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CHILD AND DEVELOPMENTAL PSYCHIATRY (K FITZGERALD, SECTION EDITOR)

Reducing Pediatric Anxiety through Training: an Integrative Neurocognitive Approach

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Abstract
Purpose of Review Neurocognitive interventions that target specific cognitive mechanisms underlying anxiety symptoms (e.g., attention bias to threat, negatively biased interpretations) have been applied to youth samples. Here, we review the current attention bias modification (ABM) and cognitive bias modification (CBM) literature together and discuss approaches to develop additional neurocognitive interventions for anxious youth.
Recent Findings In youth, ABM which trains attention away from threat typically does not change threat bias, but yields anxiety symptom reductions. However, few ABM studies show enhanced anxiety-related gains for active ABM compared to placebo training (i.e., attention directed equally to threat and neutral). Attention training towards positive information also reduces anxiety symptoms, but effects on behavior are mixed. In contrast to ABM, CBM in youth samples usually changes interpretations, but has little impact on anxiety symptoms. Furthermore, neurocognitive approaches for pediatric anxiety can be extended from adult anxiety treatments, adapted from other forms of psychopathology, or created to target other cognitive processing deficits in anxiety using novel methodology.
Summary More work, especially in clinical samples, is needed. To apply neurocognitive interventions in youth and to elucidate the mechanisms underlying changes in targeted behavior and anxiety, the development of cognitive function and the underlying neural circuitry must be a key factor when designing training programs. Future research is needed to refine, investigate, and create neurocognitive interventions for anxiety, especially in developmental samples.

Keywords Development · Treatment · Attention bias modification · Cognitive bias modification · Reconsolidation update mechanisms · Discrimination · Approach-avoidance · Generalization · Flexibility

Introduction

Treating anxiety disorders in developmental populations can be challenging; therefore, alternate treatment approaches, such as neurocognitive interventions, are needed. Anxiety disorders are commonly treated with exposure-based cognitive behavioral therapy (CBT) or psychopharmacological intervention using selective serotonin reuptake inhibitors (SSRIs) [1, 2]. One clinical challenge for anxiety disorders is the variability in treatment response. While first-line treatments for anxiety disorders are effective for some youth, many remain symptomatic following these treatments [3, 4] and approximately 20–35% of youth show no response [5, 6]. Combination treatments facilitate symptom reduction relative to CBT or pharmacological interventions alone [6], suggesting either the individual treatments work synergistically when combined or operate on different mechanisms of action to influence anxiety levels. Although combination treatments involving

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medications may improve treatment response, parents often hesitate to accept pharmacological interventions and favor psychological treatments alone [7–11]. Moreover, the potential for SSRIs to affect human development remains poorly understood [12], leading parents to fear the possibility of long-term, negative consequences of medication therapies. On the other hand, CBT-based interventions require experienced clinicians and may be both time-consuming and costly [13, 14], limiting access to this first-line, non-medication treatment approach. As a result, alternative strategies are needed to improve treatment options, access, and outcomes. Neurocognitive approaches that specifically target anxiety-related deficits in information processing may be able to address such issues.

To improve treatment response, different neurocognitive approaches aimed at ameliorating anxiety symptoms have been tested in youth. In this review, we will briefly summarize anxiety-related perturbations in different cognitive domains, which may serve as treatment targets. Next, we will review the current work on the most commonly used neurocognitive strategies tested in youth samples. Here, we will focus on attention bias modification (ABM), which aims to alter attention-related threat bias, and cognitive bias modification (CBM), which aims to alter threat-related interpretations of ambiguous situations. Next, we will propose several ways to target other perturbations of cognitive processing that may underlie pediatric anxiety (Fig. 1). First, neurocognitive approaches used to treat adult anxiety may be extended to youth. Second, neurocognitive approaches applied to other mental health disorders (e.g., disruptive mood dysregulation, substance use disorder) may be applied to anxiety disorders. Third, novel neurocognitive approaches may also emerge to target other anxiety-related cognitive mechanisms. Through this exploration, we will provide examples of published work, including reconsolidation update mechanisms targeting extinction learning, discrimination training targeting misattributions, approach/avoidance training targeting behavioral avoidance, as well as studies targeting fear generalization and cognitive flexibility. Finally, while considering the developmental trajectory of cognitive and neural function, we encourage further testing and advancement of developmentally-sensitive neurocognitive interventions to improve treatment outcome for pediatric anxiety.

Anxiety-Related Perturbations in Response to Threat

Like adults, youth with anxiety disorders have threat-related disruptions in multiple aspects of information processing, which may be targeted in neurocognitive interventions. Individuals with anxiety show heightened cognitive, emotional, and behavior responses to fear and threat cues [15], suggesting dysregulation in the bottom-up processing of salient input in the environment. Attention biases to threat have been observed in both rapid attention capture [16, 17] and/or sustained engagement to threat stimuli [18, 19]. Preferential and automatic orientation towards threat can be impairing and can impact cascade of higher-order, cognitive processing of threat (e.g., reappraisal, regulation, and inhibition). In both youth and adult populations, preferential orientation towards threat facilitates worries, physiological arousal, and avoidance behaviors that characterize anxiety [15, 20, 21]. Due to threat-biased attention allocation, anxious youth face difficulties in appraising emotionally salient information, emotion regulation, and the ability to control repetitive negative thinking. For example, anxious youth often report exaggerated fear levels compared to healthy peers [22–24] and negatively interpret ambiguous situations [25–27]. While anxious youth can use adaptive emotion regulation strategies, they appear to be less effective in down-regulating arousal symptoms compared to healthy peers [28]. At the behavioral level, anxious youth also exhibit dysregulated actions or behaviors (i.e., avoidance) in response to anxiety-provoking stimuli [29] and ambiguous stimuli such as neutral facial expressions [30]. Importantly, avoidance of anxiogenic stimuli impairs an individual's ability to behaviorally confront or process information related to such stimuli [31]. As a result, avoidance behavior may reinforce other aberrant cognitive processes (e.g., attention towards threat, negatively biased interpretations). Specifically, avoidance of anxiogenic stimuli is problematic in part because the anxious individual misses the opportunity to regulate and reappraise threatening situations. To most effectively address the cognitive, emotional, and behavioral deficits that occur in association with pediatric anxiety, interventions must target attentional biases towards threat along with impairments of higher-order cognitive processes and dysregulated behavior.

Attention Bias Modification and Cognitive Bias Modification

In this section, we will review the most commonly used neurocognitive strategies aimed to reduce pediatric anxiety symptoms, attention bias modification (ABM) and cognitive bias modification (CBM). Both ABM and CBM (also known as CBM for interpretations or CBM-I) use learning techniques and repeated training to target automatic, implicit processes that bias towards threat and potentiate anxiety. These implicit processes are difficult to access through top-down mechanisms, such as effortful control, although effortful control may play a moderating role [32].

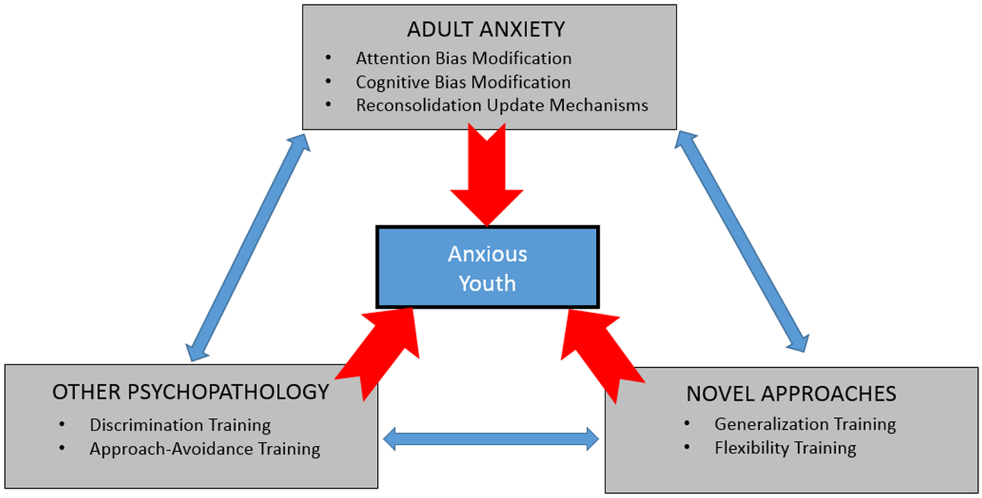

Fig. 1 Strategies for developing and testing neurocognitive interventions for anxious youth

