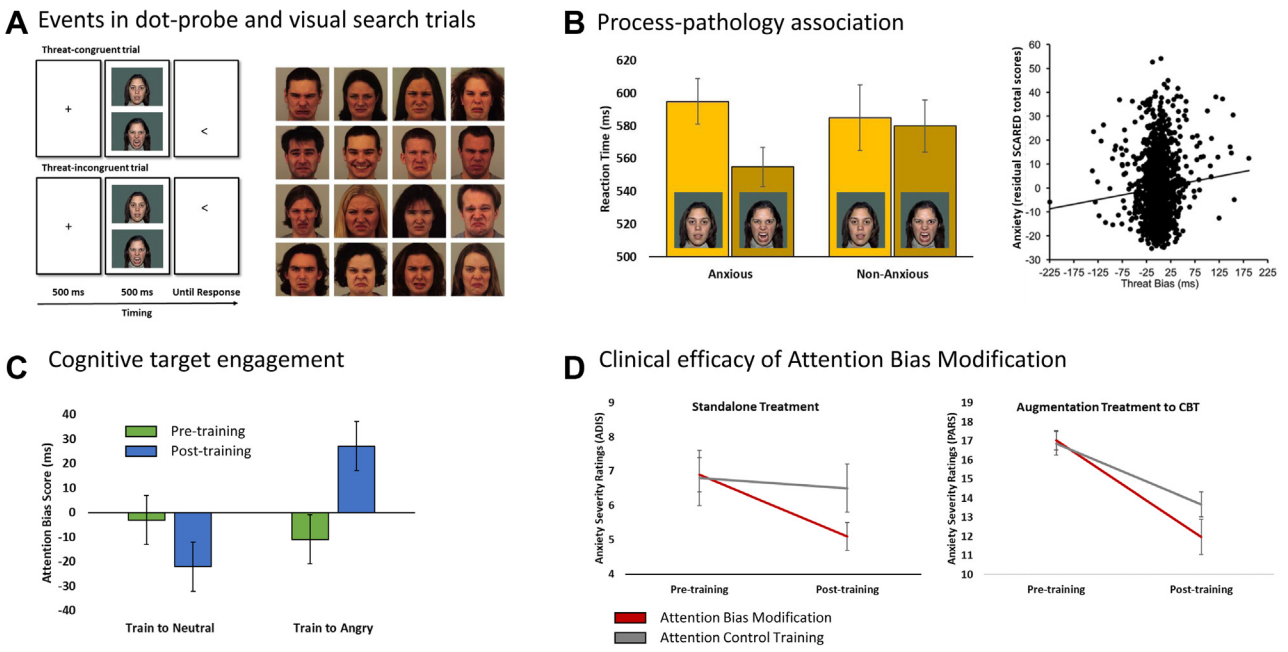

Figure 1. Threat-related attention in youth, from target establishment through efficacy testing: illustration of key findings concerning threat-related attention bias in anxiety. **(A)** Attention measurement and training tasks. In a dot-probe task (left), the trials begin with a fixation and end with a cue probe (e.g., arrowhead pointing left or right). These events are separated by a stimulus pair consisting of one threat-related stimulus (e.g., angry face) and one neutral stimulus (e.g., neutral face). Attention bias is calculated by subtracting threat congruent trials from threat incongruent trials. The indices of attention bias variability can also be calculated [e.g., (132,133)]. The training protocols present cue probes with higher probability at the location of the intended training direction (e.g., 80% at neutral location), with anywhere between 100 and 500 trials per-session and 1 to 20 sessions. Most typical ABM protocols deliver 8 sessions, twice a week, of 160 trials per session. In a visual search task (right), the trials present a picture grid with 15 rejecting and 1 accepting face. In training protocols the participants are instructed to identify the smiling face as quickly as possible [see (134)]. **(B)** Meta-analyses [e.g., (21,23)] and a large international sample [scatterplot adapted from (22)] establish a medium effect size association between attentional threat bias and anxiety in youth. **(C)** Summary of results [from (135)] showing that bias training using the dot-probe task successfully induced training-congruent attention biases in healthy nonanxious youth [for similar results in adults, see (136)]. **(D)** Left panel: Summary of results [from (32)] showing that stand-alone attention bias modification training successfully reduces anxiety severity (ADIS; Anxiety Disorders Interview Schedule) relative to attention control training in youth. Right panel: Summary of results [from (40)], showing augmentation of cognitive behavior therapy (CBT) by attention bias modification relative to attention control training (PARS; Pediatric Anxiety Rating Scale).

variation in the attentional threat bias–anxiety association (22,28). Therefore, the model suggesting a limited role for development currently receives the strongest support, rendering threat-related attention biases viable targets for intervention in anxious youth of all ages.

