Current Clinical Psychiatry
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Roma A. Vasa
Amy Krain Roy *Editors*

Pediatric Anxiety Disorders

A Clinical Guide

Humana Press

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Jerrold F. Rosenbaum, MD

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Roma A. Vasa • Amy Krain Roy
Editors

Pediatric Anxiety Disorders

A Clinical Guide

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Editors
Roma A. Vasa
Director of Education and Training
Kennedy Krieger Institute
Baltimore, MD, USA

Amy Krain Roy
Fordham University
Bronx, NY, USA

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Preface

Over the past decade, significant advances in research methodology have stimulated dramatic progress in the field of child psychiatry in general and pediatric anxiety disorders, more specifically. Advances in neuroimaging, developmental and affective neuroscience, and genetics have provided a solid foundation for the development of novel etiological models that are now being tested. Further, the publication of several rigorous multisite trials of pharmacological and psychotherapeutic interventions has substantially improved our knowledge of the most effective methods to treat pediatric anxiety disorders. The *Diagnostic and Statistical Manual of Mental Disorders* is currently under its sixth revision, with changes driven by these empirical findings, including the integration of dimensional assessment approaches, which has not been done before. Thus, this volume, *Pediatric Anxiety Disorders: A Clinical Guide,* is being published at an exciting time in the field of psychiatry. The aim of this text is to bridge the most up-to-date research findings with relevant clinical perspectives making it a unique and essential resource to established clinicians and researchers, as well as students and trainees.

This book is organized into four sections, each of which includes chapters on a specific area of interest. The first section reviews the current research regarding etiological mechanisms of pediatric anxiety. It begins with a comprehensive overview of the animal literature showing cross-species homology in the neural mechanisms underlying fear processing, which has been essential to delineating the pathophysiology of anxiety disorders and, more recently, has provided the foundation for novel treatment approaches. The next chapter illustrates how advances in neuroimaging techniques have allowed translation of basic animal fear models to humans, including children and adolescents, with anxiety disorders. The final chapter of this section focuses on temperamental risk factors for pediatric anxiety disorders, an area that has grown significantly in recent years due to unique longitudinal work.

The second section provides in-depth descriptions of the anxiety disorders that affect children and adolescents. Each chapter includes descriptions of any proposed changes for DSM5, as well as the most current research findings regarding etiology, assessment, and treatment. Clinical case scenarios provide real-world examples of presenting concerns and putative responses to treatment.

The third section summarizes the literature on empirically supported assessment tools and evidence-based cognitive-behavioral and pharmacological interventions for pediatric anxiety disorders. The authors of these chapters have included comprehensive summary tables that can serve as quick reference tools.

The final section of the text is dedicated to understanding how anxiety manifests in two special populations, children with chronic medical illnesses and those with autism spectrum disorders. The authors of these chapters explore how anxiety is conceptualized in the context of these primary disorders and discuss special considerations for assessment and treatment.

The editors are fortunate to have leading authorities in pediatric anxiety from the fields of cognitive neuroscience, cognitive-behavioral practice, and pharmacology to author the chapters of this book. We are grateful to them for all of their time and efforts. We also wish to thank Fawad Viqar, Rachel Chizkov, Rachael Tillman, and Laura Carroll for their assistance with the editing process. Finally, we wish to thank our editor, Barbara Lopez-Lucio, at Springer for her dedicated guidance and editorial expertise.

Baltimore, MD, USA
Bronx, NY, USA

Roma A. Vasa
Amy Krain Roy

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Contributors

Nicholas W. Affrunti Department of Psychological and Brain Sciences, University of Louisville, Louisville, KY, USA

Anne Marie Albano Department of Psychiatry, Columbia University Clinic for Anxiety and Related Disorders, Columbia University, New York, NY, USA

Aleta G. Angelosante NYU Langone Medical Center, New York, NY, USA

Kristin A. Buss Department of Psychology, The Pennsylvania State University, University Park, PA, USA

Rachel R. Chizkov Department of Child and Adolescent Psychiatry, NYU Langone Medical Center, New York, NY, USA

Maria J.W. Cowart Virginia Tech, Child Study Center, Blacksburg, VA, USA

Colleen M. Cummings Department of Psychology, Temple University, Philadelphia, PA, USA

Emily J. Frosch Division of Child and Adolescent Psychiatry, Department of Psychiatry and Behavioral Science, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Golda S. Ginsburg Division of Child and Adolescent Psychiatry, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Damion J. Grasso University of Connecticut Health Center, Farmington, CT, USA

Amanda E. Guyer Department of Human Ecology and Center for Mind and Brain, University of California, Davis, CA, USA

Louis Hagopian Neurobehavioral Unit, Department of Behavioral Psychology, Kennedy Krieger Institute, Baltimore, MD, USA

Catherine A. Hartley Department of Psychology, New York University, New York, NY, USA

Heather Jennett Director of Clinical Services, Little Leaves Behavioral Services, Washington, DC, USA

Joan Kaufman Yale University School of Medicine, New Haven, CT, USA

Courtney P. Keeton Department of Psychiatry and Behavioral Sciences, Johns Hopkins Medical Institution, Baltimore, MD, USA

Alex Eve Keller Department of Child and Adolescent Psychiatry, Weill Cornell Medical College, New York, NY, USA

Patrick M. Kelly Division of Child and Adolescent Psychiatry, Department of Psychiatry and Behavioral Sciences, The Johns Hopkins Hospital, Baltimore, MD, USA

Philip C. Kendall Department of Psychology, Temple University, Philadelphia, PA, USA

Elizabeth J. Kiel Psychology Department, Miami University, Oxford, OH, USA

Adam B. Lewin Neuropsychiatry – University of South Florida, St. Petersburg, FL, USA

Vasco M. Lopes Department of Psychology, Fordham University, Bronx, NY, USA

Carla E. Marin Florida International University, Miami, FL, USA

Carrie L. Masten Department of Psychology and Human Development, Peabody College, Vanderbilt University, Nashville, TN, USA

Ella L. Milliner Griffith University, Gold Coast, QLD, Australia

Justin W. Mohatt Child Division, Department of Psychiatry, Weill Cornell Medical College, New York, NY, USA

Thomas H. Ollendick Virginia Tech, Child Study Center, Blacksburg, VA, USA

Magdalena A. Ostrowski Kean University, North Avenue, Hillside, NJ, USA

Jennifer M. Park Department of Psychology, University of South Florida, Tampa, FL, USA

Elizabeth A. Phelps Nathan S. Kline Institute for Psychiatric Research, Departments of Psychology and Neural Science, New York University, New York, NY, USA

Daniel S. Pine Section on Development and Affective Neuroscience, National Institute of Mental Health, Bethesda, MD, USA

Connor M. Puleo Department of Psychology, Temple University, Philadelphia, PA, USA

Kendra L. Read Department of Psychology, Temple University, Philadelphia, PA, USA

Yasmin Rey Florida International University, Miami, FL, USA

Wendy K. Silverman Department of Psychology, Florida International University, Miami, FL, USA

Eric A. Storch University of South Florida, St. Petersburg, FL, USA

Roma A. Vasa Division of Child and Adolescent Psychiatry, Education and Training, Kennedy Krieger Institute, Baltimore, MD, USA

John T. Walkup Child Division, Department of Psychiatry, Weill Cornell Medical College, New York, NY, USA

Chiaying Wei Department of Psychology, Temple University, Philadelphia, PA, USA

Part I
Neurobiology and Temperament

Fear Models in Animals and Humans

Catherine A. Hartley and Elizabeth A. Phelps

Abstract While fear learning is an adaptive behavior critical to our survival, excessive fear can markedly impair one's ability to function and is a central characteristic of anxiety disorders. In this chapter, we review research detailing the neurobiological mechanisms underpinning fear learning and regulation. We draw on research in both animal models and humans, highlighting developmental research whenever possible. In the first section we review the brain systems that support fear acquisition through both direct experience and social learning. In the second section, we focus on the various means by which learned fears can be lessened, including extinction, cognitive regulation strategies, actively coping with fear, and persistently inhibiting fear through reconsolidation. This basic fear-learning model provides a neuroscientific framework for understanding the role of Pavlovian fear learning in anxiety disorders and suggests potential approaches for treatment.

Keywords Fear • Conditioning • Extinction • Emotion regulation • Anxiety

The ability to recognize and respond to potential sources of harm in the environment is critical for survival. The state of fear that results from the detection of proximal threat serves many important functions. Fear facilitates information gathering through heightened vigilance, enables rapid reactions, and gates learning to promote the long-term retention of salient information. While fear plays a central role in promoting adaptive behavior, excessive fear can markedly impair one's ability to function and is a central characteristic of anxiety disorders. Detailed research examining fear learning in animal models and humans has generated a detailed neuroscientific understanding of how fear responses are acquired. More recent research has begun to elucidate the various methods by which learned fears can be modified or controlled.

This research provides a framework for understanding the neural systems underlying anxiety disorders and may yield novel insights into possible treatments. Of note, the majority of both human and animal studies have examined the acquisition and control of fear in adults, with few examinations of how these learning and regulatory processes might differ in childhood or adolescence. Thus, the bulk of this review will focus on adult studies with reference to pediatric research whenever possible.

C.A. Hartley
Department of Psychology, New York University, New York, NY, USA
e-mail: cate@nyu.edu

E.A. Phelps (✉)
Nathan S. Kline Institute for Psychiatric Research, Departments of Psychology and Neural Science, New York University, New York, NY, USA
e-mail: liz.phelps@nyu.edu

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In this chapter, we review research detailing how fear responses are learned and regulated. In the real world, objects, sounds, or places that are associated with previous traumatic events in our lives can come to elicit fear responses. In addition, humans can readily acquire fears through social means of transmission, such as through verbal instruction or observation of another person's negative experiences. Experimental studies examining Pavlovian cued conditioning, contextual conditioning, and social learning of fear have shed light on the neural mechanisms supporting such fear associations. In the first part of this chapter we review the brain systems linked to fear acquisition. The latter sections of this review focus on the range of techniques by which fears can be lessened, including simple exposure in extinction training, cognitive strategies to regulate fear, developing means to actively cope with fear, and persistently inhibiting the fear by targeting memory reconsolidation.

Fear Acquisition

Below we review experiential and social means by which novel fears may be acquired. Pavlovian cued conditioning and contextual conditioning, respectively, model the processes by which negative affective value may be assigned to a stimulus or context. Fears may also be acquired through observation or explicit instruction. Here we describe each of these means of fear learning and review their neural substrates.

Pavlovian Cued Conditioning

Pavlovian fear conditioning provides an experimental model for the process by which neutral stimuli in the world acquire negative affective value [1]. In a typical Pavlovian fear conditioning paradigm, a neutral stimulus, such as a tone, is paired with an intrinsically aversive unconditioned stimulus (US), such as a shock. The shock elicits a range of unconditioned autonomic, endocrine, and behavioral responses, including freezing in rodents, and increases in skin conductance in humans. After one or more pairings, the previously neutral stimulus, now a conditioned stimulus (CS), acquires the capacity to elicit these fear responses, or conditioned responses (CRs).

Extensive research in animal models has delineated the neural circuits that support Pavlovian fear conditioning (see [2, 3]; Fig. 1). This work highlights the necessary role of the amygdala in acquisition, storage, and expression of fear learning. The amygdala is a heterogenous structure composed of several subnuclei that play distinct roles in fear learning. The lateral nucleus of the amygdala (LA) receives convergent thalamic and cortical projections signaling the presence of the CS and US [4–7]. Pairing of the two stimuli gives rise to synaptic plasticity within the LA [8, 9]. When the CS is then presented alone, the LA activates the central nucleus of the amygdala (CE) [10], which controls the expression of the fear response via projections to brainstem and hypothalamic regions [11]. Distinct cells within the LA maintain the long-term representation of this fear memory [12] and remain responsive to the presentation of a CS even when the behavioral fear response is not expressed. This persistent encoding of the fear association may support the commonly observed return of fears that have been previously diminished through extinction learning [13].

Although studies of fear acquisition have focused primarily on the role of the amygdala, recent evidence in animal models suggests that the prelimbic medial prefrontal cortex is necessary for the expression of learned fear (Fig. 1). Lesions of the prelimbic cortex do not prevent initial fear acquisition or expression [14, 15]; however, pharmacological inactivation of the prelimbic cortex following conditioning disrupts fear expression [16] while prelimbic stimulation increases fear expression [17]. Neurons in prelimbic cortex exhibit sustained responses to CS presentation that parallel the duration

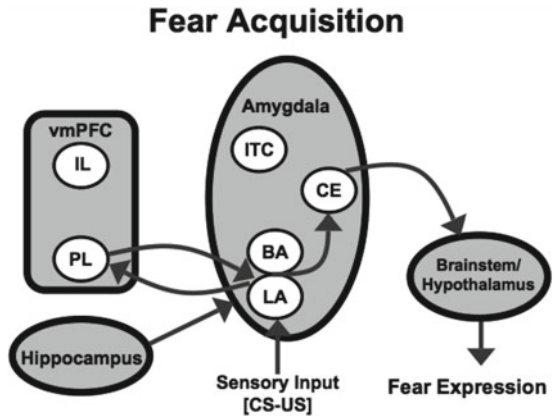

Fig. 1 Neurocircuitry supporting fear acquisition. The lateral nucleus (LA) of the amygdala receives afferent sensory input regarding experienced, observed, or instructed information about the CS–US relationship and is the site of plasticity representing the fear memory during conditioning. The LA and BA are interconnected and both project to the central nucleus (CE), which has outputs to brainstem and hypothalamic regions that control the expression of the CR. Following conditioning, the prelimbic (PL) region of the ventromedial prefrontal cortex (vmPFC) is activated via the BA following CS presentations and drives the expression of conditioned fear. Projections from the hippocampus to the basal nucleus (B) of the amygdala process contextual information during conditioning and may gate fear expression through the CE

of the behavioral freezing response [18], suggesting that the prelimbic cortex drives the expression of conditioned fear. The prelimbic cortex receives inputs from the LA [19] and projects to the basal nucleus of the amygdala (BA), which in turn projects to the CE. Following CS presentation, the prelimbic cortex might transform phasic signals from the LA into sustained prelimbic firing that directly influences fear expression via its CE projections.