ABM

Since attentional bias towards threat is often observed in individuals with anxiety disorders [33], most ABM attempts to train attention away from threat. Computerized tasks used to assess attention biases, like the dot-probe paradigm, have been modified for this purpose (Fig. 2a). In classic dot-probe tasks, individuals view a threatening and neutral face simultaneously. Following the face pair, subjects must press a button to identify a probe that either appears in the position of the threatening (i.e., congruent trial) or the neutral face (i.e., incongruent trial). Attention allocation to the faces can be measured by reaction times (RT), with attention bias towards threat, or "threat bias," calculated as the RTdifference between conditions (e.g., RTincongruent − RTcongruent). Positive scores (i.e., faster reaction times to congruent trials) reflect a bias towards threat, whereas negative scores (i.e., faster reaction times to incongruent trials) reflect a bias away from threat.

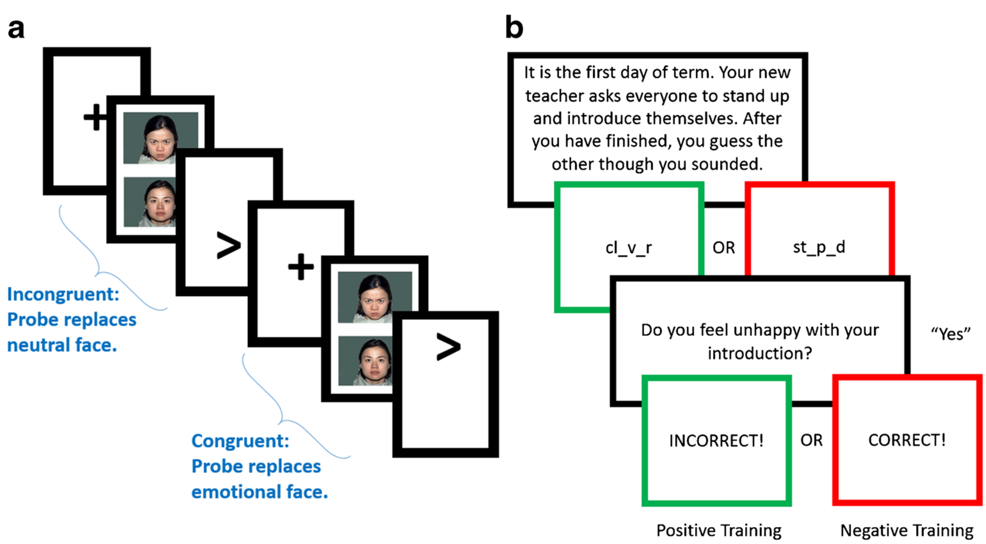

Fig. 2 Attention bias modification and cognitive bias modification tasks. **a** In attention bias modification (ABM), the classic dot-probe task is manipulated to train attention away from threat. In classic dot-probe trials, following a 500-ms fixation cross, two faces (one emotional and the other neutral) appear simultaneously. After 500 ms, the faces are replaced with a single probe located in one of the previous locations. The probe may appear in the location of the neutral face (incongruent trial) or the emotional face (congruent). Reaction time differences denote attention bias scores. Positive scores reflect a bias towards emotion and negative scores reflect a bias away from emotion. In active ABM aimed to train attention *away* from threat, only *incongruent* trials with negative-neutral face pairs are presented. In ABM designed to train attention *towards* positive stimuli, only *congruent* trials with positive-neutral face pairs are presented. In bias assessment and placebo training, both incongruent and congruent trials are presented with equal probability. In all versions, neutral-neutral face pairs are also presented. **b** In cognitive bias modification (CBM), ambiguous situations are resolved according to training type. In one example provided in previous work [34], completed word fragments are either positive in the positive training condition or negative in the negative training condition. A question follows to assess recognition and feedback consistent with the training condition is presented

During active ABM, attention is trained away from threat implicitly by administering incongruent trials only (i.e., eliminating congruent trials). Through repeated incongruent trials, in which the probe always appears in the same position as the preceding neutral face, individuals learn to attend to the neutral faces (i.e., attend away from threat). Most often, active ABM is compared to placebo training. During placebo training, attention is not trained in a particular direction because the probe appears equally likely in the location of threat and neutral faces. However, one study randomized individuals to receive attention training away from threat or towards threat [35]. Based on the Posner attentional cueing task [36], other studies are designed to specifically train attention disengagement [e.g., 37]. In the emotional spatial cueing trials, a single face, either threatening or neutral, is presented to the left/right of a fixation cross. To train attention disengagement, the subsequent target would always appear in the location opposite the threatening face (i.e., invalid trial); whereas, during placebo training, the target would appear in the location of the threatening face (i.e., valid trial) 25% of the time. Standard ABM in adult studies is typically delivered twice weekly for 4 weeks; however, studies vary in the duration of administration from a single session to 16 weeks. In meta-analytic reviews of ABM delivered to healthy, high anxious and clinical samples of anxiety-disordered adults [38], anxiety symptoms were reduced with medium effect size and threat bias was reduced with large effects. Of note, these effects on threat bias were significant if attention training used words; whereas, training involving face stimuli was not as effective at reducing threat bias [38].

ABM generally reduces anxiety in youth, but changes in attention do not usually accompany the symptom reduction. In Table 1, we summarize the ABM studies that have attempted to train attention away from threat according to training type, population, and age. Although similar tables have been presented elsewhere (e.g., [87••]), studies are continuing to emerge in developmental samples. Here, we extend the previous reviews to draw comparisons between ABM [87••] and CBM [88••] in this single review.

Following ABM, anxiety reductions are detected in community [39], high anxious [37] and clinically anxious youth [40–46]. For example, in a multiple baseline study, two clinically affected male children exhibited anxiety symptom reductions to subclinical levels, suggesting ABM can be used clinically [40]. In another study, ABM was effective in reducing symptoms in clinically anxious youth who did not respond to CBT [42].

Of the studies including a control group, some report greater anxiety symptom relief in active ABM than control training conditions [41, 45, 46, 89], as detected in adults [38]. However, other studies show anxiety reduction after both ABM and placebo training conditions [37, 39]. Although group differences may not be detected in some studies, active ABM training reduces stress reactivity to experimental challenges compared to placebo training [35, 37]. Moreover, clinically anxious youth assigned to receive active ABM as a combined treatment with CBT or medication exhibit greater symptom reductions than youth assigned to the placebo training condition [45, 46, 89]. However, not all anxiety measures exhibited these enhanced ABM-related effects (i.e., active ABM > placebo training) [e.g., 89]. In summary, this work suggests that ABM (i.e., training attention away from threat) may resolve anxiety in youth over and above placebo training, although placebo-related reductions in anxiety in some studies raise interesting questions about the potential mechanisms of attention training as a treatment for anxiety.

Additional research is needed to understand the mechanisms of attention training in youth, as highlighted by the observation that ABM-related anxiety reductions are rarely associated with concordant changes in threat bias [e.g., 37, 41, 89]. A number of considerations may help to explain this apparent disconnect; for example, alterations of threat bias may vary depending on training stimulus (e.g., emotional words vs. faces), the type of bias assessment measure (e.g., attentional disengagement) [37], magnitude of threat bias at baseline (i.e., >8 ms) [41], or training duration [89], which have also been considered as moderators in other research [38, 90]. In addition, the dot-probe task is widely recognized to have poor psychometric properties which may contribute to the failure to find significant changes in threat bias [30, 91, 92]. Alternatively, changing threat bias may not be the mechanism that underlies the anxiety reduction in ABM. For example, individuals may learn attention flexibility and/or attention control in the face of threat through repeated exposure to the dot-probe trials, regardless of ABM training condition [93]. This possibility may explain in part why some studies report anxiety reductions in both active and placebo training groups. Future work should consider other underlying mechanisms independent of changing threat bias, as this mechanism may be different in adult and youth samples.