Attention bias modification (ABM) treatments use training protocols to modify biased attentional patterns in anxious patients (29,30). Seven RCTs of ABM as a stand-alone treatment for clinically anxious youth (age range: 6 to 18 years) have been reported to date (31–37). The combined efficacy of these studies indicates that as in adults (38,39), ABM in youth has a medium effect size on symptom reduction. No heterogeneity was detected among the studies, and no study was identified as an outlier. Only one of these RCTs (31) directly tested age as a moderator of treatment outcome, noting that relative to younger youth, older youth benefited more from ABM.

ABM has also been used as an adjuvant to CBT for anxious youth in three RCTs, yielding mixed results. White *et al.* (40) found that ABM augmented CBT relative to a placebo ABM condition. Shechner *et al.* (41), reported that both active and placebo ABM yielded greater reductions in clinician-rated anxiety than CBT alone. And relative to placebo, active ABM yielded greater reductions in self- and parent-rated anxiety. Finally, Salum *et al.* (42) reported significant symptom improvements in both the active and placebo conditions with no difference between them.

Examining ABM in treatment-resistant youth, continuing to meet diagnostic criteria for an anxiety disorder after completing CBT (43), showed that the youth in both the ABM and the control conditions showed significant decreases in anxiety severity. Despite the mechanistically unclear nature of this result, it is worth noting that 50% of the youth who continued to meet criteria for a primary anxiety disorder after CBT showed diagnostic recovery after ABM (43). In another open trial of stepped-care treatment in anxious youth, the participants were first treated with ABM and then given the option to either stop or step up to CBT (44). The participants showed significant reductions in anxiety severity at each step. Clinical global impressions indicated that after ABM, 38.4% of the youth were rated as very much or much improved, 37.5% as minimally improved, 16.1% as no change, and 8.0% as minimally worse. Across the entire protocol, 69% of the youth were much improved, and 60% opted not to step up treatment after ABM. Compared with CBT only, the ABM-first stepped-care approach offered a nearly 50% reduction in clinician time (44), supporting the promise of initiating interventions for pediatric anxiety with a low-intensity treatment (e.g., ABM) and then stepping up to higher intensity treatments as needed.

In conclusion, the extant evidence supports threat-related attention biases as a relevant mechanism in pediatric anxiety and as a viable target for intervention. Evidence from RCTs suggests that ABM is efficacious in reducing symptoms in youth with anxiety disorders when applied as a stand-alone treatment, and that it shows preliminary promise as an adjuvant treatment to CBT. Importantly, first-generation ABM training protocols relied on manual reaction times as the training vehicle, which currently seem to produce only small to medium clinical effects, and only when delivered in person but not at home (38). Applications of novel, possibly more potent second-generation eye-tracking–based ABM interventions are starting to emerge (45–49). Their efficacy and clinical utility will be determined in the coming years. In the same vein, a more detailed focus on specific characteristics of attention (e.g., bias toward and away from threat, or attentional engagement and disengagement) may improve the utility of threat bias measurement and modification in clinical practice (50).

INTERPRETATION

The tendency to interpret ambiguous information as negative or threatening has also been assigned a role in the onset and maintenance of anxiety disorders (51–53). Interpretation biases are commonly assessed by presenting the participants with ambiguous scenarios, which they are asked to disambiguate (54,55). A negative bias is inferred when an individual more frequently disambiguates the scenarios in a negative rather than neutral or positive manner (4,54,56–58). Such measurements can be applied with different levels of content specificity by adapting the presented scenarios to the relevant disorder being studied (54,59). Another approach to assessment is through the presentation of homophones entailing either threat or nonthreat interpretation (e.g., morning/mourning) and asking the participants to apply them in a sentence (60). Usage favoring the threat meaning is taken to reflect biased interpretation (4,54).

Evidence from a meta-analysis of 77 studies indicates that anxious youth show a negative interpretation bias with a medium effect size [mean effect size 0.63 (54)], marking interpretation biases a viable target for CBM of interpretation (CBM-I) in pediatric anxiety. As with threat-related attention, the association between negative interpretation bias and anxiety increases with age (54), and with the specificity of the scenarios used to the anxiety disorder examined (54,59,61).