Discrimination conditioning paradigms are often used in human fear research. In these paradigms, two conditioned stimuli are presented. These may be auditory tones or more typically, neutral visual stimuli such as colored shapes. Some studies use visual stimuli as CSs that are capable of eliciting fear responses even prior to conditioning (e.g., images of snakes, spider, or fearful faces). These so-called "prepared" stimuli may elicit more robust physiological responses and more persistent conditioned associations [20]. In a discrimination paradigm, one stimulus, the CS+, is paired with a US on a subset of the trials, while the other, the CS− is never paired with shock. Measurable correlates of sympathetic nervous system activity, such as skin conductance responses or pupil dilation, are recorded and assessed for each stimulus. The difference in responding to the threat stimulus (CS+) versus the safety signal (CS−) serves as a measure of the discriminative CR that is assumed to reflect one's degree of threat-specific fear expression.

Studies in humans suggest that the neurocircuitry underlying Pavlovian fear conditioning is conserved across species (see [21] for a review). Both human lesion and neuroimaging studies support the central role of the amygdala in fear conditioning. Patients with both unilateral and bilateral lesions of the amygdala fail to display a conditioned skin conductance response to a reinforced CS [22, 23]. Functional magnetic resonance imaging studies (fMRI) of Pavlovian fear conditioning observed increased blood oxygen level-dependent (BOLD) signal in the amygdala to a conditioned stimulus versus a neutral stimulus [24–27].

In addition to the engagement of the amygdala, fMRI studies of fear conditioning commonly report increases in BOLD activation in the dorsal anterior cingulate cortex (dACC) in response to CS presentation. Both cortical thickness in this region and CS-evoked BOLD activation correlated positively with the magnitude of conditioned fear expression [28], suggesting that the dACC may mediate fear expression in humans. While homology across species is difficult to ascertain, the

authors of this study propose that the dACC may play a similar role in fear expression to the rodent prelimbic region.

Studies in humans examining differences in fear conditioning across development suggest that discrimination between threat and safety stimuli improves with age [29, 30]. An fMRI study examining age effects on discriminative fear conditioning reported that the increased differentiation of the CS+ versus CS− in adults versus adolescents correlated with their recruitment of dlPFC regions during fear conditioning [30]. While not typically proposed to play a key role in fear learning, the authors suggest that the dorsolateral prefrontal cortex (dlPFC) activity in this task may reflect a more general stimulus classification function. In contrast, adolescents showed significant differential activity (CS+>CS−) in the amygdala and hippocampus, while adults did not. Another study comparing discriminative fear learning in healthy versus anxious adolescents found that while both groups showed comparable degrees of discrimination, anxious adolescents displayed higher fear ratings overall, independent of stimulus type [31].

Collectively, convergent evidence in both animal models and humans suggests that the amygdala is necessary for the acquisition, storage, and expression of cued Pavlovian conditioned fear. Furthermore, in both species, prefrontal cortical regions appear to modulate conditioned fear expression.

Contextual Conditioning

While the amygdala is critical for fear learning to specific cues, in many circumstances the learned fear response extends to the larger context in which the aversive event occurred. This contextual fear is adaptive in that the location and circumstances under which dangerous events occur can be as informative about the impending danger as a specific cue that immediately precedes the event. In addition, the same cue may be dangerous in one context (e.g., a gun on a battleground) and safe in another context (e.g., a gun at a sporting store). Context allows one to adaptively modulate the cued-fear response, so it is appropriate to the situation. However, context can comprise many aspects of the environment, and how one interprets the context can be flexible. At times fear of context can generalize excessively, resulting in disorders such as phobias (particularly agoraphobia).

The contextual fear response requires the involvement of the hippocampus (Fig. 1), which is important in encoding contextual aspects of memory more broadly [32]. In rodents, conditioned fear to the context is assessed by placing the animal in a novel cage or context prior to the Pavlovian conditioning protocol and the presentation of the CS–US pairing. After fear conditioning, the animal exhibits not only a conditioned fear response to the CS but also the context in which the conditioning occurred. If amygdala damage follows, the animal fails to show conditioned fear to both the cue and context; however, if damage is localized to the hippocampus, conditioned fear to the CS is intact, but the animal no longer exhibits fear to the context [33]. Interestingly, unlike amygdala lesions, which impair conditioned fear even if damage occurs long after fear conditioning, the impact of hippocampal damage on contextual fear expression diminishes with the amount of time that passes following conditioning. This temporal gradient of retrograde amnesia for contextual fear following hippocampal damage suggests that once the contextual fear memory is fully consolidated, the hippocampus is no longer needed for its expression.

Studies on the development of contextual fear conditioning in rodents suggest pronounced qualitative differences in learning across the lifespan. Both pre-weanling (postnatal day 17, P17) and post-weanling (P24) rats show intact tone shock conditioning; only post-weanling rats exhibited freezing to the conditioning context on the subsequent day [34]. This contextual conditioning deficit is thought to reflect the increased maturation of the hippocampus in the older animals. Furthermore, a recent finding in mice suggests that the expression of contextual fear appears to be temporarily suppressed during adolescence [35]. In this study, contextual fear memories learned during or prior to adolescence were not expressed during this developmental stage; however, these memories reemerge during

adulthood. This temporary suppression of contextual fear expression is proposed to foster the exploratory behavior necessary for the transition from maternal care into independence, which typically occurs during this developmental stage.

In humans, finding independent conditioned fear effects for cue and context in the laboratory is somewhat difficult. The experimental setting is itself a strong context, and the use of techniques like brain imaging does not permit alterations of the actual context (i.e., the MRI machine). As a result, most investigations in humans examine the impact of context on cued conditioned fear expression. One such study, using images of two rooms as contexts and the colors of a light in the rooms as cues (CS+ and CS−), demonstrated that cued fear learned in one context and extinguished in another shows renewal upon reintroduction to the fear context [36]. However, there is evidence for enhanced fear to the context in conditioning paradigms where there is no distinct predictive cue CS [37, 38], and neuroimaging studies assessing the effect of context independent of cue report enhanced activation of the hippocampus [38, 39]. More recently, virtual reality techniques, similar to those that have been used in exposure therapy treatments for phobias [40], have been used to examine contextual fear in humans [38, 41]. Manipulating the context with virtual reality has enabled the independent assessment of cue and contextual fear-learning effects in a single learning paradigm in humans [42], revealing that contextual fear is acquired more rapidly than cued fear and that conducting cued-fear extinction in the acquisition context impedes extinction learning.

Social Learning of Fear

Although Pavlovian fear conditioning is a powerful model for understanding fear across species, it requires direct experience with an aversive event. In humans, many of our fears are learned through social means without direct aversive experience. For instance, a common phobia is fear of germs. Although science tells us germs exist, our perceptual systems do not detect them. Nevertheless, by learning about germs and their consequences through verbal instruction from parents and others, we routinely take preventative steps to diminish their potentially harmful effects. For some, this symbolic knowledge of the dangers of germs results in unwarranted fear and excessive preventative measures. This is an example where learning fear through social communication can result in a robust fear response and psychopathology.

In general, learning fears through social communication is adaptive in that one does not need to have painful experiences to know about potential threats. Social fear learning also expands the range of stimuli and events that can be associated with potential aversive outcomes. There are two primary means of social fear learning. The first, verbal instruction, is dependent on language and is unique to humans. The second is learning through direct observation of conspecifics in aversive circumstances. Observational fear learning has been shown to occur in some nonhuman primates and a few other vertebrates, such as birds and rodents (see [43] for a review).

In a typical instructed fear study, a participant is told she/he might receive a shock when presented a neutral stimulus (the instructed CS). This symbolic communication of threat has been shown to lead to robust fears that are difficult to distinguish from those learned through direct aversive experience [44]. One of the few differences is that Pavlovian CS's biologically "prepared" by evolution to yield more lasting fear responses (e.g., spiders, snakes, angry faces) will continue to show fear expression when presented subliminally (see [20] for a review). In contrast, awareness of the presentation of the instructed CS is necessary for the expression of instructed fear [45]. Although it is unlikely the amygdala is the site of storage for the symbolic representation underlying instructed fear, the amygdala seems to be necessary for instructed fear expression. An fMRI study of instructed fear in which subjects were told which stimulus carried the threat of shock (CS+) and which was safe (CS−) reported activation of the left amygdala in response to threat versus safe conditions that correlated with the

degree of fear expression [46]. A study examining the effect of right versus left temporal lobectomy on instructed fear learning found that lesions of the left, but not right, amygdala result in impaired expression of instructed fear [47]. This left hemisphere lateralization of instructed fear is consistent with left hemisphere representation of language more broadly. Unlike instructed fear, Pavlovian conditioned fear has been shown to involve both the right and left amygdala [23, 48].

Like instructed fear, observational fear leads to robust fear responses that are difficult to distinguish from Pavlovian conditioning. However, observational fear appears to be more similar in some ways to Pavlovian fear than instructed fear in that its expression is intact with subliminal presentation [45]. Furthermore, although being told about potential dangers may not result in an emotional response unless danger is imminent, observing a conspecific in an aversive circumstance can lead to an empathetic emotional response in the perceiver. For example, Olsson and colleagues [49] showed participants a video of a confederate undergoing a Pavlovian fear conditioning paradigm to serve as a model for the procedures the participant would experience in the following session. This comprised the learning phase. When observing the confederate receiving a shock, the participants showed an increase in skin conductance and bilateral amygdala activation indicating an emotional response during the observational fear learning. Consistent with observational fear, the participants also showed a fear response to the observational CS in the later test session, along with bilateral activation of the amygdala. Because there is a fear response during learning, as well as later expression of observational fear, it appears the observation itself acts as a social US, similar to a direct US, such as shock. Interestingly the strength of expression of observational fear correlated with activation during the learning phase in the insula, anterior cingulate cortex, and medial prefrontal cortex, regions that have been implicated in empathy and mentalizing about others [50, 51].

Control of Fear

Research on the neural mechanisms underlying fear learning provides insight in to the mechanisms underlying anxiety disorders in humans. However, translation of this knowledge into more effective treatment of fear-related anxiety disorders requires a better understanding of how learned fears can be diminished. Recent research in both humans and animal models has highlighted several means by which conditioned fear can be diminished. In this section, we describe the neural mechanisms underlying four fear-reduction techniques, extinction, cognitive regulation, active coping, and reconsolidation (Fig. 2).

Extinction

Extinction refers to the gradual decrease in fear expression that typically occurs when a conditioned stimulus is repeatedly presented without aversive reinforcement [1, 13]. This decrease reflects the occurrence of a new learned association that the CS that was once predictive of threat is now safe. The formation of an extinction memory does not overwrite the initial fear association between the CS and this aversive outcome, as evidenced by the fact that fear expression can return following extinction under a number of circumstances (see review by [13]). The term renewal refers to the return of fear following reexposure to the context in which an extinguished fear memory was initially learned. Reinstatement is the return of expression of an extinguished fear that occurs after the unsignalled presentation of the aversive unconditioned stimulus. Spontaneous recovery refers to the increase in fear expression that typically occurs following extinction with the mere passage of time. These situations in which extinguished fear reemerges suggest that extinction memory and the original fear memory