Understanding the neural correlates of ABM in pediatric anxiety samples may help uncover this mechanism. In adults, neuroimaging studies suggest a bottom-up mechanism as ABM influences amygdala activation; however, the direction of change across studies is mixed, with studies reporting both decreased and increased amygdala activation [94–96]. However, other studies suggest a top-down mechanism evidenced by changes in prefrontal cortex (PFC) activation (e.g., dorsolateral PFC, ventrolateral PFC, and subgenual ACC) [95, 97, 98] and late event-related potential (ERP) components (e.g., negative event-related negativity (ERN) [99], P2, P3, and N2 [100]). Although neural investigations of ABM have emerged in adults, only one neuroimaging study has examined the neural changes associated with ABM in youth [45].

Table 1 Attention bias modification (ABM)

Author	Participants	Groups	Training duration	Training task and stimulus type	Behavioral outcome	Anxiety outcome
Training away from threat						
Community samples						
Eldar et al., 2008 [35]	Children 7–12 year olds Normal levels of anxiety (STAIC)	26 Randomized Train away from threat Train towards threat	1 session. 672 trials, presented in 2 blocks	Dot-probe task Angry-neutral face pairs	No change in threat bias was observed in the group trained away from threat, but threat bias increased in group trained towards threat.	NA Stress reactivity: After completing difficult puzzles, stress reactivity was detected in the group trained towards threat group but not the group trained away from threat.
de Voogd[a] et al., 2016 [39]	Adolescents 13–16 year olds	128 ABM 48 placebo	8 sessions, twice a week for 4 weeks. 160 trials per session	Dot-probe task Angry-neutral face pairs	No change in attention bias to threat was observed.	Across groups, anxiety reductions (SCARED) were observed; however, no group differences were detected.
High anxious samples						
Bar-Haim et al., 2011 [37]	Children 10 year olds Chronic high anxiety (top 50% of SCARED scores)	18 active training: 0% threat valid targets: 100% threat invalid targets 17 control training: 25% threat valid: 75% threat invalid targets For neutral faces, both conditions had 25% valid: 75% invalid ratio	1 session. 768 trials, presented in 2 blocks	Emotional-spatial cueing task Angry or neutral faces	After training, active training group exhibited facilitated disengagement (i.e., faster response on invalid angry trials) compared to baseline.	Across both groups, trait anxiety (STAIC) was lower after training. Stress reactivity: After completing difficult puzzles, the control training group exhibited stress reactivity (analog scale). The ABM group reported less anxiety.
Clinically anxious samples						
Cowart & Ollendick, 2011 [40]	Male children 8–9 year olds Diagnosed with social anxiety disorder	2 ABM No control group	Multiple baseline study, 10 biweekly sessions. 160 trials per session	Dot-probe task Angry-neutral face pairs	Both individuals had attentional avoidance at baseline. Post-measures were not obtained.	At post-treatment, both children exhibited subclinical levels of social anxiety disorder (ADIS-P) and self-reported anxiety (SCAS) was reduced.
Eldar et al., 2012 [41]	Children and adolescents 8–14 year olds Diagnosed with anxiety disorder and has ≥8 ms threat bias at baseline	15 active ABM 15 placebo 10 neutral control	4 weekly sessions. 480 trials per session	Dot-probe task For ABM groups, angry-neutral face pairs. For the control group, neutral-neutral face pairs	Threat bias decreased in the active ABM group only.	The average number of symptoms and symptom severity (ADIS) reduced in the active ABM group, but not the control groups. More children remitted in the active (33%) than the placebo group (13%), which both showed more improvement than the neutral condition (0%). Across groups, parent and self-reported anxiety symptoms (SCARED) reduced, but no group differences were noted.
Bechor et al., 2014 [42]	Children 10–13 year olds Diagnosed with an anxiety disorder and non-responsive to 12–14 weeks of CBT	6 active ABM No control group	8 sessions, twice a week for 4 weeks. 160 trials per session	Dot-probe task Angry-neutral face pairs	Across participants, threat bias decreased, but non-significantly.	Child-reported, but not parent-reported, anxiety ratings (MASC and RCMAS-C) decreased with training.
Rozenman et al., 2011 [43]	Youth 10–17 year olds	16 active ABM No control group	12 sessions,	Dot-probe task	No change in attention bias was noted.	Overall, symptoms on PARS and SCARED decreased with training.

Table 1 (continued)

Author	Participants	Groups	Training duration	Training task and stimulus type	Behavioral outcome	Anxiety outcome
	Diagnosed with anxiety disorder and treatment-seeking		3 sessions/week for 4 weeks. 160 trials per session	Angry-neutral and disgust-neutral faces	Bias change was positively associated with clinician-rated symptom change (PARS).	75% of sample remitted with traing.
Shechner et al., 2014 [44]	Youth 7–18 year olds Diagnosed with anxiety disorder and treatment-seeking	18 active ABM + CBT 25 placebo + CBT 20 CBT only	16 weekly sessions. 160 trials per session	Dot-probe task Disgust-neutral face pairs	Attention bias to threat decreased in all groups. No group differences were detected.	Number of anxiety symptoms (ADIS) reduced significantly in both active and placebo + CBT groups and at trend-level for CBT group. All groups showed symptom severity (ADIS) reductions, with larger effects in the ABM groups. The percentage of individuals who had ongoing disorders in the training groups was less (32–33%) compared to CBT only (72%). Self-reported symptoms (SCARED) decreased in the ABM + CBT group only.
White et al., 2017 [45]	Youth 8–17 year olds Diagnosed with anxiety disorder and treatment-seeking	43 active ABM + CBT 42 placebo + CBT	12 weeks, 1 session before and after CBT session. 160 trials per session	Dot-probe task Angry-neutral face pairs	Change in attention bias was not reported. No group difference in attention bias was observed. Neural connectivity: In the placebo group, the relationship between right amygdala-posterior insula connectivity to the threat bias contrast (i.e., incongruent vs. congruent) was negatively correlated with post-treatment PARS. This relationship was absent in the active ABM group.	Both groups exhibited anxiety reduction (PARS), but the active ABM group had greater gains.
Riemann et al., 2013 [46]	13–17 year olds In-patient diagnosed with OCD or anxiety disorders	21 active ABM + CBT 21 placebo + CBT *Note: Both groups received intensive CBT, 2–4.5 h CBT/day for an average of 74.4 days. Most (88%) were also taking medication.	Every weekday. 160 trials per session	Dot-probe task Disgust-neutral face pairs	Pre- and post-treatment attention bias was not assessed	Anxiety (SCARED) and OCD (CY-BOCS-SR) symptoms decreased in both groups; however, greater gains were observed in active ABM/CBT group.
Training towards positive Community samples						
De Voogd[b] et al., 2016 [39]	Children and adolescents 11–18 year olds	140 active ABM 41 placebo	8 sessions, twice a week for 4 weeks. 144 trials per session	Visual search paradigm For active ABM, happy target among angry, fearful or sad face distractors For placebo ABM, flower targets and distractors	In the active group, negative attention bias was reduced. This reduction was larger for individuals completing more sessions.	Across groups, anxiety reductions (SCARED) were noted; however, no group differences emerged. Stress reactivity: in response to Cyberball, stress task, no significant changes were noted.
De Voogd et al., 2014 [47]	Adolescents 13–16 year olds	16 active ABM	Two sessions, separated by 1–7 days.	Visual search paradigm	At baseline, both groups had negative bias. After training, the active	

Table 1 (continued)