CBM-I protocols are designed to modify the patients' negative interpretations by training them to interpret ambiguous stimuli in a more positive or benign manner (4). CBM-I typically creates a contingency between the desired interpretive choice and performance on a subsequent seemingly unrelated task. For example, interpreting the homophone "dying/dyeing" as meaning "coloring" rather than "the termination of life" could enhance a subsequent completion of "CO_O_" as COLOR (4). With practice, patients are expected to automatically favor one interpretive style over the other, overriding automatic negative interpretational tendencies and reducing anxiety symptoms (8,55,58).

Efficacy research on CBM-I among youth has been limited, with most studies examining either healthy participants or analog samples. The findings suggest moderate but significant effect sizes for modifying biased interpretation patterns (8,55,58,62). However, the findings concerning the efficacy of CBM-I in reducing anxiety symptoms have been mixed (58,62). A recent meta-analysis of 26 studies among 1786 youth indicated medium effect sizes on negative and positive interpretations (0.70 and 0.52, respectively) and a small but clinically insignificant effect on anxiety (8).

It has been speculated that CBM-I may yield stronger effects in adolescents relative to adults because attributional styles are more malleable during adolescence (8,63–65). In contrast, CBM-I may be less effective in younger children because their interpretational capacities are not yet sufficiently

mature (8,66). However, these assertions have received only limited support (8).

In conclusion, the findings of CBM-I for anxious youth are mixed. Most studies report effective change in interpretation (the targeted mechanism) but no evidence for change in symptoms (4,8,55,58,62). Such results are disconcerting because they suggest that even with clear target engagement, a change in symptoms does not necessarily follow, which casts serious doubt on the causal effect of interpretation change on anxious symptomology among youth. This results pattern may be related to the fact that interpretation bias is usually measured using the same tasks used for training (8,62). Hence, post-training bias reduction may simply reflect near-transfer changes on the trained tasks, with no corresponding changes in "real-world" interpretation patterns. Adopting more ecological training or measurement procedures is advised (45). Also, as extant CBM-I research has mainly used nonclinical samples, it remains to be seen whether current CBM-I interventions are efficacious for clinical pediatric anxiety.

ERROR MONITORING AND ERROR-RELATED NEGATIVITY

Error-related negativity (ERN) is an event-related brain potential associated with error commission in choice reaction-time performance (67,68). It is a response-locked waveform extracted from an electroencephalogram, computed as the difference between error trials and correct trials. The onset of the ERN occurs with erroneous button press and peaks around 100 ms later, with maximal amplitude over frontocentral scalp locations. Neuroimaging, neurophysiological, and lesion studies have indicated that the ERN is most likely generated in the anterior cingulate cortex, a key structure associated with cognitive control functions, pain processing, punishment, and negative affect (69–72).

Because errors are a salient marker of performance breakdown (73), they are experienced as distressing and aversive. It has been proposed that anxious people are highly sensitive to committing errors and excessively contemplate their potential consequences (74,75). The ERN is thought to reflect a trait-like individual difference in threat sensitivity that drives vigilance and defensive responses (76). The ERN remains largely unchanged after successful treatment (77–80), a finding that is consonant with theories of stable and early-emerging individual differences in temperamental styles such as behavioral inhibition (81) and related forms of dispositional anxiety (82,83), making it a potential biomarker for anxiety disorders in youth.

The ERN is larger among youth with anxiety disorders (77,84,85), and behavioral inhibition in early childhood predicts a larger ERN in adolescence (86). The ERN amplitude moderates the relation between behavioral inhibition and the development of anxiety disorders in adolescence (86–88). These data suggest that increased error-related brain activity may help delineate anxious versus nonanxious trajectories across development. However, its resistance to change, even with therapy, casts doubt on its clinical utility, and the exact nature of the relation between anxiety and error monitoring is yet unclear. Only a few attempts (all in nonselected adult populations) have been made to target ERN reduction, which we will now review.

Meyer *et al.* (89) applied a computerized intervention—Treating the ERN (TERN)—to undergraduate participants and compared their ERN to participants who were assigned to a control condition. TERN is a 1-hour protocol that includes information provision and quizzes about the nature of, implications of, and coping with making mistakes. The participants are introduced to the concept of "error sensitivity," and they take a quiz to determine the severity of their own error sensitivity. The participants are then taught about common faulty beliefs held by people with elevated error sensitivity and how to deal with them. Finally, TERN participants are taught about safety behaviors and how those behaviors could maintain anxiety and error sensitivity. The participants then create a plan for fading their use of safety behaviors. The results suggested that TERN reduced the ERN, particularly among individuals with an increased baseline ERN. This provides a preliminary proof-of-concept that the ERN may be modulated by applying mechanized CBT-like protocols. The clinical utility of such interventions in anxious youth is yet unclear.