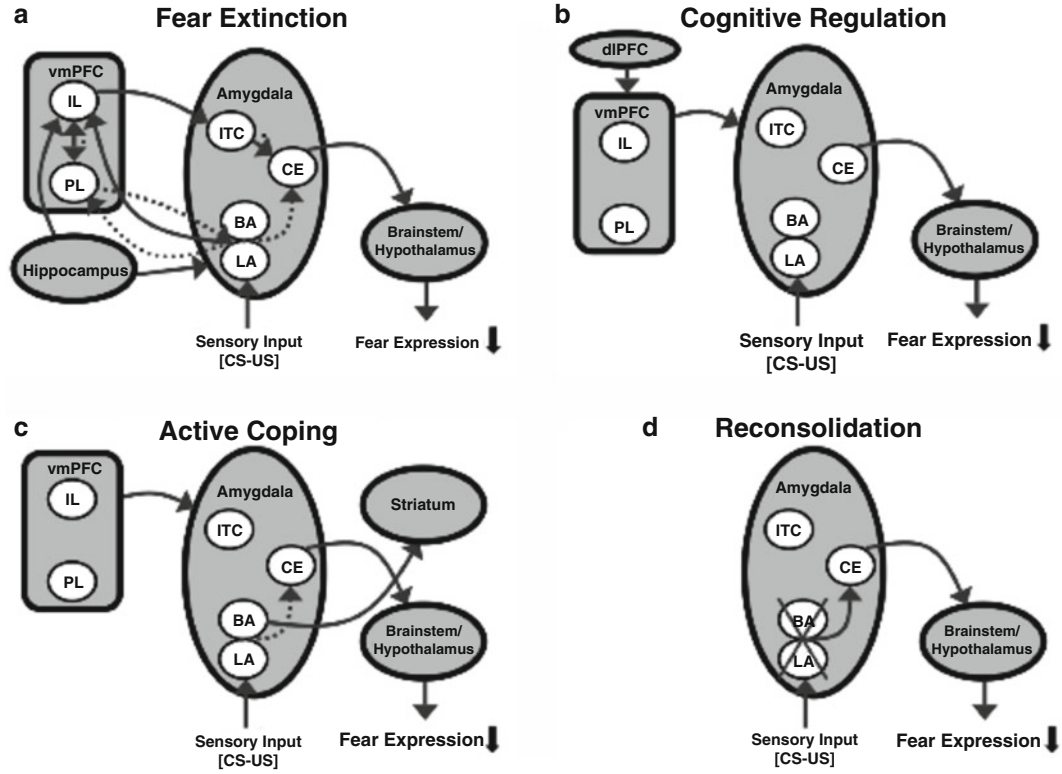

Fig. 2 Neural mechanisms of changing conditioned fear. (**a**) During fear extinction learning and consolidation, connections are established between the infralimbic (IL) subregion of the vmPFC and the inhibitory intercalated (ITC) cell masses, which inhibit activity in the CE. During extinction recall, these connections are activated, inhibiting fear expression. The IL and PL inhibit one another, mediating the competition between the fear and extinction memory for expression. Contextual modulation of extinction expression is mediated by projections from the hippocampus to the vmPFC and/or LA. (**b**) During cognitive regulation, the dorsolateral prefrontal cortex (dlPFC) regulates fear expression through projections to the vmPFC, which in turn inhibits amygdala activity. (**c**) During active coping, information from the LA is routed not to the CE, which drives fear expression, but to the B, which in turn projects to the striatum. The striatum is thought to reinforce instrumental action taken during instrumental learning. Following active coping, changes occur in the vmPFC such that it is activated by subsequent exposure to a stressor, inhibiting the fear response. (**d**) Reconsolidation diminishes conditioned fear expression through alteration of the original CS–US association stored in the LA

are engaged in a competition to determine which controls the behavior of the organism, a view that is consistent with our current understanding of the neurocircuitry supporting fear extinction.

Studies in animal models have made substantial progress in clarifying the neural circuits that underlie extinction learning (Fig. 2a). This research suggests that the acquisition of initial extinction learning, like the original fear memory, depends upon the amygdala. Pharmacological blockade of NMDA and glutamate signaling or mitogen-activated protein kinase (MAPk) activity within the basal and lateral nuclei or basolateral amygdala complex (BLA) impairs extinction learning [52–54]. BLA synapses appear to exhibit plastic changes following extinction training that support the consolidation of the extinction memory [55–58].

While the amygdala appears necessary for the initial acquisition of extinction learning, the ventromedial prefrontal cortex (vmPFC) plays a critical role in both the consolidation and retrieval of extinction memory (see [59] for a review) (Fig. 2a). While not essential for the initial acquisition of extinction learning [15], evidence from electrophysiological, pharmacological inactivation, and lesion studies implicates the infralimbic region (IL) of the vmPFC as a site of extinction consolidation [15, 60–62].

Following initial learning, the retrieval of extinction memory is mediated by the IL, which inhibits conditioned fear expression via its projections to the intercalated cell masses (ITC) within the amygdala, which in turn have inhibitory projections to the CE [63–65]. Projections from the hippocampus to the vmPFC and the amygdala appear to mediate the context-dependent expression of extinction [66, 67], providing information that determines whether extinction learning is retrieved or the original fear memory returns (see [13] for a review).

Growing evidence suggests that following extinction, distinct amygdala–prefrontal subnetworks control whether extinction memory or fear memory is expressed (see [68] for a review). A recent study demonstrated that distinct populations of cells within the BA are responsive to CS presentation during fear expression and extinction retrieval and that this region mediates the switches between these high and low fear states [69]. The BA is proposed to drive or inhibit fear expression in concert with the PL and IL prefrontal regions, respectively [68]. Further research is required to elucidate the detailed dynamics of this competition for behavioral control; however, this model suggests how the same CS may give rise to opposing behavioral responses depending on the available information about the contextual circumstances.

Studies in rodents have highlighted pronounced changes in extinction learning across development. Following extinction learning, post-weanling rats (24 days old) exhibit contextual renewal, spontaneous recovery, and reinstatement of conditioned fear, suggesting the existence of competing threat and safety memories; however, pre-weanling animals show none of these fear reemergence phenomena [70–72]. Unlike in adults, extinction learning in these pre-weanling animals does not recruit the vmPFC [73] but instead appears to overwrite the initial fear memory within the amygdala [72, 74]. This suggests that early-life extinction may yield fear erasure, suggesting a developmental window of opportunity for the treatment of fears acquired early in life. In contrast, adolescent rats show impaired retention of extinction learning [75, 76], suggesting that adolescence may represent a period of vulnerability to persistent fear.

An early functional neuroimaging study of extinction learning in humans [27] used a two-day paradigm in which subjects learned to discriminate between a visual CS+ and CS− on day one and then immediately underwent extinction, during which the CS+ was no longer paired with shock. On day two, subjects returned for a second extinction session to assess the retention of their extinction learning. This study reported increases in BOLD signal in a subgenual anterior cingulate/vmPFC region during initial extinction learning, as well as a corresponding decrease in amygdala BOLD activation. Further increases in vmPFC BOLD activation were observed during extinction recall on the following day [27]. Subsequent fMRI studies of extinction have also reported increased activation in the vmPFC during extinction retrieval [77, 78]. Furthermore, both the magnitude of vmPFC BOLD signal and the thickness of the cortex in this region have been found to correlate with the degree of extinction retrieval [78–80]. These findings suggest that this subgenual ACC/vmPFC region may be a human homologue of the rodent IL region and may directly inhibit fear expression via projections to the amygdala.

Studies in humans corroborate the role of the hippocampus in the context-dependent retrieval of extinction [77, 78]. Using a paradigm in which extinction learning is associated with a distinct visually identifiable context, increases in hippocampal BOLD activation were reported during extinction retrieval [77, 78]. Consistent with the evidence that the hippocampus mediates the context-dependent recall of extinction via connections with the vmPFC, hippocampal BOLD activation correlated positively with vmPFC activation [78]. Finally, individuals with hippocampal lesions show impaired context-dependent fear reinstatement [81], a finding that parallels observations in rodents [82].

In summary, studies examining extinction learning in humans have been largely consistent with the findings in animal models, suggesting that the underlying neurocircuitry is conserved across species.

Extinction-based techniques are commonly employed in cognitive-behavioral therapy to treat anxiety disorders. Exposure therapy involves establishing prolonged contact with the specific stimuli, thoughts, or experiences that elicit anxiety in a safe context [83]. As the current models of extinction

suggest, this process may result in the formation of a new safety memory that may override the expression of the fear memory. Thus, the ability to acquire and consolidate extinction learning may be critical for successful treatment. Consistent with this notion, a recent study reported that degree of extinction retention between exposure sessions predicted the long-term efficacy of treatment at reducing anxiety symptoms [84]. Furthermore, exposure therapy outcomes are improved by the administration of D-cycloserine, a drug that enhances extinction learning [85, 86]. A number of pharmacological agents have been identified that facilitate extinction learning in rodents [87], suggesting promise for the development of drug treatments that enhance the efficacy of exposure therapy.

Cognitive Regulation

While research in animal models has critically informed our understanding of how fear is attenuated during extinction, humans also regularly use an array of cognitive regulatory techniques to modulate emotional responses. Cognitive regulation refers to a range of automatic and intentional mechanisms by which thoughts are used to change emotions [88, 89]. Prominent theories propose that emotional responses arise when we attend to a stimulus and judge it to be motivationally significant [90, 91]. These models suggest that our allocation of attention and the manner in which we ascribe meaning to an event can be important determinants of our emotional experiences. Accordingly, recent studies in humans have demonstrated that intentional cognitive regulation techniques can be used to diminish negative emotional responses and have suggested a provisional model of the neurocircuitry underlying these effects [92, 93].

An early neuroimaging study of cognitive emotion regulation examined whether changes in our appraisal of a potentially unpleasant stimulus could diminish negative emotional responses [94]; see also [95]. In this study, participants viewed images with negative emotional content and were instructed to reinterpret the scene in a more positive manner, reducing their emotional response. For example, a participant viewing an image of a grieving man might instead interpret the scene as depicting a man shedding tears of joy at wedding. This "reappraisal" technique, in which the individual changes the affective significance of a stimulus, also reduced subjects' ratings of negative affect [94]. This study provided a preliminary outline of the neural mechanisms underlying the cognitive regulation of negative affect. The neuroimaging data showed that during reappraisal of the negative scenes, in comparison to simply attending to them, BOLD activation in the amygdala decreased, while activation in both dorsolateral (dlPFC) and ventrolateral (vlPFC) prefrontal cortex increased [94].

Several subsequent studies employing similar cognitive regulation techniques have observed reductions in self-reports and physiological measures of negative affect evoked by diverse stimuli including unpleasant pictures and films (see [93] for a review) and even aversion to monetary loss [96, 97]. Those studies that conducted functional imaging of these tasks largely confirm the provisional neurocircuitry described above, in which regulation evokes an increase in BOLD activation in dlPFC and/or vlPFC accompanied by a decrease in amygdala activity that mirrors the associated decrease in negative affect (see [93, 98] (Fig. 2b)). The interpretation of this pattern of activation is that engagement of the dlPFC reflects executive control processes involved in carrying out the cognitive strategy, while the vlPFC is involved in the selection of the novel emotional interpretation of the stimulus [92, 98]. The reduction in amygdala activation is typically interpreted as evidence of successful deployment of a top-down control process that changes the affective value of the stimulus and the associated measure of negative affect. However, one neuroanatomical conflict with this model is that the dorsolateral prefrontal cortex does not have direct projections to the amygdala [5, 99]. One suggestion is that ventromedial prefrontal regions may mediate the reduction in amygdala activity via strong projections to this region [100, 101]. Thus, cognitive regulation may recruit the same vmPFC–amygdala neurocircuitry implicated in attenuating fear following extinction learning.

A recent study directly examined whether intentional cognitive regulatory strategies and fear extinction share overlapping neural substrates [102]. In this study, participants viewed conditioned stimuli that were colored squares while instructed to either attend to their natural response or regulate these responses by generating a pleasant mental image of something soothing in nature associated with the CS color. Conditioned responses in the regulation condition were significantly lower than when participants simply attended to their anticipatory responses. This reduction in fear was accompanied by decreased amygdala activity and increased activity in both the dlPFC and a region of the vmPFC that, when compared to a previous study of extinction learning, overlapped with a region activated during extinction. Furthermore, activity in the vmPFC was correlated with that of the amygdala and dlPFC, providing further evidence that dlPFC inhibition of amygdala activity is mediated by the vmPFC. Thus, despite the fact that the regulation of fear through the use of cognitive strategies may be unique to humans, this suggests that cognitive fear regulation recruits the same vmPFC–amygdala extinction circuitry that is evolutionarily conserved across species.

Few studies have examined the use of cognitive regulation strategies to reduce negative affect in individuals with anxiety disorders [103, 104]. However, two recent neuroimaging studies highlight differences in the functioning of the neurocircuitry supporting cognitive regulation between patients and healthy individuals. In these studies [105, 106], cognitive regulation of emotional responses to negative stimuli (negative self-beliefs and physical and social threat-related images) was effective in reducing both ratings of negative affect and neural activity in the amygdala in both healthy controls and patients with social anxiety disorder. However, activity in prefrontal regions differed between controls and patients. While controls show robust early activity in dlPFC and vmPFC that decreased over trials, patients displayed increases in these regions across time with both smaller and later peaks. Furthermore, analysis of regions correlated with amygdala activity during regulation revealed a greater extent of the dlPFC inversely correlated with amygdala activity in controls than in patients [106].

Cognitive therapy techniques taught in a clinical context encourage individuals with anxiety or depression to overcome their biases toward negative situational appraisals, thus diminishing their corresponding negative emotional responses [107]. Experimental studies of cognitive regulation in the laboratory delineate the neural pathways through which this regulation takes place. While the deployment of cognitive regulation techniques may be improved through instruction and practice, the efficacy of treatment of fear-related disorders via cognitive therapy may depend on the functional and structural integrity of the prefrontal–amygdala regulatory neurocircuitry [108]. The structural integrity of the white matter tract that comprises this inhibitory pathway varies between individuals and is inversely correlated with trait anxiety [109]. Such individual variation may contribute significantly to the heterogeneity in individual responses to clinical cognitive interventions.

Active Coping

To date, experimental research on the control of fear has focused primarily on how cognitive processes, such as implicit safety learning during extinction or intentional cognitive regulation, can alter fear expression. However, a common means by which we regulate our emotions in everyday life is through the performance of actions that improve our emotional state. The term “active coping” can refer to any action taken to mitigate or avoid aversive experiences or to bring about a positive experience.

Actively coping with a fear-eliciting stimulus requires a sequence of distinct learning processes. First, one must learn that a stimulus or a context poses a threat via the formation of a Pavlovian fear association. Next, the exercise of control over the fear-eliciting situation requires that one learn an action that can be taken to avoid or escape the feared stimulus. Finally, recent research suggests that neural changes occurring following the exercise of control over a stressor diminish subsequent fear

expression [110] and buffer the effects of future exposure to uncontrollable stressors [111]. Through these processes, active coping enables the modulation of fear responses to both present and future aversive situations.