Author	Participants	Groups	Training duration	Training task and stimulus type	Behavioral outcome	Anxiety outcome
		16 control (randomized to 1 of 3 control conditions)	144 trials per session	For the active ABM, happy target among angry, fearful or sad faces distractors Control conditions: (1) visual search, search for target flower (2) 1-back task, monitor visual and auditory information (3) Block tapping task, reproduce the locations of emotional pictures	group developed a positive bias. The placebo group exhibited no happy bias.	Anxiety (RCADS) decreased in the active ABM condition, but not in the placebo condition.
Sportel[c] et al., 2013 [50]	Adolescents 13–15 years olds Top quartile of anxiety on RCADS	86 ABM/CBM 84 CBT 70 no treatment	10 weeks of ABM/CBM treatment Twice weekly at-home internet-based sessions (8 ABM, 9 CBM, 3 social-evaluative conditioning) or 10 weeks of CBT For ABM, 450 trials per session For CBM, 60 trials per session For conditioning, 240 trials per session	Dot-probe task Happy-neutral and threatening/social rejection-neutral face or word pairs See Table 2 for CBM details	Happy bias increased in the ABM/CBM condition compared to the control group. No changes in threat bias were noted.	Relative to baseline, anxiety (RCADS) was lower after training, at 6-month follow-up and 12 month follow-up. After 6 months, anxiety (RCADS) decreased more for CBT than no treatment condition. At trend-level, a similar effect was detected for the ABM/CBM group. No group differences were noted after training or 1 year follow-up. Compared to baseline, test anxiety (TAI) decreased with training. CBT group showed stronger test anxiety (TAI) reductions compared to the control condition following training and at 6 months.
Clinically anxious samples						
Waters et al., 2015 [48]	Children 6–12 years olds Diagnosed with anxiety disorder	31 active ABM 28 waitlist control	12 at-home sessions 224 trials per session	Visual search paradigm Negative picture array with 1–3 positive or neutral targets	No significant changes in threat or happy bias. Greater pre-treatment threat bias predicted greater symptom reduction (SCAS) at post-treatment, but not at 3-month follow-up.	Clinician-rated symptom severity and number of diagnoses (ADIS) decreased in both groups; however, more reduction was observed for the active ABM compared to waitlist control. The number of children no longer with principal diagnosis was larger in the ABM group (35%) compared to waitlist control (7%). Child-reported anxiety symptoms (SCAS) declined in both conditions, but parent-reported reductions were only observed in the active ABM group. Global functioning (CGAS) improved in the ABM but not the waitlist control.
Waters et al., 2013 [49]	Children 7–13 year olds Diagnosed with anxiety disorder	18 active ABM 16 placebo	12 at-home training sessions (4 sessions per week for 3 weeks) 160 trials per session	Visual search paradigm Happy face target among angry face distractors. For placebo, bird targets	Using dot-probe assessment task, happy bias increased in the active group and was significantly higher than the placebo condition.	Clinically rated symptoms (ADIS) reduced in both groups; however, the active training group had fewer diagnoses after training. Compared to the placebo group (8%), more children in the ABM group (50%) did

Table 1 (continued)

Author	Participants	Groups	Training duration	Training task and stimulus type	Behavioral outcome	Anxiety outcome
				among flower distractors		not meet criteria for principal diagnosis following training. Parent and child ratings of anxiety symptoms (SCAS) were reduced.
Britton et al., 2013 [51]	Youth 8–17 year olds Diagnosed with an anxiety disorder and treatment-seeking	18 active ABM + CBT 18 placebo + CBT 17 CBT only 16 healthy controls	8 weeks, training session completed prior to CB 160 trials each session	Dot-probe task. Angry-neutral face pairs	At post-treatment, an attention bias away from happy faces emerged. However, no changes in bias was detected across time. Healthy groups showed stability of happy bias, but not threat bias, across time.	Clinician ratings (CGI and PARS) decreased in all treatment groups. Active and placebo ABM groups reported earlier symptom reductions (SCARED) at mid-treatment compared to CBT only group. The groups were not different at post-treatment.
Waters et al., 2014 [52]	Youth 6–17 year olds Diagnosed with spider phobia	19 ABM + single session exposure (3 h) 18 control + single-session exposure (3 h)	1 session 160 trials	Dot-probe task Happy-angry face pairs	Happy bias increased in the active group, but no change was observed in control. No changes to threat bias were observed. In the active group, individuals with greater happy bias at post-treatment had lower symptom severity at 3 months.	During exposure, fear expectancies (analog scale) decreased significantly in the ABM group, who exhibited greater improvements than the control group. Gains remained at 3-month follow-up for the active group. Both groups showed reduced symptom severity of phobic diagnosis (ADIS) and self-reported anxiety more generally (SCAS) across time points; however, no group differences were noted Global functioning (CGAS) increased across time points.

ABM attention bias modification, *ADIS* Anxiety Disorder Inventory Scale [53], *AIBQ* Adolescent Interpretation and Believe Questionnaire [54], *CBM* cognitive bias modification, *CBT* cognitive behavioral therapy, *CGAS* Children's Global Assessment Scale [55], *CGI* Clinical Global Improvement, *CY-BOCS-SR* Child Yale Brown Obsessive Compulsive Scale—Self-Report [56, 57], *MASC* Multi-dimensional Anxiety Scale for Children [58], *OCD* obsessive compulsive disorder, *PARS* Pediatric Anxiety Rating Scale [6], *RCADS* Revised Child Anxiety and Depression Scale [59], *RCMAS-C* Revised Children's Manifest Anxiety Scale Child-version [60], *SCARED* Screen for Child Anxiety Related Emotional Disorders [61], *SCAS* Spence Child Anxiety Scale [62], *STAIC* State Trait Anxiety Inventory-Child Version [63], *TAU-NIMH* Tel Aviv University and National Institute of Mental Health [64], *TAI* Test Anxiety Inventory [65]

[a] Cross-listed, Included training towards positive

[b] Cross-listed, Included training away from threat

[c] Included in Table 2

Anxious youth receiving CBT randomized to active ABM (i.e., training away from threat) exhibited greater anxiety reductions than placebo. At baseline, anxious youth, relative to healthy youth, exhibited less right amygdala-insula functional connectivity to the threat bias contrast (i.e., incongruent relative to congruent dot-probe trials), which resulted because anxious and healthy youth exhibited greater connectivity to congruent and incongruent trials, respectively. Moreover, lower pre-treatment connectivity between the right amygdala and insula in response to the threat bias contrast (i.e., greater connectivity to congruent trials) predicted more persistent anxiety symptoms following treatment. This effect characterized both active ABM + CBT and placebo + CBT groups, but was most pronounced in those youth treated with placebo training. This study may suggest that amygdala-insula connectivity during attentional processing of threat may predict treatment response. Significant changes in amygdala-insula connectivity were not noted following ABM, suggesting the mechanism remains to be elucidated. Given previous work showing perturbations in amygdala and ventrolateral PFC activation and amygdala-PFC connectivity in anxious youth [19, 101, 102], treatment targets may involve a network of regions rather than a single region in isolation.

Like attention training away from threat, attention training towards positive information also targets anxiety symptoms and attention-related behavior in community, high anxious samples, and clinically anxious youth (Table 1). Using the dot-probe task with happy-neutral or happy-negative face pairs, attention can be trained towards positive information if the probe repeatedly appears in the location of the happy face. In a randomized control trial, anxiety benefits were detected earlier in anxious youth receiving 8-week CBT if assigned to either active or placebo dot-probe training using happy-neutral face pairs compared to the group receiving CBT only (i.e., CBT + active ABM, CBT + placebo > CBT) [51]. These benefits did not extend to clinician-rated symptoms, but were limited to self-report measures of anxiety, which may suggest exposure to happy faces during training improved self outlook or expectation. Contrary to training condition, attention was biased away from happy faces at post-treatment, but was unchanged relative to baseline [51]. In youth with specific phobias, attention training towards positive information using happy-angry face dot-probe trials enhanced positivity bias and produced greater reductions of fear expectancy during a single exposure session and 3 months later. However, group differences were not detected in either clinician or self-reported measures of anxiety [52]. These studies suggest positive training may not be as clinically-effective compared to training attention away from threat using the dot-probe task, but with only two studies, more work is needed to draw conclusions.