Another attempt at ERN modulation has been via ABM. It has been hypothesized that an association exists between the malleability of negative attention bias and the ERN amplitude, and that successful intervention in the former may lead to reductions in the latter. Indeed, Nelson *et al.* (90) found that the ERN was smaller among study participants who had completed ABM training before ERN measurement relative to participants who completed ABM training after ERN measurement. Furthermore, greater attentional disengagement from negative stimuli during ABM training was associated with a smaller ERN, suggesting an association between malleability of negative attention bias and ERN amplitude. In a different study, ERN was measured before and after either ABM training or a control task (91). The ERN decreased from before and after training among the participants who had completed ABM; no ERN change was noted in the participants who had completed the control task. These results also suggest that ABM training reduces the neural correlates of error monitoring (91), but again, their relation to symptom reduction in pediatric anxiety is still unknown.

In conclusion, extant evidence from adults and youth supports the notion that hypersensitivity to error commission as indexed by enhanced ERN amplitude may be a stable biomarker of anxiety disorders and could therefore potentially also serve as a target for intervention. Three studies in nonanxious adults have indicated that the ERN may be malleable to focused intervention. It remains to be seen whether 1) such interventions also effectively reduce the ERN in anxious youth and 2) ERN reduction is associated with symptom reduction in anxious patients.

WORKING MEMORY

Working memory (WM) is broadly defined as the ability to temporarily retain a limited amount of information in mind, work with it as needed, and respond based on its internal representation (92). It is considered a core cognitive function in the service of more complex executive functions (93–95), and it has been included as a relevant component in different cognitive models of anxiety (94,96–99).

Individual differences in WM capacity in anxiety are measured using a wide range of tasks, including simple span measures, which require the storage and rehearsal of the to-be-remembered items; complex span measures, in which the presentation of the to-be-remembered items is interwoven with a secondary demanding task; and dynamic tasks, most popular among anxiety researchers, during which the participants need to continuously update a to-be-remembered item list based on a continuous stream of presented items (94).

Although most theories suggest that anxiety is associated with impaired performance on WM tasks, they diverge on the hypothesized causal direction of this relation (94). Some theories suggest that anxiety interferes with WM (96,100,101); other theories suggest WM as a causal factor in anxiety (97,99,102). However, extant evidence unequivocally indicates that WM performance is impaired by anxiety induction, with only minimal support for the opposite causal direction (94).

Despite such theoretical formulations and rather extensive research on WM–anxiety associations in adults, research in youth has been relatively scarce. A meta-analysis (94) indicated impaired WM function among anxious relative to nonanxious youth, with a small effect size. Age emerged as a nonsignificant moderator, but the developmental course of anxiety-related impairments in WM was not studied directly (94). Given that most studies and theory suggest that anxiety impacts WM function and not the other way around, it is not entirely clear whether WM constitutes a viable and direct target for mechanized training protocols.

Mostly unrelated to anxiety, numerous WM training programs have been developed, including direct engagement of WM functions, personally adjusted increases in difficulty level, numerous trials, and multiple sessions conducted over several weeks [for reviews, see (103–105)]. Although research among normally developing youth has provided evidence for training-induced improvements in WM, these improvements were mostly restricted to gains on the trained tasks themselves (95), with limited durability of training effects and no transfer to novel WM tasks or generalization to "real-world" situations (95,106–108).

Despite the preliminary nature of the evidence in relation to anxiety, some studies have applied WM training protocols among anxious youth. Roughan *et al.* (109) found WM training to reduce anxiety among children with school-related difficulties. In a different study that examined the effects of WM training relative to CBT among adolescents with elevated anxiety and low attention control, Hadwin *et al.* (110) found that WM training and CBT had similar reductions in anxiety symptoms after treatment, which were maintained at a 3-month follow-up evaluation. Schweizer *et al.* (111) investigated the effects of an affective WM training compared with a placebo control in treatment-seeking adolescents with post-traumatic stress disorder and found that relative to the control condition, affective WM training led to a greater increase in cognitive control and to a greater reduction in symptoms. Finally, Beloe *et al.* (112) examined the effects of WM training on anxiety in a nonselected sample of adolescents; the results suggested that anxiety decreased after training relative to a control condition.