Relative to other fear-reduction techniques, our understanding of the neural substrates that support actively coping with fear is rudimentary. However, existing studies provide a provisional model of the neural circuits involved in each stage of the active coping process (Fig. 2c). As described above, once a Pavlovian fear memory has been learned, the presentation of a conditioned stimulus activates the LA, which in turn activates the CE, triggering fear expression via descending projections to the brainstem and hypothalamus. Evidence that an alternative amygdala pathway plays a critical role in instrumental learning phase comes from a study employing an escape from fear (EFF) task, in which an instrumental response terminates exposure to a tone CS that was previously paired with shock [112]. This study showed that lesions to the CE impaired the expression of the Pavlovian conditioned freezing response. Lesions to the BA prevented the acquisition of an EFF avoidance response. Lesions to the LA prevent both fear expression and instrumental learning, suggesting that the LA plays a critical role in both Pavlovian and instrumental learning. The LA projects to the BA, which in turn has striatal projections that play a key role in instrumental reinforcement learning [113]. Engaging the LA–BA pathway likely guides instrumental learning in the EFF task by providing conditioned reinforcement signals that motivate the avoidance response.

In contrast, engagement of the LA–CE pathway, which drives fear expression, may prevent the performance of active coping behavior. In an active avoidance task in which rats had to learn to shuttle across a chamber in order to avoid a shock [114], post-training lesions of the CE had no effect on shuttling behavior in animals that had learned to avoid the shock. Surprisingly, in animals that had not learned to consistently avoid the shock, lesions to the CE revealed that they had indeed learned the avoidance contingency. When the CE-mediated freezing response was disengaged, these animals were then able to perform the avoidance response. This suggests that excessive fear may impair active coping by preferentially engaging defensive Pavlovian responses.

The experience of control over a stressor that occurs during active coping appears to foster resilience to subsequent stressors, reducing fear-related behavior even in future uncontrollable situations [111]. Studies demonstrating this effect used a triadic design, in which rats were first exposed to escapable shock, yoked inescapable shock of identical intensity and duration of that experienced by a paired individual in the escapable condition, but that could not be escaped, or a control condition involving no shock exposure. One week later, these animals underwent fear conditioning [110]. Exposure to inescapable stress increased conditioned fear in comparison to control animals. However, surprisingly, animals exposed to controllable shock exhibited less fear than animals with no prior shock exposure, suggesting the experience of controllable stress inhibited subsequent fear. Evidence suggests that the vmPFC mediates the effects of prior behavioral control on future stressor-evoked behavior. Inactivation of the vmPFC during controllable stress or during exposure to a subsequent stressor negates the effects of controllability on later behavior [115, 116]. Either the vmPFC or an afferent input region appears to detect when a stressor is under an organism's instrumental control and, in turn, inhibits the physiological and behavioral effects of uncontrollable stress [115]. Furthermore, the experience of controllable stress appears to give rise to long-term changes in the vmPFC that enable it to be activated during subsequent uncontrollable stress, regulating the behavioral response [117]. The IL subregion of the vmPFC is activated by controllable stress [118] and may later inhibit the CE directly, mitigating fear expression [116].

Consistent with this notion that control over stressors engages the same vmPFC–amygdala pathway active during extinction retrieval, active coping appears to prevent the spontaneous recovery of fear [110, 119]. In one such demonstration [119], animals first were fear conditioned; then one group of animals learned an EFF response, terminating exposure to a tone CS, while a second group received yoked tone exposure, essentially undergoing classic extinction. Both groups showed reduced fear during their respective learning phase; however, in a subsequent retrieval test, the extinction group

showed the typical recovery of fear, while the group that had learned an active coping response did not. A major shortcoming of the extinction-based therapies that are typically used to treat fear-related anxiety is that extinguished fears often reemerge. This finding suggests that therapeutic approaches employing active coping techniques may yield a more lasting reduction in fear.

Few studies have explored fear reduction through active coping in humans; however, the preliminary data suggest that the underlying neurocircuitry is shared across species. An fMRI study examining the neural substrates of avoidance learning found that when subjects learned to avoid a shock by performing a key press during CS presentation, performance of this response led to an increase in striatal activation, as well as a decrease in amygdala activation that was accompanied by a reduction in fear expression [120].

Given that the avoidance of fear-eliciting situations is a hallmark of anxiety disorders, the notion that avoidance behaviors might foster resilience might appear counterintuitive and warrants clarification. Avoidance of a stressor can occur through either a passive or active route. A passive avoidance response involves withdrawal from threat, preventing encounters with a fear-eliciting stimulus through the suppression of thoughts or behavior, akin to the freezing response displayed by rodents. In contrast, an organism may show a proactive exploratory avoidance response, attempting to escape or "disarm" a present threat through action. Evidence from studies in rodents suggests that individuals may show stable biases toward active or passive coping styles [121], and a recent study suggests that a bias toward active or passive fear responses may be determined by the function of an intra-amygdalar circuit [122]. While cognitive-behavioral therapy often aims to reduce avoidance behavior, research suggests that the active type of avoidance response may be adaptive, yielding long-term resilience. Thus, it may be that forms of avoidance behavior that engage the individual in action to directly mitigate the aversiveness of a feared object or situation have beneficial consequences. An important area for future investigation is to examine the effect of active versus passive coping responses (including active avoidance behavior) in humans to clarify its effects on subsequent fear expression.

Reconsolidation

All of the techniques to diminish fear described above control the fear response through inhibition of the amygdala via the prefrontal cortex. Although these techniques can be very effective, they leave the amygdala's fear representation largely intact. As described earlier in the section on extinction, one consequence is that the fear can return under a range of circumstances. In the clinic, this intact fear representation may be an important factor linked to the potential for relapse following successful treatment. Due to this limitation, there has been growing interest in emerging techniques to target the amygdala's fear representation by influencing memory reconsolidation.

Reconsolidation refers to a process by which a previously consolidated memory is brought back to a fragile or labile state when retrieved and requires a second consolidation process, or reconsolidation, for re-storage. For most of the last century, the standard model of memory suggested that immediately after information is learned, it is fragile and prone to disruption because the synaptic processes that form the memory require time. This memory formation process is called consolidation. However, once a memory has been fully consolidated, it was assumed that the memory was stable and no longer prone to disruption. New learning about a stimulus could create a second memory trace, but the original memory trace was still intact. Over the last decade, however, there has been renewed interest in the notion that every time a memory is retrieved, it is once again in a fragile state and requires a second consolidation process, or reconsolidation, and new synaptic plasticity to once again become stable. If memory is fragile after retrieval, this provides a second opportunity to potentially disrupt or permanently alter the memory before it is reconsolidated. In the case of fear memories, this provides an avenue to alter the original fear memory, as opposed to inhibit its expression (Fig. 2d).

Initial evidence for fear memory reconsolidation was provided in a seminal study by Nader and colleagues [123]. As mentioned earlier, the LA is thought to be the site of fear memory storage. Nader and colleagues hypothesized that if fear memory reconsolidation requires new synaptic plasticity, which requires protein synthesis, then injecting a protein synthesis inhibitor into the LA after retrieval should prevent reconsolidation and permanently alter the original fear memory. To test this, they conditioned rats to fear a tone CS. After initial consolidation of this fear memory, the rats were exposed to the tone again to reactivate the memory. This was immediately followed by administration of the protein synthesis inhibitor anisomycin into the lateral amygdala. A day later, the conditioned fear response was assessed. The rats that received the injection immediately after cue retrieval showed reduced expression of conditioned fear in comparison to rats receiving placebo, no reminder and injection of the drug, or injection of the drug 6 h after the reminder cue when the reconsolidation process was complete.

Since this study, there have been hundreds of studies in nonhuman animals investigating the mechanisms of fear memory reconsolidation. This research has basically supported these initial findings suggesting that the original fear memory is significantly altered by targeting reconsolidation, although some important distinctions in both the temporal molecular requirements and the brain regions involved in reconsolidation and initial consolidation have emerged (see [124] for a review).

In humans, however, there has been less success in demonstrating fear disruption by targeting reconsolidation. A primary reason is that the protein synthesis inhibitors typically used to target reconsolidation in other species have not been verified as safe for use in humans. In an effort to introduce a safe pharmacological intervention, Debiec and LeDoux [125] examined whether propranolol, a beta-adrenergic blocker that has been shown disrupt some forms of amygdala-dependent consolidation [126], would also disrupt fear memory reconsolidation. Propranolol is commonly prescribed to help with stage fright and has also been used in treating high blood pressure. Using both systemic and intra-amygdala injections in rats, they showed administering propranolol immediately after fear memory reactivation abolished the conditioned fear response at later test. Unfortunately, studies examining the efficacy of propranolol in human fear memory reconsolidation have been mixed. In an initial attempt, Brunet and colleagues [127] administered propranolol after the retrieval of traumatic memories in patients suffering from post-traumatic stress disorder (PTSD). Although at later test these patients showed some evidence of diminished physiological fear responses when cued with these memories, this manipulation did not have a lasting impact on PTSD symptoms. In a laboratory Pavlovian paradigm examining the influence of propranolol administration after reactivation on later fear expression found only a transitory reduction of later fear expression (see [128] for a discussion). Finally, a series of studies examining the impact of propranolol administration prior to cued-fear memory reactivation found some evidence that later fear expression was impaired but only for a limited range of fear assessments [129]. In these studies, however, it is possible that the administration of propranolol prior to fear memory reactivation disrupts a mechanism of fear expression, as opposed to reconsolidation [130].

Given some of the difficulties of using pharmacological manipulations to target fear memory reconsolidation in humans, a recent series of studies have used a different approach. These studies take advantage of the potential adaptive function of reconsolidation. If the purpose of reconsolidation is to update old memories with new relevant information available at the time of retrieval, then it is possible that introducing new information during the reconsolidation process will alter the original memory and have a lasting impact on the memory expression. This basic effect was demonstrated in humans in a clever series of studies on motor memory, in which introducing a new motor sequence after reminding participants of a previously learned motor sequence impaired later memory for the older sequence [131]. In fear learning, this behavioral interference of reconsolidation effect has been observed in mice [132], rats [133], and humans [134] using extinction training precisely timed to coincide with memory reconsolidation to interfere with the original fear memory. The primary difference between using extinction training to update the fear memory during reconsolidation and standard

extinction training is the timing. Fear memory reconsolidation is initiated by the retrieval or reactivation of the fear cue. After reactivation, it takes somewhere between 3 and 10 min for the reconsolidation process to begin [133, 134]. If extinction training begins too early, both the return of the fear response and indicators of synaptic plasticity within the LA [133] are consistent with standard extinction training. However, if extinction training is slightly delayed until the reconsolidation process has begun, the fear does not return, in contrast to standard extinction. In addition, changes in the LA under this behavioral interference protocol suggest learning-induced plasticity consistent with reconsolidation [133]. In humans, it has been shown that this diminished fear response with behavioral interference of reconsolidation is apparent even after a year [134]. More recently, in an examination of the molecular mechanisms underlying this effect, Clem and Huganir [132] demonstrated that the behavioral interference of reconsolidation might be linked to calcium-permeable AMPA receptor dynamics within the LA.

Although research on reconsolidation in humans is just emerging, it provides an exciting avenue for future research because it potentially eliminates the necessity for prefrontal inhibition of the amygdala. Variation in function of the amygdala–prefrontal pathway has been linked to both the recovery of fear following extinction and PTSD [135]. As of yet, the efficacy of these techniques has not been investigated in clinical interventions, and there may be significant limitations, such as the ability to target specific memories. However, if these techniques prove to be clinically useful, fear reconsolidation research has the potential to yield more lasting and effective treatments of anxiety disorders.

Conclusion

Through cross-species research in animal models and in humans, we have obtained a detailed model of the neurobiological underpinnings of fear learning. As described above, the amygdala plays an important role in cued, contextual, and social means of fear acquisition, highlighting its central role in fear acquisition and expression. Additionally, the hippocampus modulates the acquisition and expression of fear to a context. Drawing upon this detailed neurobiological model of fear conditioning, research in the past decade on fear extinction has delineated how safety learning following conditioning activates a prefrontal–amygdala pathway, inhibiting fear expression [59]. This inhibitory circuit is also modulated by contextual information relayed via the hippocampus. Notably, cognitive regulation and active coping, means of fear regulation that differ substantially from extinction, also recruit this phylogenetically shared inhibitory pathway [136, 137]. However, as these methods inhibit intact fear memories that can return under certain circumstances, they may all yield a transitory attenuation of fear. Recent work on reconsolidation suggests that pharmacological or behavioral interference with a fear memory following retrieval may permanently alter its representation, suggesting a mechanism for long-term prevention of fear recovery [128].

A central goal of fear research is to understand the origins of pathological anxiety in humans. Fear conditioning serves as an experimental model for the real-world associative learning that causes stimuli in our environment to evoke negative affective responses. Excessive generalization or poor regulation of such learning is proposed to underlie the persistent fear that characterizes anxiety disorders [138] and may contribute to the biased decision-making associated with these clinical conditions [139]. While neuroscientific fear research has outlined the mechanisms modulating fear expression in the typical “average” individual, one important question that remains poorly understood is what gives rise to the substantial variation between individuals in fear acquisition and regulation. Future research elucidating how variation in both the genetic and experiential background of the individual shapes the neurocircuitry governing fear learning will play a critical role in translating fear research from the laboratory to clinical treatment methods. Furthermore, the small body of research on the developmental

trajectory of fear learning and regulation indicates that there are important qualitative differences in these processes across development. An improved understanding of the development of fear conditioning will be a necessary step toward understanding the origins of vulnerability to and resilience against anxiety disorders across the lifespan.