As mentioned above, several ABM studies have used a modified dot-probe task to train attention towards positive information [51, 52], but the most common approach for positive training involves emotional visual search tasks (EVST), especially in younger children. In the EVST, individuals search a matrix (e.g., 4 × 4 grid) and locate the positive target (e.g., happy face) among negative distractors. For example, one recent study found that compared to waitlist controls, clinically anxious children searching for positive or calm targets among negative distractors exhibited greater symptom reduction after a 12-week treatment. Although attention biases towards positive or negative information remained unchanged, clinical gains persisted for at least 6 months [48]. In a similar study of slightly older clinically anxious children and early adolescents, greater reductions in clinician-rated anxiety were obtained in active training vs. placebo and a positive bias emerged in those receiving active training [49]. Across studies of positive bias training (Table 1), positive bias is usually increased [49, 52] and negative bias is usually reduced as expected [39, 47]; however, sometimes attention biases remained unchanged [48] or changed in unexpected directions [51].

CBM

In addition to attention biases, negative interpretation bias is characteristic of anxiety symptoms [103]. Biased interpretations may be assessed by asking individuals to resolve ambiguous situations, which often are interpreted more negatively for more anxious individuals. For example, some studies in children ask individuals to read a situation with an incomplete ending and select between positive and negative outcomes [66–73, 80]. Alternatively, adolescents often identify the missing letter in a word fragment (i.e., l_ke or disl_ke) to resolve the ambiguity [34, 50, 75–77, 82]. Then, adolescents are asked whether the resolution to the ambiguous situation matched their interpretation. For anxious individuals, negative resolutions are endorsed more often than positive resolutions.

CBM aims to alter biased interpretations. Through feedback learning [103], individuals are directed to interpret the situations more positively, more negatively, or in a neutral manner (Fig. 2b). It should be noted that the precise training parameters vary across studies. For example, CBM is commonly administered in one to three sessions [88••]; however, the number of sessions may be increased, especially in children with greater symptoms (e.g., [50, 83]).

CBM is largely successful at changing behavior (i.e., shifting interpretations) in youth; however, the impact on mood and/or anxiety is inconsistent. As indicated in Table 2, which extends a previous review [88••], interpretation biases are malleable, but studies report variations in whether positive or negative interpretations are changed with CBM training. For example, positive training may increase positive interpretations but have different or no effects on negative interpretations, or alternatively, may decrease negative interpretations but have different or no effects on positive interpretations. Unlike ABM studies that show anxiety reductions, CBM does not produce consistent changes in anxiety. However, most CBM studies have been conducted in community samples of children [66–73, 78, 104–106] and adolescents [32, 75–77, 79]. Some studies demonstrated reduced trait anxiety following positive training [67, 70, 72]; yet, more often no changes in mood or anxiety levels were detected. Reductions may emerge when considering reports of daily life stress [77], anticipating stressors [106], or in the context of experimental social stress [79]. Alternatively, experimental procedures have been employed to increase the effects of CBM (e.g., mental imagery). For example, adolescent males used mental imagery to resolve ambiguous pictures involving social situations using a word caption. For example, a cell phone picture could be resolved with "funny text" or "ignoring me." Positive mood and bias interpretations were altered in the expected training direction (i.e., greater positive interpretations following positive imagery training), especially when imagined from a first-person perspective [74]. At-risk populations, such as children classified as behaviorally inhibited, follow similar patterns as the community samples, demonstrating changes in interpretations. However, anxiety levels were not assessed and only minimal changes in stress reactivity were noted [80].

Few CBM studies have been conducted in youth with high levels of anxiety [50] or diagnosed with anxiety disorders [82, 83]. In Chinese adolescents diagnosed with anxiety disorders, threat-interpretations were successfully modified, but no treatment-related changes were observed in self-reported measures of interpretation bias or anxiety symptoms [82]. In a multiple baseline study with small sample sizes (n = 5–6 per group), CBM was administered to both parents and clinically anxious children. Using child-reported symptom reductions, treatment responders were identified in each group, but larger sample sizes are needed to understand the treatment response variability across patients [83]. Although no longer categorized as an anxiety disorder in DSM-5, adolescents with obsessive-compulsive disorders (OCD) did experience therapeutic benefit after CBM (i.e., self-reported and clinician-rated reductions of obsession symptoms) [107], suggesting the potential of CBM in clinical samples.

Combinations of ABM and CBM

Threat biases can negatively affect interpretation biases. For example, adults trained to attend to threat endorsed greater negative interpretations than individuals in the placebo group [108]. One study in adolescents combined ABM and CBM along with socio-evaluative conditioning into a single intervention [50]. Adolescents were randomized to CBT or ABM/CBM over 10 weeks. Both the CBT and ABM/CBM groups exhibited overall improvement after training over 6 months [50], and which remained after 2 years [81]. Although training usually targets one cognitive process, further work is needed to understand how ABM and CBM alter both attention biases and interpretation biases when administered in isolation and when combined.

Different Neuroscience-Based Treatment Approaches

While ABM and CBM are promising, other neurocognitive approaches may be applicable to pediatric anxiety. In this section, we review several strategies for implementing and/or developing treatment interventions targeting anxiety-related perturbations in cognitive processing.

Treatment Insights from Adult Studies

Neurocognitive treatments used in anxious adults may be applicable to children and adolescents with anxiety. For instance, this progression documents the history of ABM [38, 87••] and CBM [88••, 103]. ABM and CBM were administered to adults with anxiety and now studies are emerging in younger samples because threat biases and negatively biased interpretations are documented across development. This example is consistent with downward treatment extensions, like exposure-based CBT. Exposure-based treatments for anxious adults have been modified to be age-appropriate for use in anxious children. For example, David Barlow's Unified Protocol for the Treatment of Emotional Disorders (UP) [109] has been adapted for adolescents (UP-A, [110, 111]) and younger children (UP-C) [112]. While exposure-based CBT reduces anxiety symptoms for some youth, some continue to be symptomatic at post-treatment [3, 4]; therefore, further developmental adaptations of this treatment protocol may need to be considered.

Exposure-based CBT aims to desensitize the individual by repeatedly presenting the anxiety-provoking cue to reduce fear levels. Exposure-based CBT is based on the principles of fear extinction, which is perturbed in anxious adults [113] and youth [22, 114, 115•]. Traditionally in fear learning and extinction studies, two neutral cues (e.g., colored squares, shapes) are presented to the participant over a set number of trials. During fear learning, one of the cues (CS+) on occasion is paired with a threatening stimulus (US, shock or an aversive noise), while the other cue (CS−) is never paired with a threatening stimulus. Over repeated presentation of the CS+ and CS−, participants learn to associate the US with the CS+. Through measures of subjective and autonomic nervous system arousal, we can measure the learned fear response when participants view the CS+ in the absence of the US. Through a

Table 2 Cognitive bias modification (CBM), altering positive and negative interpretations

Authors	Participants	Groups	Duration of training	Training task and stimulus type	Behavioral outcome	Anxiety outcome
Community samples						
Lester et al., 2011 [66]	Children 6–11 year olds	34 positive CBM 33 negative CBM	Single session 30 trials	Ambiguous animal task with valence selection Positive or negative resolution reinforced	Negative interpretation bias decreased with positive training, but increased with negative training.	Increased anxiety (STAI-C trait) was detected in the negative training condition only. Stress reactivity: Avoidance behavior was greater following negative training than positive training.
Lau et al., 2013 [67]	Children 7–11 years olds	19 positive CBM 17 no training	Three sessions on 3 consecutive days 15 trials per session	Ambiguous situations task with valence selection Read by parents as bedtime stories Positive or negative interpretations Benign resolutions reinforced	Endorsement of benign interpretation increased in both groups, but this increase was greater in the training group compared to the control group. Negative interpretation decreased in the active group, but remained unchanged in the control group.	Anxiety (SASC-R) was reduced in the training group, but not the control group. Social anxiety symptoms (SASC-R) correlated with negative interpretation at baseline and post-test.
Muris et al., 2008 [68]	Children 8–12 year olds	36 positive CBM 34 negative CBM	Single session 30 trials	Ambiguous space odyssey task with valence selection Positive or negative resolution reinforced	No pre-training measures of interpretation bias were obtained. After training, negative interpretation was significantly greater following negative training compared to positive training in high anxious children.	NA
Muris et al., 2009 [69]	Children 9–13 year olds	63 positive CBM 57 negative CBM	Single session 30 trials	Ambiguous space odyssey task with valence selection Positive or negative resolution reinforced	Children in the positive training group exhibited a decrease in negative interpretation bias and avoidance tendencies. Children in the negative group exhibited an increase in negative interpretation and avoidance. Based on high vs. low anxiety (SCARED), no group differences in the effects of training were detected.	At baseline, but not at post-training, anxiety (SCARED) was positively related to interpretation bias and avoidance tendencies.
Vassilopoulos, et al., 2009 [70]	Children 10–11 year olds	22 positive CBM 21 no training	Three sessions over 2-week period 15 trials per session	Ambiguous situations task with valence selection Positive/benign or negative interpretations Only positive resolution reinforced	The positive training group exhibited a reduction of negative interpretation bias. No change was noted in the control group.	The positive training group exhibited a reduction of anxiety symptoms (SASC-R). No change was noted in the control group. Changes in social anxiety were correlated with changes in negative interpretation. Stress reactivity: Children in the training group reported less anticipatory anxiety (analog scale) than the control group. Negative interpretation at post-training predicted