Taken together, these results offer a proof-of-concept for use of WM training as an intervention for anxious youth. However, larger-scale replications in formal RCTs with additional control arms are needed to clarify the clinical potential of WM training for pediatric anxiety.

FEAR LEARNING AND RELATED PROCESSES

Theoretical accounts assign a key role to abnormalities in fear learning and related processes in anxiety disorders (113,114). The complementary suggestion of targeting aberrant fear processes in the treatment of anxiety disorders dates back more than 50 years, when basic learning principles were first translated to the treatment of fear; systematic exposure to feared stimuli has become an integral module of behavior-focused psychotherapies (115,116). In science, fear conditioning and extinction learning paradigms have been commonly used to elucidate the underlying behavioral, neural, and cognitive aspects of fear learning (117,118). It has been suggested that the capacity to discriminate threat from safety, a critical distinction in fear learning, matures with age and is characterized by a maturational shift around the age of 10 years (119,120). Developmental delays in this discrimination capacity are thought to contribute to persistent anxiety (121–123).

In a standard differential conditioning paradigm—the most frequently used paradigm in human studies—two distinct phases, fear acquisition and fear extinction, are applied, with fear reactions (e.g., autonomic activity, neural activation, and self-reported fear) being continuously monitored. During fear acquisition, an unconditioned stimulus (US) (e.g., electrical shock) is repeatedly paired with a neutral conditioned stimulus (CS+) (e.g., a blue flower), while a second stimulus is never paired with the US (CS−) (e.g., a red flower). As a result, the once-neutral stimulus now elicits the fear response even without US presentation. During extinction, the original CS+ is repeatedly presented without the US, with a successful extinction evident when the fear response to the CS+ gradually declines with increased repetitions (117,118,124). Some paradigms also explore the processes of fear generalization, namely, broadening of the fear response to stimuli sharing similar characteristics with the CS+. During the acquisition phase, several variants ranging between CS+ and CS− are presented (e.g., flowers ranging in color between blue and red). Fear generalization is quantified as a quadratic pattern of the fear response, with higher fear elicited by the stimuli most similar to the CS+ and fear decreasing as similarity declines (124).

Extensive fear learning research in adults suggests that reduced fear extinction (118) and overgeneralization (125) are associated with anxiety; therefore, both emerge as viable targets for therapeutic intervention in anxious adults. Indeed, these two targets are specifically treated using dedicated modules in standard CBT for anxiety disorders. In marked contrast, the results of fear learning in youth have been highly inconsistent. A meta-analysis of fear conditioning and extinction among youth (117) revealed increased fear response to both CS+ and CS− during both acquisition and extinction in anxious patients vs. nonanxious controls subjects. Given these results, no group differences emerged for discrimination learning either. The potential moderation effect of age was not explored. Hence, targets for interventions related to fear

acquisition and extinction in pediatric anxiety are currently not established.

Regarding overgeneralization of conditioned fear, research in healthy youth suggests that while 11- to 13-year-olds demonstrate the typical pattern of generalization observed in adults, 8- to 10-year-olds do not (120). To our knowledge the only study to examine fear overgeneralization among anxious youth found that patients displayed wider generalization when compared with nonanxious control subjects. Here too, overgeneralization was more prominent in adolescents relative to younger children (126).

Studies specifically targeting one of the previously outlined fear processes in pediatric anxiety that apply a mechanized training protocol have yet to emerge, possibly due to lack of a clear therapeutic target. A proof-of-concept study has shown that perceptual discrimination training can reduce fear overgeneralization among healthy adults (127) and typically developing children (128). In these studies, the participants who were trained to increase their perceptual discrimination exhibited less fear overgeneralization relative to placebo training and no-training conditions. However, without application in clinically anxious youth, no conclusions can be drawn in relation to pediatric anxiety.

In conclusion, although fear extinction and fear overgeneralization seem to be viable treatment targets in anxious adults, this has not been the case for pediatric anxiety. The development of technology-based interventions for pediatric anxiety in the realm of fear learning appears premature because research is still struggling to establish reliable treatment targets. A research focus on fear learning processes in pediatric anxiety could benefit from a developmental approach that elucidates the maturational processes in these systems (126). Such a focus may give rise to specific therapeutic targets emerging with development.