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Neurobiology of Pediatric Anxiety Disorders

Amanda E. Guyer, Carrie L. Masten, and Daniel S. Pine

Abstract Anxiety during childhood and adolescence is a highly prevalent problem that contributes to long-term dysfunction in adulthood. This chapter highlights research on the neurobiology of pediatric anxiety disorders aimed at understanding how anxiety takes hold in the brain and the mechanisms that fuel its developmental course. We present an overview of anatomical and functional brain-based differences in children and adolescents with and without anxiety disorders. With regard to work focused on brain function in pediatric anxiety, we discuss four key psychological processes that are highly relevant to clinical characteristics in anxiety: attention orienting, threat learning, social–emotional information processing, and reward processing. We also review recent work that delineates connections between and within neural regions that appear to be distinctly modulated by anxiety both in response to specific tasks and while at rest. We close the chapter with a summary of emerging work on neurobiological response to treatments for anxiety in children and adolescents, followed by conclusions and future directions for this course of work.

Keywords Anxiety • Adolescence • Childhood • Neuroimaging • Brain structure • Brain function • Neural connectivity

Introduction

Anxiety disorders are highly prevalent and exert adverse effects on children and adolescents in both the short and long term [1, 2]. Despite their high prevalence and major impact on functioning over time, pediatric anxiety disorders have been largely understudied, particularly from a neuroscience perspective [3, 4]. Relative to less common conditions that arise in childhood, such as attention deficit hyperactivity disorder and autism, far fewer studies examine the pathophysiology of pediatric anxiety [5].

A.E. Guyer (✉)
Department of Human Ecology and Center for Mind and Brain, University of California, Davis, CA, USA
e-mail: aeguyer@ucdavis.edu

C.L. Masten
Department of Psychology and Human Development, Peabody College, Vanderbilt University, Nashville, TN, USA

D.S. Pine
Section on Development and Affective Neuroscience, National Institute of Mental Health, Bethesda, MD, USA

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This chapter presents four sections that review research on the neurobiology of pediatric anxiety disorders with an emphasis on neuroimaging studies. First, we briefly introduce the primary brain regions involved in fear responses. Next, we highlight the development of these regions during childhood and adolescence. In the third section, we review neuroimaging findings in pediatric anxiety with a focus on research directed at mapping relationships among brain function, psychological processes, and clinical characteristics. In particular, we review four constructs reflecting key cognitive and emotional processes associated with differentiated behavioral and neural responses in anxious and non-anxious individuals: (1) attention orienting, (2) threat learning, (3) social–emotional information processing, and (4) reward processing. In the fourth section, we present recent work focused on understanding the connections between and within neural regions that appear to be distinctly modulated by anxiety both in response to specific tasks and while at rest. Finally, we discuss emerging work on neurobiological responses to treatment for anxiety in children and adolescents.

Discussions throughout this chapter primarily review studies of pediatric samples with one of three anxiety disorders: generalized anxiety disorder (GAD), social phobia (SoPh), or separation anxiety disorder (SAD), as they are highly prevalent among children and adolescents [2]. These three disorders also are frequently comorbid and exhibit similarities in many features, such as course and treatment response. As a result, questions remain concerning the degree to which they represent unique conditions or alternative manifestations of the same underlying syndrome. This chapter reviews data both on their similarities and differences, although very little research documents clear differences among these disorders from a neurophysiological perspective. Thus, in the following discussion, we refer to these disorders together as "pediatric anxiety."

While other anxiety disorders occur in children, they are not the focus of this chapter. Obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) are not a main focus here given their unique pathophysiological profiles. Similarly, panic disorder is rare before late adolescence and accordingly is only minimally discussed. Finally, specific phobia is not discussed as it has been the focus of very little neurobiological research with children. For in-depth discussion about these disorders, readers are referred to Chaps. 9 and 10 in this volume. In addition, given our focus on neuroimaging and pediatric anxiety, the research reviewed herein primarily focuses on studies of individuals in late childhood through late adolescence given greater availability of research published in this age range relative to younger ages.

Brain Regions Implicated in Fear Processing

Considerable work has delineated the engagement of a neural fear circuitry that processes and guides responses to threat in one's surroundings [6–8]. In this basic science work, the term "threat" refers to collections of cues that signal the presence of danger to the organism. When such threats are proximal, immediately present, and extremely dangerous, they are thought to evoke a state of "fear" in the organism; when they are more distal, less immediate, and more ambiguous in terms of their dangerousness, they evoke a state of "anxiety." Such work provides useful cross-species models for understanding the neurobiology of threat processing, fear, and anxiety responses in humans across various stages of development [3, 9]. Drawing on research in both animals and humans, the neural circuitry implicated in threat processing and fear-related behaviors centers on the amygdala, located in the medial temporal lobe, as well as the ventral prefrontal cortex (vPFC). The amygdala aids in processing information about salient stimuli either positive or negative in valence and in mediating emotional responses [10–12]. The vPFC encompasses at least two subregions [13]. One of these subregions encompasses the lateral PFC and is involved in attention control along with other related processes. The other subregion encompasses the medial PFC, which has been implicated in fear extinction.

Lesion studies have confirmed hypotheses about the amygdala's role in processing stimuli that signify threat and translating reactions to fear-induced behaviors. For example, the application of lesions to the amygdala in nonhuman primates results in decreases in anxious behavior and blunted fear responses [6, 14, 15]. Similarly, a series of studies in humans show that adults with amygdala lesions cannot recognize fearful facial expressions, despite the ability to identify other facial expressions of emotion [7, 16, 17].

Facets of Brain Development Relevant to Pediatric Anxiety

Adolescence is a period of heightened emotionality and cognitive-regulatory changes driven in part by maturation of brain structures and their functions [18]. Subcortical brain structures that support basic functions such as detecting danger and safety in the environment (e.g., the amygdala) and forming memories that guide future behavior (e.g., the hippocampus) follow a relatively early maturational trajectory given their role in human survival [19]. Cortical brain structures such as the prefrontal cortex (PFC) show a more prolonged and continued maturation pattern across adolescence and into early adulthood. During this time, the PFC shows a decline in gray matter volume reflecting the pruning of unused and unnecessary neural circuits [20] and an increase in white matter as signal transmission becomes faster and more efficient [21]. Such a prolonged maturational period suggests that frontal brain areas do not reach full functional status until late adolescence or early adulthood [22]. Thus, adolescents may be vulnerable to the onset of mental illnesses such as anxiety and depression due to immaturity of PFC-based cognitive-regulatory functions [23]. Indeed, adolescents in the middle-late stages of puberty relative to those in early stages of puberty show altered patterns of amygdala and ventrolateral PFC responses that vary based on the emotional and social nature of stimuli and that relate to negative affect and mood [24].

Because the amygdala and associated projections are implicated in the detection and evaluation of potentially threatening stimuli [6, 25], developmental changes in structural characteristics of the amygdala should be considered with regard to understanding the emergence of pediatric anxiety. For example, the rate of amygdala growth in the nonhuman primate is most accelerated within the early postnatal period after which amygdala growth begins to decelerate and flatten [26]. The timing of damage to the amygdala also shows unique effects on fear responses as a function of development. For example, amygdala lesions applied to monkeys in adulthood result in reduced social fears, whereas such lesions applied in childhood lead to increased social fears [27]. In humans, structural changes in the amygdala generally extend from one year of age into late childhood [19]. Sex differences have also been noted in amygdala development, whereby females show adult volumes by age 4 and males show continued amygdala volume growth from ages 4 to 18 [28–30]. Finally, as amygdalo-cortical fibers thicken in adolescence, better regulatory control with respect to harm avoidant behaviors may be coming online [31].

Brain Function in Pediatric Anxiety

Before beginning discussion of studies of brain function, it is important to review the two published studies of brain morphology in pediatric anxiety. These studies, which include early adolescent samples, have reported discrepant results. Specifically, compared to samples of typically developing children, youth with GAD exhibited greater amygdala volumes [32], whereas reduced amygdala volume was identified in adolescents with GAD, SAD, or SoPh [33]. Morphometry of other regions has also differentiated healthy youth from those with anxiety. Notable patterns in children with anxiety

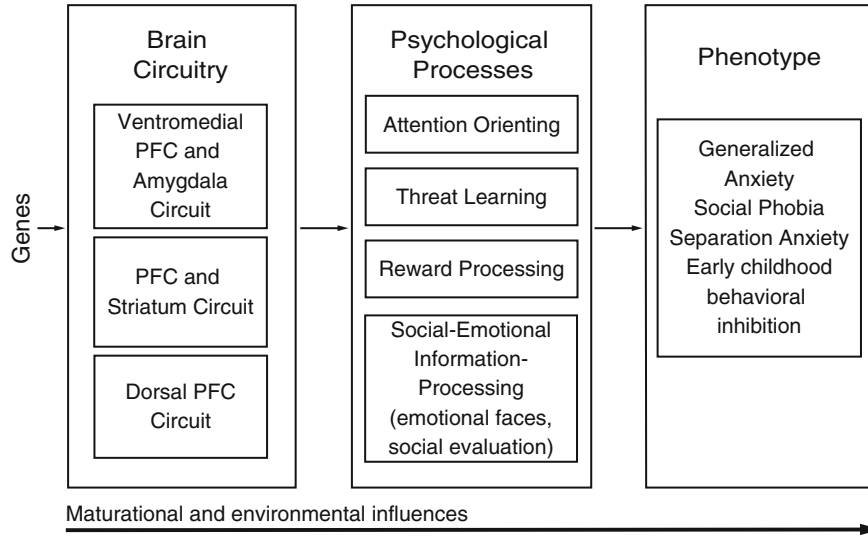

Fig. 1 A schematic framework of the mechanisms underlying associations among brain circuitry, psychological processes, and phenotypes, accounting for the influences of genes, environments, and maturation. *PFC* prefrontal cortex

compared to healthy comparisons show larger superior temporal gyrus [34] and decreased volume of the ventrolateral PFC and precuneus [33]. While these studies provide preliminary evidence of structural differences associated with pediatric anxiety, more work is clearly needed to elucidate characteristic structural perturbations of these disorders.

Relative to the number of structural neuroimaging studies in pediatric anxiety, functional neuroimaging studies are a burgeoning area. A goal of this work is to link neural function with psychological processes that are characteristic of specific anxiety phenotypes and symptoms, while also accounting for genetic, maturational, and environmental influences (see Fig. 1) [4]. In pediatric anxiety, it has been hypothesized that both fear and reward circuits are involved. Thus, much of the functional neuroimaging work in children and adolescents has examined amygdala function in response to threatening stimuli such as fearful or angry faces. However, intriguing findings are now emerging in pediatric anxiety regarding the role of the striatum and vPFC, which support reward processing and regulatory processes that may provide new avenues of research on, and treatment approaches for, pediatric anxiety.

In this section, we highlight evidence gathered from a growing body of work that uses functional magnetic resonance imaging (fMRI) to examine the neural substrates of different psychological processes relevant to the symptoms of anxiety in children and adolescents. FMRI has proven to be a useful technique to pursue these investigations because of its excellent temporal and spatial resolution. In addition, fMRI procedures are safe, noninvasive, and tolerable for use with young populations. Below we focus on pediatric fMRI studies that assess the neural correlates of core anxiety-related cognitive and affective processes including attention orienting, threat learning, social–emotional information processing, and reward processing (refer to Table 1 [35–52] for study details). Many of these studies use faces depicting emotional states as stimuli as well as other emotionally evocative (but not extremely frightening) stimuli. These stimulus types are generally used with pediatric populations in order to (1) adhere to ethical research designs due to potential harm from exposure to extremely threatening or frightening stimuli; (2) remove confounds introduced by word-based stimuli that may be associated with age-related differences in emotional and linguistic processing abilities; (3) consistently and reliably capture attention; and (4) represent stimuli encountered regularly by children in their daily lives.