Table 2 (continued)

Authors	Participants	Groups	Duration of training	Training task and stimulus type	Behavioral outcome	Anxiety outcome
						anticipatory anxiety ratings.
Vassilopoulos, Moberly et al., 2013 [71]	Children 10–13 year olds	77 positive CBM 76 no training	Three sessions over 3 weeks 16 trials each	Ambiguous situations task with valence selection Two positive or two negative endings Resolution with more positive ending was reinforced	For positive events, positive interpretation increased in the positive training group, but not the control group. For negative events, negative interpretation decreased and neutral interpretation increased in the positive training group, but not the control group.	Anxiety (SASC-R) decreased with training. Higher social anxiety (SASC-R) was associated with smaller decreases in negative interpretations to negative events.
Vassilopoulos, Blackwell et al., 2012 [72]	Children 10–12 years olds	Benign: 48 imagery CBM 46 verbal CBM	Four sessions over 3 weeks 18 trials per session	Ambiguous situations task with valence selection Negative or benign interpretations. Only benign resolution reinforced For the imagery group, individuals imagined themselves in the situation For the verbal group, individuals described the meaning of the situation	Negative interpretation decreased with training. Greater changes were observed in the verbal compared to imagined training group.	Social anxiety levels (SASC-R) were lower after the verbal training condition, but not the imagery condition, resulting in group differences at post-treatment.
Vassilopoulos, et al., 2014 [73]	Children 10–12 year olds	Verbal: 26 benign CBM 21 negative CBM Written: 20 benign CBM 27 negative CBM	Single session 15 trials	Ambiguous situations task with valence selection Negative or benign resolution reinforced Instructions were provided verbally or in written form	Benign training resulted in fewer negative interpretations. The presentation type did not influence the benign training. Negative training was more effective (i.e., increased negative interpretations) if heard (verbal condition) compared to read (written condition); whereas, negative interpretation decreased in the written group.	No training-related changes or group differences in mood were noted. Stress reactivity: Children trained to the benign interpretation using heard instructions, showed less negative on anagram completion task than the written group.
Heyes et al., 2017 [74]	Children and adolescents 11–16 year olds	Imagery: 30 positive CBM 30 mixed valence CBM	Single session 75 trials	Ambiguous picture-word task with imagery resolution Positive or mixed valence words Imagery conducted in either self-focused or	On scrambled sentence task, lower negative bias was detected in positive imagery compared to mixed valence imagery condition when self-focused.	Positive affect increased more for positive training group than mixed training group, especially when self-focused imagery used. No effects on negative affect were detected.

Table 2 (continued)

Authors	Participants	Groups	Duration of training	Training task and stimulus type	Behavioral outcome	Anxiety outcome
				observer--focused way		
Lau et al., 2013 [79]	Adolescents 12–18 year olds	20 positive CBM 20 negative CBM	Single session 60 trials	Ambiguous situations task with word fragment resolution Positive or negative words	Interpretation bias increased in the expected direction (i.e., more positive for positive training group and more negative for negative training group).	Across both groups, anxious mood (visual analog scale) decreased over the session. Stress reactivity: The positively trained group had less stress-induced anxiety on judged mental arithmetic stressor compared to the negative training group.
Lothmann et al., 2011 [34]	Adolescents 13–17 year olds	41 positive CBM 41 negative CBM	Single session 60 trials	Ambiguous situations task with word fragment resolution Positive or negative words	Positive training group reported greater similarity to the positive targets compared to the negative training group. In the positive training group, the positive targets were more similar than negative targets. The negative training did not show differences between the targets.	Positive affect decreased in the negative training group, but did not change in the negative training group. Negative affect decreased in the positive training group, but no changes in affect were detected in the negative training group.
Lau et al., 2011 [75]	Adolescents 13–18 year olds	17 positive CBM 19 negative CBM	Single session 60 trials	Ambiguous situations task with word fragment resolution Positive or negative words	Interpretation bias increased in the expected direction (i.e., more positive for positive training group and more negative for negative training group.	In individuals with low self-efficacy, positive affect decreased if assigned to negative training group.
Salemink and Wiers 2011 [76]	Adolescents 14–16 year olds	88 positive CBM 82 mixed valence/-neutral CBM	Single session 50 trials	Ambiguous situations task with word fragment resolution Positive or mixed valence (positive, negative, 2 neutral) words	The positive training group was quicker to solve positive than negative word fragments. This difference was not found in mixed valence condition. The positive group was faster to detect positive probes than the mixed valence condition.	Training group did not affect state anxiety levels (STAI-C).
Telman et al., 2013 [77]	Adolescents 15–18 year olds	23 positive CBM 23 negative CBM	Single session 60 trials	Ambiguous situations task with word fragment resolution Positive or negative words	Similarity ratings for positive resolutions were greater in the positive training group than negative training group. Similarity ratings for negative resolutions were greater in the negative training group compared to the positive training group.	No mood (Visual Analog Scale) changes were noted in the positive training group. Negative mood increased for the negative training group. No changes in trait anxiety levels (STAIC) emerged. Stress reactivity: Negatively-trained group rated stressful events as more impactful than positively trained group.
Lester et al., 2011 [78]	Children and adolescents 7–15 year olds	Animal: 25 positive CBM 26 negative CBM Social: 26 positive CBM	Single session 30 trials	Modified space odyssey paradigm with valence selection Positive or negative resolutions were rewarded	After positive training, the bias became less threatening. In younger ages, the interpretation bias changed to the animal content but not for social content. In older ages, biases were changed for	The training did not influence trait anxiety (STAI) levels. Stress reactivity: In a behavioral avoidance task involving an animal touch-box and social speech, no significance changes were noted.

Table 2 (continued)