CONCLUSIONS

Recent years have witnessed a steady increase in the development and testing of technology-based neurocognitive training protocols for pediatric anxiety, an increase that is tightly related to advances in technology and computational capacity. This continuous evolution of cognitive training techniques will hopefully create new evidence-supported treatments. Although the current research and clinical translations are promising, first-generation cognitive training protocols are still short of the overarching ambition of technology-aided cognitive interventions that are highly efficacious, easily disseminated, and available at low cost. Importantly, although some first-generation training protocols are clinically useful, the field of CBM is still in its early stages. With growing research, experimental innovation, and technological advancement, more potent second-generation protocols of cognitive training are just around the corner.

Over the next decade it will become clearer which of the cognitive targets identified for pediatric anxiety can be effectively modified to reduce symptoms, what are the most efficacious and cost-effective training procedures, and which training protocols could be integrated into a clinician's toolbox along with extant psychosocial and pharmacological treatments. Technology changes the way people interact, and by extrapolation the way they consume psychological services. CBM is at the forefront of these emerging trends.

Insight into anxiety-related cognitive biases and their modification in pediatric anxiety has considerably grown over the last 3 decades (21,29). In this review we localized each of the reviewed neurocognitive domains along the path leading to efficacious, evidence-supported, mechanistic training treatments for pediatric anxiety. As can be seen in Figure 2, progress has varied across domains, with some domains knocking on the doors of established clinical efficacy in RCTs (e.g., attention) whereas others still are working to establish process-pathology associations (e.g., fear learning). The review also highlights the need to expand research on the developmental trajectories characterizing each of the reviewed cognitive domains, their relation to pediatric anxiety, and the relevant time frames for efficacious modification.

Another aspect highlighted in this review is the currently limited information on specificity in cognitive training efficacy—that is, whether mechanistic training protocols are more useful for certain anxiety disorders than for others, or whether one type of training is more efficacious than another for a specific disorder. Extant research comparing treatment efficacy across diagnostic categories in youth is scarce. Most studies in youth either use subclinical samples (112,128,129) or lump together participants with several anxiety diagnoses (41,43,46,130,131). Establishment of reliable methods to assess and modify

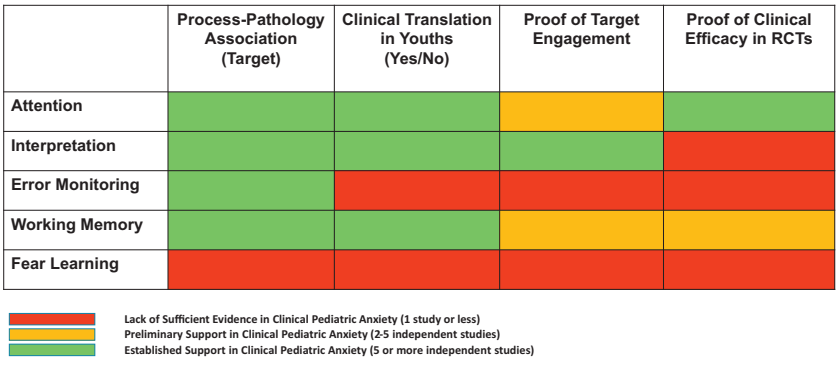

Figure 2. Domain-specific training targets and clinical translation in pediatric anxiety randomized controlled trials (RCTs). Red indicates a lack of sufficient evidence in clinical pediatric anxiety (one study or less). Yellow indicates preliminary support in clinical pediatric anxiety (two to five independent studies). Green indicates established support in clinical pediatric anxiety (five or more independent studies).

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cognitive biases in each of the relevant domains is key for advancement on specificity. Creating age-related performance norms, to which the performance of pediatric patients could be compared, could highlight the relevance of specific training protocols to specific disorders and age groups and should be one of the primary goals for pediatric CBM research.

Major advances in mechanized, science-based treatments for pediatric anxiety are expected in the upcoming years, with a steady increase in the development and testing of new technology-driven cognitive training protocols (4). Such advances crucially depend on rigorous research and application methods and on the formation of developmental norms.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was partly supported by the Israel Science Foundation (Grant No. 1811/17 to [YB-H]).

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

School of Psychological Sciences and Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel.

Address correspondence to Yair Bar-Haim, Ph.D., at yair1@tauex.tau.ac.il, or Amit Lazarov, Ph.D., at amitlaza@tauex.tau.ac.il.

Received May 2, 2020; revised and accepted Aug 19, 2020.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2020.08.030.

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