Table 1 Functional neuroimaging studies including children and adolescents with anxiety diagnoses, anxiety symptoms, or risk for anxiety

Study	Sample demographics	Anxiety status	Task
Attention orienting			
Monk et al. [35]	Age range: 9–17 years Patient group: $n=18$, 8 females Healthy group: $n=15$, 8 females	Generalized anxiety disorder	Attention to angry faces using a dot-probe task
Monk et al. [36]	Age range: 11–16 years Patient group: $n=17$, 6 females Healthy group: $n=12$, 6 females	Generalized anxiety disorder	Attention to masked angry faces using a dot-probe task
Telzer et al. [37]	Age range: 11–18 years Healthy group: $n=16$, 8 females	Trait anxiety	Attention to angry faces using a dot-probe task
Social–emotional information processing			
Face emotion processing			
Thomas et al. [38]	Age range: 8–16 years Patient group: $n=12$, 5 females Healthy group: $n=12$, 5 females	Generalized anxiety disorder and/or panic disorder Anxiety symptom severity	Fearful face processing using a passive viewing face emotion task
Killgore and Yurgelun-Todd [39]	Age range: 8–15 years Healthy group: $n=16$, 7 females	Anxiety symptom severity	Fearful face processing using a passive viewing face emotion task
McClure et al. [40]	Age range: 10–14 years Patient group: n = 17, 7 females Healthy group: $n=20$, 11 females	Generalized anxiety disorder	Attention to subjective fear of fearful faces using an attention–emotion face task
Perez-Edgar et al. [41]	Age Range: 10–15 years Behaviorally inhibited group: $n=10$, 8 females Non-Inhibited group: $n=17$, 9 females	Risk for anxiety	Attention to subjective fear of fearful faces using an attention–emotion face task
Beesdo et al. [42]	Age range: 11–16 years Anxiety no MDD: $n=16$, 5 females MDD no anxiety: $n=12$, 7 females MDD with or without anxiety: $n=26$, 15 females Healthy controls: $n=45$, 24 females	Generalized anxiety disorder, social phobia, separation anxiety disorder, and/or major depressive disorder	Attention to subjective fear of fearful faces using an attention–emotion face task
Lau et al. [43]	Age range: 10–16 years Patient group: $n=31$, 18 females Healthy controls: $n=33$, 18 females	Generalized anxiety disorder, social phobia, separation anxiety disorder, and/or major depressive disorder	Attention to subjective fear of fearful faces using an attention–emotion face task
Blair et al. [44]	Age range: 9–41 years Patient group: $n=39$, 14 adolescents, 22 females Healthy group: $n=39$, 16 adolescents, 17 females	Social phobia	Gender judgment of faces using a morphed facial emotion task
Social evaluation processing			
Guyer et al. [45]	Age range: 9–15 years Patient group: $n=14$, 10 females Healthy group: $n=14$, 10 females	Social phobia, generalized anxiety disorder + social concerns, and/or separation anxiety disorder + social concerns	Anticipation of peer evaluation using the chat room task

(continued)

Table 1 (continued)

Study	Sample demographics	Anxiety status	Task
Lau et al. [46]	Age range: 9–14 years Patient group: $n = 12$, 8 females Healthy group: $n = 12$, 8 females	Social phobia, generalized anxiety disorder + social concerns, and/or separation anxiety disorder + social concerns	Receipt of peer evaluation using the chat room task
McClure-Tone et al. [47]	Age range: 10–15 years Patient group: n = 12, 7 females Healthy group: $n = 17$, 8 females	Generalized anxiety disorder, social phobia, and/or separation anxiety disorder	Betrayal and cooperation using a Prisoner's Dilemma task
Reward processing			
Guyer et al. [48]	Age range: 10–15 years Behaviorally Inhibited Group: $n = 13$, 8 females Non-inhibited group: $n = 19$, 10 females	Risk for anxiety	Response to anticipated incentives using the monetary incentive delay task
Krain et al. [49]	Age range: 13–17 years Patient group: $n = 16$, 7 females Control group: $n = 13$, 8 females	Generalized anxiety disorder and/or social phobia	Intolerance to uncertainty using the Hi/Lo decision-making task
Bar-Haim et al. [50]	Age range: 14–18 years 15 females Behaviorally inhibited group: $n = 16$, 5 females Non-inhibited group: $n = 16$, 10 females	Risk for anxiety	Response to anticipated incentives using a reward contingency task
Helfinstein et al. [51]	Age range: 14–18 years Behaviorally inhibited group: $n = 16$, 5 females Non-Inhibited group: $n = 16$, 10 females	Risk for anxiety	Response to incentive outcomes using a reward contingency task
Guyer et al. [52]	Age range: 10–16 years GAD group: $n = 18$, 10 females Social phobia group: $n = 14$, 9 females Healthy group: $n = 26$, 11 females	Generalized anxiety disorder and/or social phobia	Response to anticipated incentives using the monetary incentive delay task

Attention Orienting

Attention orienting is a process that involves focusing one's attention on salient stimuli. A central feature of anxiety and fear-related behavior is atypical modulation of attention that manifests as hypervigilance and enhanced attention to threatening stimuli, referred to as attentional bias [53–55]. The specific role of this attention bias in the etiology and/or maintenance of pediatric anxiety disorders is unknown. However, recent randomized controlled trials have demonstrated that training anxious children to modify their attentional threat biases can facilitate disengagement of attention to threat, which in turn can reduce anxiety symptoms [56, 57]. These findings imply a direct link between attention bias towards threat and anxiety symptoms. Further, they suggest that attention biases might emerge over time through reinforcement or as a means to reconcile ambiguous situations [58].

Several paradigms (e.g., dot-probe tasks, emotional Stroop tasks) have been used to manipulate attention orienting and measure how anxious individuals orient their attention to threat stimuli, such

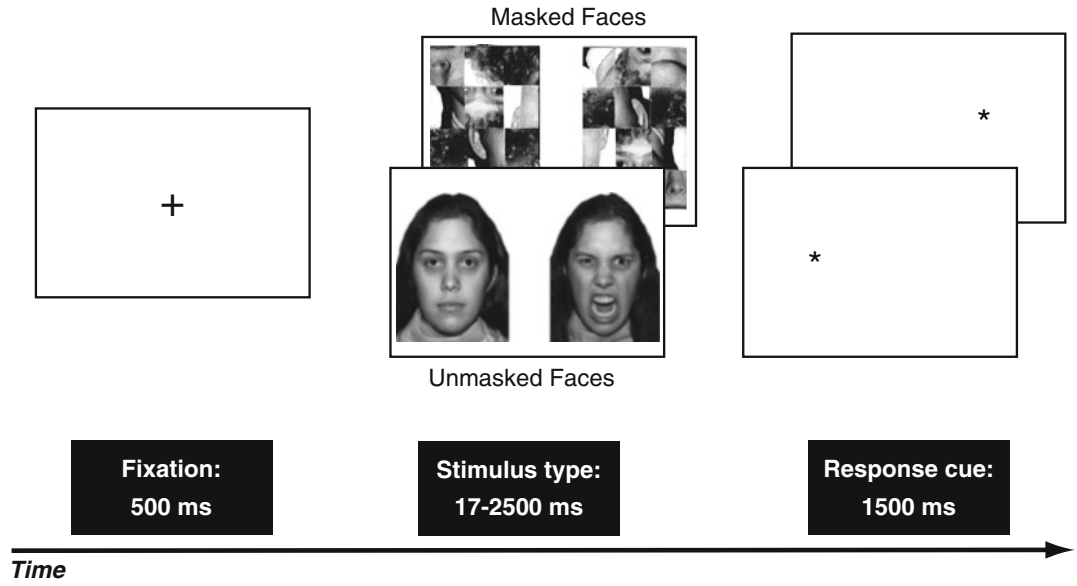

Fig. 2 An example of a trial in the dot-probe paradigm used to measure the influence of threats on attention orienting. A fixation cue is presented first. Then, pairs of stimuli depicting threat or nonthreat cues are presented. Stimulus pairs may be presented for varying time durations (e.g., 17–2,500 ms). Finally, a dot-probe cue appears to which participants respond via a button press. Attention bias to threat can be assessed through the time it takes to respond to the dot-probe cue as well as associated changes in neural response to the cue

as pictures of angry faces or words connoting threat [4, 53, 54]. Variants of the dot-probe task (see Fig. 2) have been the most widely used approaches to assess attention biases, particularly in studies of pediatric anxiety and health [35, 36, 56, 59, 60]. The dot-probe task displays two stimuli side-by-side, one depicting threat and one that is neutral. After the stimuli are removed, a target probe such as an asterisk (e.g., "*") appears in the same location as either the previously presented threat or neutral stimulus. Participants are then asked to indicate the location of the target (e.g., left or right side of the screen). Attention bias to threat is considered to be present if it takes an individual more time to draw their attention away from the location of the threat than from the neutral stimulus in order to locate the target. Anxious relative to non-anxious individuals (adults and children) tend to focus their attention toward threat stimuli to a greater extent and thus take longer to disengage from the location of the threat stimulus when turning their attention to the target [53, 60]. Some work suggests that younger versus older anxious individuals are more distracted by threat stimuli when other information demands their attention [61]. Further, adolescents who were behaviorally inhibited in early childhood have also shown heightened attention bias to threat, a bias further linked with social withdrawal [62]. However, in some situations, extremely high levels of threat can lead the anxious individual to avoid rather than linger their attentional focus on threat cues. Such patterns have been found both in adults exposed to extreme life-stress and danger [63, 64] and in youth with anxiety disorders [35]. Such tendencies to avoid acute threat appear to be transient in individuals studied in lower threat states [63, 65].

Neuroimaging techniques have been used to identify the neural substrates involved in attention orienting and to examine differences in neural responses during attention orienting to threat between youth with anxiety disorders and youth who are psychiatrically healthy. Key regions that have emerged from these investigations include the amygdala and ventrolateral regions of the PFC. For example, in one fMRI dot-probe study that used a relatively long period of exposure to threat stimuli (500 ms), greater ventrolateral prefrontal cortex (vlPFC) activation was elicited in response to angry faces in anxious relative to healthy adolescents; however, amygdala activation did not differ between the two

groups [35]. This pattern of vlPFC activity also correlated negatively with the severity of anxiety symptoms, such that more vlPFC activity was associated with less severe anxiety.

Rodent studies suggest that activation of the amygdala is particularly relevant during the rapid processing of threatening stimuli [15]. Thus, individual differences in the function of the amygdala for anxious adolescents may be predicted specifically during brief stimulus presentations. To test this hypothesis, a second fMRI study was conducted with the same dot-probe paradigm as described above but with shorter (17 ms), masked exposures to threat [36]. In this second study, greater amygdala activation occurred in response to angry faces in anxious than in healthy adolescents, and this pattern of activation correlated positively with greater attention bias, as indexed by response time to the target, and the severity of anxiety symptoms. Together, the results from these two neuroimaging studies with the dot-probe suggest that the duration of threat exposure modulates activation in different key neural regions in anxious youth.

A third fMRI study used the dot-probe face emotion task to examine whether trait anxiety in a sample of healthy children and adolescents would be associated with attention bias towards threat [37]. As expected, trait anxiety was positively associated with an attention bias towards angry but not happy faces. With regard to neural function, trait anxiety was positively related to right dorsolateral PFC activation only to angry faces. In addition, trait anxiety was associated with greater vlPFC activation regardless of the valence of the face stimulus. Finally, with regard to genetic influences, research has focused on a variant of the serotonin transporter (5-HTT) gene given its implications in anxiety [66, 67]. Although patterns of anxiety and 5-HTT variations are somewhat mixed, lower levels of 5-HTT are found among carriers of the short allele (S/S and/or S/L) relative to individuals with two long alleles (L/L). Relative to L-allele carriers, healthy adolescents who are S-allele carriers exhibit greater attentional bias to subliminally shown fear faces and greater response to fearful and angry faces in the brain's association cortex, an area implicated in attention control [68].

In sum, neural response patterns associated with attention orienting to threat show heightened amygdala response in youth with anxiety relative to those without anxiety, particularly when rapid processing of threat is required. Furthermore, greater amygdala responsivity also relates to more severe anxiety symptoms, again in the context of processing threat cues in a brief amount of time. When the time during which threat processing is lengthened, a different pattern emerges. Specifically, youth with anxiety disorders relative to healthy youth show greater vlPFC response to threat with no amygdala differences observed. Interestingly, among pediatric anxiety patients, those with the most severe anxiety symptoms had lower vlPFC activity whereas patients with less severe impairment had greater vlPFC activity. These patterns suggest that vlPFC response is not necessarily tied directly to anxiety symptoms but might modulate activity in other regions, such as the amygdala, which is closely linked to anxiety symptoms. Thus, the vlPFC could play a compensatory role by regulating and reducing perturbed function in the amygdala, particularly if it comes online further along in the sequence of reacting to threat to regulate emotions and behaviors to allow for more strategic allocation of attention [9]. This role would be consistent with higher vlPFC activity among anxiety patients with less severe functioning. Overall, vlPFC input may be recruited during longer exposures to threats to facilitate deeper, more comprehensive processing whereas the amygdala serves as a rapid threat detector that is overly responsive to immediate, even subconscious perceptions of threat, in anxious youth. As such, the vlPFC may be recruited at different time points to help modulate emotional responses related to anxiety through cognitive functions in order to inhibit behaviors or thoughts or to update rules or goals.

Threat Learning

The excessive fear responses to threat cues seen both behaviorally and physiologically in anxiety may also arise from difficulties in learning to discriminate threat cues from safety cues, also known as

threat learning [69–71]. Threat learning involves correctly determining what cues and in which situations indicate potential danger or safety. Fear conditioning paradigms have been used to assess threat learning processes relevant to anxiety. In fear conditioning experiments, a neutral stimulus is set to acquire a value signifying threat via repeated pairings with an aversive unconditioned stimulus (UCS). Over time the UCS becomes a reinforced conditioned stimulus (CS+) (see Chap. 1 for further discussion of fear learning). Perturbations in threat learning are seen in adults with high levels of anxiety who show greater fear toward a CS+ than do adults with low levels of anxiety [72]. Anxious adults also show greater fear toward non-reinforced conditioned stimuli (CS−) which are nonthreatening cues that are not followed by the UCS [72]. This latter finding represents stimulus generalization whereby the more similar a CS+ and a CS− are perceptually (e.g., hair color), which can be achieved by morphing two different faces together incrementally until they overlap, the more anxious individuals respond to both stimulus classes with excessive fear [73, 74].