Authors	Participants	Groups	Duration of training	Training task and stimulus type	Behavioral outcome	Anxiety outcome
		26 negative CBM		Content of situation concerned animal or social situation	both animal and social content.	
At-risk samples						
White et al., 2016 [80]	Children 9–12 year olds. At-risk for social anxiety disorder, Top tercile of behavioral inhibition (BIQ > 97.5)	23 positive (90% positive) CBM 22 placebo (50% positive/50% negative)		Ambiguous New School Task with valence selection Positive or mixed valence selection reinforced	Negative interpretation bias decreased more in the positive training group and the placebo group. Note: No effect on attention bias to threat.	No changes in mood were significant. Stress reactivity: Speech stressor was successful, but no group differences were noted.
High anxious samples						
Sportel[a] et al., 2013 [50]	Adolescents 13–15 year olds Top quartile of anxiety on RCADS	86 ABM/CBM 84 CBT 70 no treatment	10 weeks of ABM/CBM treatment Twice weekly at-home internet-based sessions (8 ABM, 9 CBM, 3 social-evaluative conditioning) or 10 weeks of CBT For ABM, 450 trials per session For CBM, 60 trials per session For conditioning, 240 trials per session	Ambiguous situations task with word completion Benign resolution rewarded	groups In the ABM/CBM group, interpretations became more positive compared to the control groups. On self-report measures (AIBQ), interpretation became less negative in the ABM/CBM group relative to the control group.	See Table 1
De Hullu et al., 2017 (long-term follow-up of Sportel et al., 2013) [81]	Adolescents 12–16 years olds Top quartile of anxiety on RCADS	See Sportel et al., 2013	See Sportel et al., 2013	See Sportel et al., 2013	At 2 year follow-up, negative interpretation biases remained unchanged and were similar across training groups.	At 2-year follow-up, self-reported measures of test anxiety scores (TAI) decreased, but no decrease in anxiety (RCADS) was observed.
Clinically anxious samples						
Fu et al., 2013 [82]	Adolescents 12–17 year olds Diagnosed with anxiety disorders	16 positive CBM 12 mixed valence CBM	Single session 60 trials	Ambiguous situations task with word fragment (Chinese version) Positive, neutral, or negative words	Both groups assigned greater familiarity to positive than negative targets; however, the effect was more pronounced in the positive training group. Interpretation biases (ASSIQ) were unchanged.	Negative mood (analog scale) reduced in both training groups, but no group differences were noted.
Reuland et al., 2014 [83]	Children and adolescents 10–15 year olds Diagnosed with anxiety disorder	Positive CBM: 6 child 5 parent 6 parent and child	Multiple baseline study. 8 sessions 50 trials per session	Ambiguous situations task with word fragment Positive words	Parent and child's positive interpretation increased with training. Larger effects were detected in the parent than the child interpretation bias.	Treatment responders (SAS-A) were observed in each group (2/6 parent/child training., 1/6 child, 2/5 parent only).

ABM attention bias modification, *ASSIQ* Ambiguous Social Situation Interpretation Questionnaire [84], *BIQ* Behavioral Inhibition Questionnaire [85], *CBM* cognitive bias modification, *CBT* cognitive behavioral therapy, *RCADS* Revised Child Anxiety and Depression Scale [59], *SASC-R* Social Anxiety Scale for Children—Revised [86], *SCARED* Screen for Child Anxiety Related Emotional Disorders [61], *STAIC* State Trait Anxiety Inventory—Child Version [63], *TAI* Test Anxiety Inventory [65], *VAS* Visual Analog Scale

[a] Included in Table 1, training towards positive

process known as fear extinction, the CS+ and CS− are presented to the participant; however, during these trials the US never occurs with the CS+. Through repeated presentation of the CS+ in the absence of the US, participants habituate and learn to associate the cue as no longer threatening. Perturbations also are observed when recalling previously extinguished fear [22]. For example, anxious youth, like anxious adult, exhibit blunted subgenual anterior cingulate activation when appraising threat of previously extinguished stimuli compared to healthy age-matched peers. Additionally, unlike healthy youth, anxious youth elicited heightened ventromedial PFC activation to CS+ and CS− relative to perceptually-similar stimuli, possibly indicated heightened sensitivity to threat and safety cues [22].

Recent studies in healthy adults and youth have shown that fear can be attenuated by altering the initial fear memory through memory reconsolidation [116–118]. Recalled memories enter an active, labile state, whereby new information can update and modify the prior memory. In the context of fear conditioning, a single reminder of the CS+ aims to recall the fear memory, thereby making the original CS-US association unstable and open for disruption. Extinction learning conducted during the reconsolidation update window serves to alter the original fear memory. Compared to adults completing traditional extinction, healthy adults that completed extinction training during the reconsolidation update window (i.e., 10 min after CS+ reminder) exhibited reduced activation of the ventromedial prefrontal cortex (vmPFC) during extinction. Furthermore, subjects who received the reminded CS+ showed decreased functional connectivity between vmPFC and the amygdala [117], suggesting that regulatory regions are recruited less when safety information (i.e., extinction learning) is incorporated into the original fear memory. Preliminary behavioral research suggests the reconsolidation update mechanisms can be applied to healthy adolescents [116]. Adults and adolescents who completed extinction during reconsolidation window, compared to individuals completing extinction without a reminder, exhibited diminished fear response 24 h later following reinstatement (i.e., US presentation). Although these procedures have not been conducted in anxious populations yet, the preliminary findings suggest that the process may be easily implemented into a clinical setting. Clinicians can provide patients with a fear reminder to reactive threat-related memories, which could then be more effectively updated through additional exposure-based treatments.

Treatment Insights from Other Psychopathologies

Treatments used initially for other disorders may have utility in anxious youth, especially if a central feature of anxiety is targeted. For example, CBM studies have predominantly used written ambiguous situations. However, few studies have investigated ambiguity in facial stimuli, which individuals with social anxiety disorder often interpret as threatening [119]. In other psychopathologies, similar overgeneralization or misattributions are observed. For instance, youth at high risk for criminal activity and delinquency tend to recognize hostility more readily than healthy youth. Computerized training programs have been developed to shift individual's emotion-related judgments [120]. In addition, youth with disruptive mood dysregulation disorder (DMDD) have difficulties recognizing facial expressions, often mislabeling ambiguous faces as threatening [121•]. Recently, a discrimination training program has been used in youth with and without DMDD to shift the labeling of ambiguous faces to be less threatening [122]. These interventions used for youth with conduct disorder and DMDD may also have utility in pediatric anxiety, but further testing is required. Although neurocognitive interventions for various pediatric psychopathologies may be applied to anxiety disorders, this literature in youth is only starting to emerge.

For a more established example, modification of automatic action tendencies first employed to reduce symptoms of substance abuse and problematic substance abuse-related behaviors in adults [e.g.; 123] have been applied to other psychiatric conditions, such as eating and anxiety disorders. Compared to non-disordered adults, adults exhibiting symptoms of alcohol abuse/dependence exhibit elevated automatic approach tendencies to alcohol cues, but not non-alcohol cues [e.g., soft drinks; 123]. Importantly, research suggests biased automatic actions can be modified to reduce both symptomology and alcohol consumption [124, 125]. Subsequent studies have demonstrated promising clinical utility of utilizing such modification protocols in adolescent smokers [126]. Research from the substance abuse domain provides a fairly straightforward extension model for other psychopathologies in which similar neurocognitive perturbations are identified. For example, modification of automatic action tendencies may be used in patients with eating disorders using towards food-related stimuli; however, initial studies in healthy adults has produced inconsistent results and, at least in some instances, paradoxical changes in subsequent behavior. Specifically, training adults to avoid unhealthy food stimuli produces unreliable changes in automatic action tendencies, which may be attributable to complex interactions with other factors such as self-control [127]. Moreover, training adults to avoid specific food-related stimuli (e.g., chocolate) can paradoxically *increase* consumption behaviors [127]. However, utilizing control stimuli that are similar in motivational value (e.g., non-chocolate sweets vs. chocolate sweets) yielded reliable changes in behavior consistent with training [128]. Following the success of these protocol modifications, current work is examining the clinical efficacy of modifying automatic action tendencies in pathological consumption behaviors such as anorexia nervosa and bulimia nervosa [e.g., 129, 130]. These findings suggest that parameters of the training regimens (e.g., stimuli selection) may need to be optimized when applying neurocognitive interventions to other disorders.

Like eating disorders, modification of automatic action tendencies has also been extended to social anxiety disorder. Modification of automatic associations and actions produces reductions in both anxiety symptoms and anxiety-related behaviors; therefore, implementing these procedures in pediatric anxiety disorders may be useful. In socially anxious adults, for example, modifying threat-related associations ascribed to social cues reduces avoidance behaviors that maintain symptoms [131]. Similarly, implicitly training socially anxious adults to automatically approach, rather than avoid, positive social cues produces greater adaptive behaviors during social stressors [132, 133], but not always [134]. In other disorders such as OCD, modification of automatic action tendencies reduces overt avoidance of contaminated objects [135•]. Taken together, research in adults suggests that modifications to implicit processes produces behavioral changes independent of self-reported cognitions [124, 125, 133, 135•], which provides evidence of modification to implicit processes. Similar to ABM, CBM, and other neurocognitive interventions, modification of automatic associations and actions may resolve anxiety-related perturbations that are not targeted by traditional treatment modalities such as CBT.