Research on threat learning in adults has set the stage for both behavioral and neuroimaging studies of threat learning in pediatric anxiety. Behavioral studies have found that, relative to healthy children, children with anxiety disorders show difficulty discriminating between CS+ and CS− cues and greater arousal via skin conductance during fear conditioning, and stronger orienting and anticipatory sensitivity to emotional valence during extinction [75, 76]. Evidence also suggests that children with anxiety disorders experience a CS+ stimulus as more unpleasant than healthy children or children at familial risk for anxiety disorders [75]. Other work has shown that even when both anxious and healthy children similarly experience discriminative conditioning, children with anxiety relative to healthy children show greater arousal (via larger skin conductance responses) to CS+ and CS− cues during acquisition, report that the CS+ relative to the CS− cue is more arousing, and exhibit more resistance to extinction as measured by skin conductance responses but not as measured by arousal ratings to the CS+ versus the CS− cues [77]. Together, these studies indicate that anxious children have greater difficulty discriminating between threat and safety cues and modulating their emotional arousal and orientation to such cues and, subsequently, do not easily dissociate during extinction the previously established connections between threat and neutral cues. These patterns suggest that pediatric anxiety, as adult anxiety, is clearly associated with perturbations in the ability to make flexible and adaptive associations between emotionally valenced cues and outcomes.

While behavior-based threat learning difficulties have been documented in anxious children [75–77], less work has focused on assessing the neural correlates of threat learning difficulties in pediatric anxiety. An experimental task has been developed recently using a UCS that maintains its aversive meaning but remains appropriate for use with pediatric populations and lends itself to use within a neuroimaging context. This task paradigm presents a fearful female face that is accompanied by an extremely loud scream [70], two cues that imbue high biological and social salience. Presentations of the aversive UCS (fearful female face + scream) are paired with a neutral face to probe conditioning and extinction to a neutral cue that becomes a threat cue (CS+). A second stimulus, novel neutral face, is used as a safety cue since it is not presented with the UCS in order to assess generalization from threat to safety cues (CS−). This fear conditioning paradigm has been tested in an fMRI study of healthy adolescents and adults to ascertain typical neurodevelopmental correlates of threat learning and to generate a baseline in healthy development against which the atypical pediatric anxious pattern may be compared in the future [78]. Three key results emerged from this study. First, behavioral data indicated weaker discrimination between threat and safety cues in adolescents than adults. Second, adolescents relative to adults showed greater amygdala and hippocampus activation to CS+ versus CS− conditions, indicating enhanced sensitivity of these early-maturing subcortical regions in younger individuals when distinguishing between threat and safety cues [78]. Finally, adults relative to adolescents showed a positive association between dorsolateral PFC (DLPFC) recruitment and fear ratings when discriminating between threat and safety. Because prefrontal areas such as the DLPFC follow a more protracted developmental course [79], enhanced engagement of the DLPFC in adults suggests that it helps support making distinctions between relatively similar-looking cues to inform correct

categorization of stimuli. Overall, these neural data suggest age differences in the degree to which subcortical and prefrontal regions are engaged during threat learning.

To date, the fear conditioning paradigm described above has only been studied behaviorally in adolescents with anxiety disorders [70]. In this initial study, conditioning was established based on higher ratings to the CS+ versus the CS−, but it did not vary as a function of anxiety diagnosis; thus, all adolescents were more afraid of the threat than the safety cue. Pediatric anxiety was associated with high levels of reported fear after conditioning, but the levels of fear were not associated with greater discrimination between the classes of conditioning cues, rather they were associated with both the CS− and the CS+ neutral faces. Future work will need to establish whether distinct neural correlates are associated with these patterns of behavior in youth with anxiety disorders.

Taken together, the available work on the developmental course of threat learning and anxiety suggest that the neurodevelopmental differences in subcortical and prefrontal brain responses during the discrimination between threat and safety cues may play a role in the emergence of anxiety in childhood or adolescence and its maintenance into adulthood. In cases of immature prefrontal development, flexibility in adapting to increased ambiguity may be compromised and lead to difficulties in threat learning and a greater generalized fear response to threat and safety cues encountered in day-to-day life. Future work should include longitudinal studies of large groups of similarly aged individuals at this developmental transition and follow them well into adulthood as well as compare them to anxiety-disordered age mates.

Social–Emotional Information Processing

Moving beyond cognitive functions such as attention orienting and fear conditioning, the processing of affect displayed by social cues and within different social contexts is another key, symptom-relevant construct well represented in fMRI studies of pediatric anxiety. By targeting how the brain responds to social–emotional information such as emotions displayed on faces, specific neural patterns have emerged in relation to type of emotion, attentional focus, and stimulus class. For example, during very specific instances of potential social evaluation, socially anxious adolescents react with an exaggerated fear response even to positive smiling faces [45]. Moreover, as noted above, lesion work in monkeys suggests that neural correlates of social–emotional information processing exhibit unique developmental changes [27]. As such, it is particularly important to chart the neural correlates of social threat processing in adolescents and adults. In the sections that follow, we review results from neuroimaging studies of pediatric anxiety that involve either processing emotional faces or responding to conditions of social evaluation or judgments.

Face Emotion Processing

Initial studies used facial expressions of emotions to probe whether patient groups with impaired emotion processing and regulation would show aberrant neural responses to different facial emotions. Fearful facial expressions have been particularly useful because of their ability to increase amygdala activity, a region highly relevant to anxiety, even if an individual does not necessarily report feeling fearful of such a face [80]. One reason for this threat-related response to fearful relative to angry faces may be due to the ambiguity conveyed by a fearful face about the location of potential threat. Furthermore, fearful faces are not encountered frequently in one's environment, but when they are present, they signal that there is a threat and the source of potential threat needs to be determined to remain safe.

In the first functional neuroimaging study of children and adolescents (8–16 years old) with anxiety disorders, higher levels of amygdala activity were found in response to simply viewing fearful faces as compared to youth with no psychiatric disorders [38]. An additional comparison showed a blunted amygdala response in a small group of depressed youth relative to anxious youth, suggesting that increased amygdala response during fear processing is specific to anxiety disorders. Similarly, in other work, greater amygdala response to fearful faces was associated with greater severity of daily anxiety symptoms [38] as well as severity of social anxiety symptoms [39].

A series of neuroimaging studies in adolescents with anxiety disorders have also reported enhanced amygdala response to fearful faces, particularly when anxious adolescents are asked to contemplate how afraid they felt while looking at the faces [40, 42, 43]. In contrast, when asked to just view fearful faces without monitoring emotional responses, both anxious adolescents [40] and those at temperamental risk for anxiety [41] have shown reduced amygdala response to fearful relative to neutral faces, a pattern that opposes that seen in healthy adolescents [81]. These studies suggest that attentional focus matters in youth with anxiety insofar as it modulates amygdala response. One possibility is that amygdala hyperactivation occurs when attention is drawn to the act of monitoring one's feelings of fear but not when attention is unconstrained. This could occur because anxious youth avert their attention away from the face to avoid a feared stimulus. When required to focus on the feared stimulus, amygdala perturbation could reflect high sensitivity to processing subjectively experienced feelings of fear in the anxious child.

Research on the genetic and developmental variations in amygdala response to fearful faces has also started to emerge. These approaches are important because pediatric anxiety disorders strongly predict adult anxiety disorders [1, 82, 83]. As such, for some individuals, the association between anxiety disorders in early and later life may be shaped by genetic influences on the brain during critical developmental transitions such as from adolescence to adulthood. Thus, brain function may serve as a potential intermediate phenotype worthy of attention for understanding the underpinnings of adult anxiety.

To examine developmental mechanisms underlying associations between genetic influences on brain responses to emotional stimuli and anxiety, Lau et al. [43] examined the effects of the 5-HTT gene variant and diagnoses on amygdala response to emotional faces. While focused on internal feelings of fear, healthy adolescents who were S/L carriers had greater amygdala activation than L/L individuals, whereas L/L adolescents with anxiety or depression diagnoses showed greater amygdala response than their S/L counterparts. While the effect of heightened amygdala response to fearful faces found in healthy adolescents with the S/L allele was consistent with past findings in healthy adults, the opposite effect of increased amygdala response to fearful faces in adolescent patients with the L/L allele was contrary to past reports in adult patients [84]. The former result suggests that the risk conveyed by the short allele 5-HTT gene variant may be conserved across development; however, the latter result is harder to interpret as very few studies have examined gene–brain function relationships in affected individuals (including youth or adults), and more work is needed to reconcile inconsistent results from these studies.

Given its role in affect dysregulation, research has targeted the Val, Met, and Val-Met polymorphisms of the human Brain Derived Neurotrophic Factor (BDNF) gene in adolescents with anxiety and/or depressive disorders [85]. Results from this study found that Met-carriers showed greater amygdala and hippocampal responses to emotional faces than Val/Val homozygotes among adolescent patients relative to controls. Although preliminary, these new data from "imaging genetics" pediatric studies suggest that a continued focus on brain function and genes may reveal vulnerability mechanisms for anxiety across development.

Other work has taken a developmental approach to investigate potential vulnerability mechanisms given the persistence and long-term risk that adolescent anxiety predicts for adult anxiety. In a recent study, neural response to emotional facial expressions was compared between adults and adolescents with social phobia [44]. Results from this study indicated greater activation in the amygdala and

rostral anterior cingulate cortex (rACC) in response to angry and fearful, but not neutral faces in both adolescents and adults with social phobia. In adults but not adolescents, greater severity of social phobia was also associated with greater rACC activation. Although these findings are cross-sectional, the similar neural correlates in adolescent and adult social phobia suggest persistence in the neural mechanisms underlying social phobia.

Social Evaluation Processing

A series of studies have used a type of face viewing task that simulates potential social evaluation, a prominent experience for adolescents overall but also a main fear experienced by individuals with social anxiety [45, 46, 86, 87]. The task used in these studies was designed to create a context for measuring neural response while an adolescent anticipates receiving feedback from an unknown peer and another context to assess their emotional and neural responses to actually receiving either positive or neutral feedback. These constructs were selected specifically to give ecological validity to the neuroimaging task by mimicking adolescents' daily life experiences but also to reflect core symptoms in social anxiety.

With regard to the anticipation of peer feedback, as expected, greater amygdala activity was observed among socially anxious versus healthy adolescents when judging how interested unknown peers would be in chatting with them during a later interaction [45]. This was particularly evident when viewing peers the adolescent had judged as being of low interest to them for an interaction. Additional results from functional connectivity analyses showed that amygdala and vlPFC activations were more strongly correlated in socially anxious adolescents than in healthy adolescents when anticipating social evaluation from the negatively perceived peers. In addition to these findings in socially anxious adolescents, data in typically developing adolescents reveal neural activation within key areas implicated in affective processing (e.g., ventral striatum, hippocampus, insula, and hypothalamus) that varies by age and sex [86]. Specifically, neural activation increased with age in older (14–17 years old) relative to younger females (9–13 years old) but showed no association with age in males. These developmentally based results suggest that vulnerabilities to anxiety problems may be more prominent at certain ages for females. Thus, further work is clearly needed using this paradigm in healthy and anxious children and adolescents of various ages and sexes.

Examination of adolescents' emotional response to the receipt of peer feedback has yielded intriguing findings as well. Both healthy adolescents and those with social anxiety showed activation in the amygdala–hippocampal complex just prior to receiving positive or negative peer feedback relative to baseline [46]. However, after being rejected by peers, anxious relative to healthy adolescents showed persistent amygdala–hippocampal activation, whereas the healthy adolescents showed reductions in amygdala activity once they received negative feedback. This poor neural recovery from a negative emotional experience seen in adolescent anxiety may relate to problems with inhibiting amygdala response or with regulation of amygdala sensitivity [88, 89]. Though not directly examined in this study, these anxiety-related neural perturbations may be associated with greater cognitive distortions about emotional events, which, in turn, may result from the imbalance between cognitive and affective processing during the adolescent period [18, 90].

Finally, another form of social interaction and evaluation that has been examined in conjunction with fMRI involves the Prisoner's Dilemma game in which participants must choose to cooperate or betray a co-player in an attempt to earn as much money as possible. Behaviorally, anxious adolescents were more likely than healthy adolescents to maintain positive interactions when possible through cooperation with co-players, particularly after a co-player chose to betray the participant [47]. FMRI data showed increased activation in the anterior precuneus and right temporal parietal junction among anxious versus healthy adolescents but increased medial PFC and ACC activation in healthy relative to anxious adolescents [47]. These results suggest that anxious youth exhibit a heightened

tendency to engage in increased self-focus and may also tend to ruminate about their behaviors during interpersonal interactions which manifests in altered brain function. Overall, these studies provide important clues to cognitive and emotional processing of social stimuli in health and anxiety [18].

Reward Processing

Across the processes involving attention orienting, threat learning, and social–emotional information processing, the repeated findings of abnormal amygdala function suggest that anxious adolescents are readily influenced by threatening cues; in turn, this set of processes may compromise emotion regulation and perpetuate chronic, extreme anxiety. While the amygdala clearly processes social threat, research on social–emotional development in primates suggests that structures beyond the amygdala are likely to play equally important roles in facilitating response to social threats. For example, findings of enhanced social fear in juvenile primates without a functioning amygdala demonstrate that social fears in juveniles must also be instantiated in neural circuitry that extends beyond the amygdala [91, 92]. Moreover, given that removal of the amygdala heightens social fears, components of the circuitry mediating response to social threats are likely to be involved in feedback loops with the amygdala. Although most work on social fears and anxiety in humans examines amygdala function, these data in nonhuman primates highlight the need to examine other structures early in development.