Although anxiety-related perturbations among these processes emerge early in development, no research to date has examined the clinical utility of modifying these processes in anxious youth. However, typically developing children trained to automatically approach novel stimuli develop more positive evaluations of these stimuli; whereas, children trained to automatically avoid novel stimuli develop more negative evaluations [136]. Youth demonstrate plasticity in automatic actions prior to the development of fear responses, but the clinical utility of modifying fear-related automatic actions in pediatric anxiety remains unclear. For example, some research suggests that higher levels of anxiety symptoms are associated with greater plasticity of automatic actions [136]. However, other research suggests that modification of automatic actions produces no reliable reductions in anxiety symptoms [137]. Importantly, it should be noted that both studies modified automatic actions in response to novel, rather than anxiogenic stimuli. Extending interventions using feared stimuli into pediatric populations may be clinically useful.

Novel Treatment Insights

Novel neurocognitive training methods targeting the tendency to overgeneralize fear in anxiety disorders or the disturbances of more explicit information processing (e.g., perceptual, top-down processes) also hold promise. For example, anxious adults exhibit exaggerated fear generalization, whereby fear extends more readily to similar appearing stimuli [138, 139]. Development influences this generalization such that older children exhibit similar fear generalization patterns as adults, whereas younger children do not [140]. A novel perceptual generalization training paradigm has been used in healthy adults to decrease fear generalization of threat/safety cues [141] and could be extended to youth with varying levels of anxiety. Persistent fear in anxiety disorders also suggests the potential importance of cognitive flexibility for anxiety reduction. Indeed, increases in cognitive flexibility may help to explain the expected and unexpected reductions in anxiety observed in studies of ABM whether training attention away from threat or through placebo training. In adults with eating disorders, training cognitive flexibility has been implemented as a treatment strategy [130] to reveal that the training may be more effective if emotional or disorder-relevant stimuli are used. This work raises the possibility that training programs that increase emotional flexibility may decrease anxiety. For example, emotional flexibility training via cognitive reappraisal may be an effective strategy for accomplishing this aim [142], but neurocognitive interventions may be developed to target emotional flexibility independent of cognitive reappraisal. In summary, there is great potential for the development of novel neurocognitive treatments to address the range of information processing functions that may contribute to pediatric anxiety.

Development

To treat pediatric anxiety successfully using neurocognitive interventions, development impacts on treatment, cognitive function, and the brain must be considered. Exposure-based CBT, often used in clinical practice, builds on principles of fear extinction. Studies in both rodents and humans have found that adolescents have diminished fear extinction relative to younger children and older adults [115•]. Although non-significant, adolescents exhibited a diminished response to CBT treatment compared to adults [143], suggesting treatment efficacy may depend on age. Interestingly, extinction-based exposure in CBT may be more effective in younger children than adolescents, whereas the cognitive restructuring components of this treatment appear to be equally effective across age groups [144]. However, large clinical trials often group children and adolescents together, neglecting the possibility that developmental differences may impact treatment. Future work should compare children and adolescent groups or examine age continuously when investigating the utility of different neurocognitive approaches across development.

Moreover, we must also consider developmental trajectories of cognitive processes relevant for anxiety and of the neural circuitry underlying these processes. For instance, maladaptive processing of threat emerges early in the disease course of anxiety disorders, which may suggest a causal role in the development of symptomatology. These maladaptive responses are proposed to be established, reinforced, and expanded across development [145, 146], which may indicate that these mechanisms may become increasingly resistant to modification over time. As a result, the dysregulation that emerges early in development may be more amenable to change and produce maximal reductions in anxiety symptoms. In particular, adolescence, a period of profound physical and social changes, may be an ideal period to utilize neurocognitive interventions to target processes relevant for the emergence of anxiety disorders due to the increased plasticity in cognitive and brain function [147]. Administering interventions during this period of plasticity may alter the developmental course, reduce symptoms and provide more powerful, and long-lasting clinical utility [148]. However, alternative strategies may be needed to target processes that are fully developed, or that already show aberrant patterns consistent with adults [22]. Regardless, long-term outcomes of neurocognitive interventions are needed.

Developing neural systems that show anxiety-related perturbations may provide insights to effectively change behavior. Both normative developmental changes in the underlying neural circuits and perturbations in the trajectory can inform treatment approaches. While some studies show linear decreases in amygdala activation [149], others show exaggerated amygdala activation to threat cues (e.g., fearful faces) in the adolescent period of development relative to children and adults [150, 151]. Greater anxiety-related elevations coincides with this heightened amygdala activation [152]. Whereas, prefrontal cortical structures involved in decision-making (e.g., orbitofrontal cortex, dorsal anterior cingulate) are more strongly activated by adults than adolescents [153]. As a result, models have proposed an imbalance between subcortical and cortical circuitry [154]. An imbalance model of brain development posits that subcortical structures involved in the processing of emotional stimuli and motivation develop prior to structures in prefrontal regions implicated in cognitive control and emotion regulation [155, 156]. Thus, the imbalance between these developing regions may have implications for treatments in youth. The reliance on subcortical regions more than prefrontal regulatory regions highlights the possibility that targeting automatic and regulatory processes may require different approaches (e.g., ABM vs. CBT) at different developmental stages.

Of equal importance is an understanding of the development of fronto-amygdala circuitry in relation to treatment. Functional coupling between the amygdala and mPFC has been theorized to reflect top-down regulation of mPFC on amygdala activation [157]. Animal models and human functional connectivity studies that suggest that networks develop locally, strengthening connections among regions *within* a specific network or circuit, prior to the development of distributed networks, the connections *between* these neural regions across networks and circuits [158–160]. Moreover, neuronal coupling of fronto-amygdala circuitry in response to fearful faces exhibits a natural shift from positive to negative connectivity during the transition from childhood to adolescence [149]. This developmental shift in connectivity direction parallels the natural decline of separation anxiety in youth [149]; however, future work needs to determine relationships in other anxiety disorders like generalized anxiety disorder and social anxiety disorder. Developmental differences in connectivity patterns have been observed in anxious populations. When appraising threat of previously conditioned and extinguished stimuli, anxious adults and youth exhibit opposite patterns of amygdala-mPFC connectivity. However, the developmental shift is from more negative in youth to more positive amygdala-mPFC connectivity in adults [161]. Being cognizant of developmental shifts in activation and/or connectivity may help identify key transitions to administer neurocognitive interventions.

Moreover, future neuroimaging work can help identify underlying mechanisms of treatment response as well as point the field to new opportunities for development. For simplicity, we have highlighted two likely candidates, the amygdala and mPFC, and bottom-up and top-down processes, respectively; however, these structures do not operate alone. Additional regions and networks are involved in anxiety-related processes and behavior (e.g., ventrolateral PFC in attention [19, 101, 102], hippocampus, anterior cingulate in fear conditioning/extinction [156, 162, 163], and striatum, orbitofrontal cortex, and insula in approach-avoidance behavior [164]).

Conclusion

In sum, we have highlighted several neurocognitive approaches that attempt to reduce anxiety symptoms in youth. Most of the research has targeted biased attention and biased interpretations. Across studies, ABM has been more effective in reducing symptoms than CBM; however, enhanced gains compared to placebo training are not always detected. However, CBM has been more effective at altering the target cognitive process, namely interpretations, than ABM. To date, most of the work has examined how particular cognitive processes and mood/anxiety are changed in normative samples, especially with respect to CBM; therefore, more work is needed in clinical samples. Since attention and interpretation biases are not the only deficits observed in anxious youth, additional avenues for interventions using neurocognitive approaches should be explored by future research. Here, we have suggested several different approaches aimed to identify and/or develop neurocognitive treatments that can target anxiety symptoms. Successful interventions for pediatric anxiety must aim to treat symptoms by considering developmental trajectories in neural and cognitive function, integrating multiple approaches in order to effectively target neurocognitive mechanisms that interactively give rise to psychopathology across development.

Compliance with Ethical Standards

Conflict of Interest Jennifer C. Britton, Danielle V. Dellarco, and Travis C. Evans declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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