Beyond the amygdala, another key subcortical structure that has recently been investigated in relation to pediatric anxiety is the striatum. The striatum generally includes the nucleus accumbens, caudate, and putamen and encompasses a ventral and dorsal area, with strong connections to frontal cortical regions, the hippocampus, and the amygdala [93, 94]. The striatum is involved in associating emotionally salient environmental stimuli with anticipated outcomes to guide approach or avoidance behavioral responses [93, 95]. As such, striatal circuitry has been well characterized in research on substance abuse and addiction [96, 97]. Extensions of the addiction literature have focused on striatal function with other classes of motivationally salient stimuli, namely, rewards and punishments.

New discoveries have emerged in our understanding of reward processing in anxiety with the use of monetary incentive cues that highlight how incentives modulate approach and avoidance behaviors [98, 99]. A focus on neural correlates of reward processing in pediatric anxiety grew out of initial work on behavioral inhibition, an early-life temperament style that carries increased risk for later anxiety, especially social anxiety [100, 101]. One of the first neuroimaging studies in this area documented heightened sensitivity in the striatum to anticipated incentives [48]. Specifically, adolescents whose temperament had been characterized in early childhood as behaviorally inhibited showed increased striatal response as the magnitude of the incentive increased; adolescents not characterized as behaviorally inhibited did not show this modulation by incentive value. One possible explanation for this pattern is that striatal dysfunction may reflect anxiety during anticipation of uncertain outcomes or concern over performance when the stakes increase. Indeed, follow-up studies showed increased striatal activation in adolescents characterized by early-childhood behavioral inhibition relative to their non-inhibited counterparts when receipt of anticipated incentives was contingent on one's actions [50] and when anticipated incentives were not actually provided [51].

The early-childhood behavioral inhibition findings described above suggest that sensitivity of the striatum may be a neural marker in addition to amygdala sensitivity [41, 102] that links early-childhood behavioral inhibition specifically to later anxiety. Indeed, both social phobia and social subordination, which shares behavioral features of social phobia, are associated with dysfunctions in the striatal dopaminergic system [103–106] and altered striatal function [107]. Thus, identifying alterations in striatal function during anticipatory performance-based or social situations could reveal pathophysiological traits common to both social phobia and behavioral inhibition. Recent work confirmed this hypothesis by showing striatal hypersensitivity to anticipated incentives in adolescents with SoPh but not GAD [52]. It may be that striatal function is a biomarker that differentiates between

these two anxiety diagnoses while the amygdala is involved in anxiety in a nonspecific fashion that does not differentiate between the anxiety disorders. Moreover, the findings in socially anxious adolescents closely resemble those in children with behavioral inhibition. As such, adolescents with social phobia and adolescents with early-life behavioral inhibition show similar patterns in certain striatal regions during reward processing which indicates the importance of considering more than one affectively relevant neural system as well as additional psychological processes in pediatric anxiety.

Related to reward processing and anticipating outcomes, intolerance to uncertainty is a trait associated with anxiety, extreme worry, and impaired decision-making. In a study of adolescents with GAD or SoPh, the relationship between intolerance to uncertainty and neural responses to uncertainty was examined [49]. High levels of intolerance to uncertainty were associated with increased activation in frontal and limbic regions including the anterior cingulate cortex, orbitofrontal cortex, and amygdala in response to uncertainty during a decision-making task. Intolerance of uncertainty emerged as a cognitive trait associated with neural regions that may contribute to the maintenance of pediatric anxiety disorders. These results also highlight the variability related to trait characteristics that exist within adolescents with anxiety disorders and suggest that using such an approach for characterization of pediatric anxiety may prove fruitful in tailoring treatments to subgroups of patients depending on their profiles of key traits and neural response patterns.

Functional Connectivity in Pediatric Anxiety

Recently, studies have begun to examine functional connectivity in the context of anxiety disorders. Typically, the goal of studies examining functional connectivity is to determine the degree of co-activation among various brain regions. Functional connectivity can be measured during two conditions: (1) a specific task (task-dependent functional connectivity or TDFC), typically one related to emotion salience or emotion regulation in the case of anxiety disorders (i.e., how does activity in one region relate to or "regulate" activity in another region during different task-related events), or (2) a state of rest (resting state functional connectivity or RSFC) when the individual is not engaged in any particular assigned task (i.e., what neural interactions occur spontaneously while an individual has their eyes closed or is fixating on a cross). While measuring either TDFC or RSFC, the co-activations of regions within a particular known neural network may be investigated. Or, alternatively, a specific "seed" region may be identified so that the degree of covariation between activity in this seed region and activity in other regions may be measured, which can lead to the identification of new interrelated networks.

Task-Dependent Functional Connectivity

Among the handful of studies that have examined patterns of TDFC in patients with anxiety disorders versus controls, connections have been examined across a range of neural networks. Adults with anxiety disorders exhibit stronger connections between limbic regions (i.e., anterior insula) and frontal and parietal regions [108], as well as weaker TDFC within prefrontal networks [109] and within superior temporal networks [110]. Despite this range of findings, however, the majority of work on this topic has focused largely on links between subcortical/limbic regions (responsible for processing salience and affect) and cortical/frontal regions (responsible for control or regulation of affect and implicit drives). This is likely because an imbalance in the functioning of these regions

(e.g., hyperactivation of the amygdala combined with hypoactivation of the medial and lateral prefrontal cortices) is often thought to characterize anxiety disorders, as discussed in other sections of this chapter and recent reviews [111–113]. For example, one recent study of adults examined a specific type of emotion regulation during reappraisal of negative self-beliefs—one of the hallmark characteristics of social phobia. Results indicated less TDFC between the prefrontal cortex and the amygdala among patients with SoPh versus controls [114], consistent with the notion that patients are less able to regulate amygdala responses to negative emotions. Similarly, other work examining patients with GAD has shown a similar pattern such that patients fail to engage regulatory regions in response to heightened displays of amygdala activity resulting from emotional stimuli [115].

A small number of studies have examined functional connectivity in pediatric samples. Similar to the work described in adults, one study found that compared to healthy controls, adolescents with GAD displayed a relatively weaker negative TDFC between the lateral prefrontal cortices and the amygdala during an emotional attention orienting task [36], which is consistent with the notion that individuals with anxiety are less able to regulate neural responses to emotion, even prior to adulthood. Interestingly, however, another study that examined pediatric patients with social anxiety disorders found a somewhat different pattern of results. Specifically, socially anxious patients displayed stronger positive TDFC between the lateral prefrontal regions and the amygdala during the anticipation of social evaluation by peers than healthy controls who showed relatively little TDFC [45]. While more research will help clarify these patterns of results, it is possible that the distinct processes that are involved in responding to negatively valenced stimuli (i.e., anticipating, versus actually responding to, a negative stimulus) may be characterized by distinct patterns of TDFC in anxious individuals.

Resting State Functional Connectivity

In studies of clinical populations, RSFC may be a particularly useful way of studying neural interactions for several reasons [116–118]. First, RSFC analyses permit investigators to examine patterns of intrinsic functional connectivity underlying different, simultaneous functions. Thus, there is less need to isolate a particular construct of interest using a specific task. Second, when examining brain activity while individuals are resting, biases among particular clinical populations in terms of how they interpret task instructions or respond to certain stimuli will be significantly reduced. Thus, these biases will be less likely to produce group differences that are solely task dependent. Third, examining resting brain activity increases the probability of enrolling patients in studies who have a limited ability to comply with certain task demands. In other words, studies of RSFC may permit the inclusion of individuals who are more impaired than those typically included in clinical neuroimaging studies. Finally, given that RSFC is not task dependent, there is greater reliability across research sites and scanners, which facilitates the study of larger samples [119]. This is particularly important for studies of pediatric anxiety disorders that often suffer from small sample sizes.

Similar to the TDFC studies described above, most of the RSFC studies examining neural function in relation to anxiety disorders have found results that are consistent with the notion that anxiety disorders may be characterized by dysregulation between frontal and limbic networks, resulting in an inability to regulate responses to emotional events [111–113]. Here we briefly discuss some of the RSFC studies most relevant for understanding limbic/frontal connections in the context of anxiety disorders, given that this has been the focus of the majority of this work thus far. Moreover, it is worth noting that studies examining RSFC have so far focused exclusively on adult populations; nevertheless, we review them here because of their potential relevance for exploring pediatric populations in future research.

First, a few studies have specifically focused on SoPh. One of these studies found that the amygdala showed reduced RSFC with two regions commonly linked with higher-level control processing, both the medial orbitofrontal cortex and the portion of the medial posterior parietal cortex that includes both the posterior cingulate cortex and the precuneus [120]. The connectivity between these regions was particularly reduced among individuals with higher state anxiety. Similarly, another study found that adults with SoPh show reduced RSFC between the amygdala and the inferior temporal gyrus and increased RSFC between the amygdala and occipital regions [121]. This is consistent with the commonly reported finding that individuals with SoPh have exaggerated affective responses to visually observed stimuli combined with an inability to properly regulate these affective responses which likely contributes to their heightened anxiety in social situations. Other work has further demonstrated irregularities in the RSFC of several brain systems among individuals with SoPh, including altered connections between limbic/subcortical and frontal/cortical networks [122, 123], as well as disrupted connectivity within different regions of the frontal lobe, and between frontal and visual networks [124]. Moreover, many of these findings have also been associated with the degree of patients' symptom severity [122, 124].

Results from a recent study of adults with GAD indicate increased RSFC between the amygdala and a frontoparietal control network and decreased RSFC between the amygdala and regions linked with stimulus salience, including the insula and the cingulate, as compared to healthy comparisons [125]. At first glance, this finding seems to run counter to the idea that anxious individuals have weaker neural connections between limbic/subcortical regions and control/frontal regions (as well as heightened connections within the salience/affective network). However, the authors suggest a compensatory role of the frontoparietal network and suggest that heightened connectivity between limbic and control regions may reflect additional regulatory resources needed to compensate for the heightened affective responses that typify this population. Liao and colleagues [123] also propose a compensatory model in which cortical regions are more strongly connected with limbic regions among individuals with SoPh; however, it is not yet clear when compensatory models might be most relevant (i.e., compared to models focusing on the hyperactivation of limbic regions and the hypoactivation of control regions). In fact, the results from another recent study examining RSFC in healthy individuals did not appear to be consistent with this compensatory model. Specifically, this study demonstrated that healthy individuals who reported high levels of anxiety showed negative correlations between activity in the amygdala and ventromedial prefrontal cortex during rest whereas those who reported low levels of anxiety showed positively correlated activity [126]. High anxious individuals also showed uncorrelated activity in the amygdala and dorsomedial prefrontal cortex while low anxious individuals showed negatively correlated activity. One additional study has shown heightened state activity during an off-task period after an initial task involving worrying among individuals with GAD in both limbic (i.e., the anterior cingulate cortex) and frontal (i.e., the dorsomedial prefrontal cortex) regions [127], which implies that those with GAD continue to worry; however, this study did not examine functional connectivity. Thus, additional research will be helpful in better elucidating irregularities of neural connectivity among individuals suffering from anxiety disorders.

Resting state EEG has also been used to assess underlying functional connections across the brain related to anxiety. These studies focus on the relationship between slow and fast waveform activity, which is believed to index the functional connectivity between subcortical/limbic regions and cortical/frontal regions. Thus, the relationship between slow and fast activity may reflect patterns of inhibitory control over motivational goals [128]. To our knowledge, EEG investigations of RSFC have not been carried out in clinically anxious populations; however, two recent studies examined aspects of anxious functioning among healthy individuals. One study demonstrated that healthy individuals with higher ratings of anxiety displayed EEG recordings consistent with weaker connectivity (i.e., a higher ratio between slow and fast waveforms) between frontal and limbic regions [129]. A second study provided evidence that resting state EEG activity among individuals displaying greater anxiety-related threat biases (i.e., avoidance of threatening stimulus displays) was similarly indicative of a

weaker cortical/limbic connection [130]. Thus, together these studies are consistent with data from fMRI research indicating that individuals with greater anxiety may have reduced frontal control over affective processes.

Treatment of Pediatric Anxiety: Implications for the Brain

The field of clinical cognitive neuroscience has been moving in an exciting direction by examining clinically relevant cognitions, emotions, and behaviors that characterize anxiety and relate to impaired functioning. This approach offers the potential for conceptualizing and pinpointing ways in which cognitions, emotions, and behaviors could be targeted in interventions for pediatric anxiety such as CBT or pharmacological interventions (e.g., SSRIs), both of which are very effective for treating anxiety [131–138]. For example, CBT offers patients tools such as cognitive reframing and self-monitoring to gain control over their symptoms. The well-documented pattern of amygdala hyperactivation in pediatric anxiety elicited during a range of psychological processes (e.g., face emotion processing, attentional bias) represents a possible biological marker for targeted intervention efforts. Indeed, emerging evidence suggests some potential pathways for intervening that are guided by knowledge of the pathophysiology of anxiety and relate to treatment response. The application of neuroimaging to testing treatment-related changes in brain function is relatively new, but there are some intriguing patterns emerging from the existing literature.

One study, which used the same face emotion task described earlier to assess fearful face processing, found that greater pretreatment amygdala activation in pediatric anxiety-disordered patients was associated with better response to both CBT and pharmacological treatments [139]. Amygdala hyperactivation was specific to conditions during which patients attended to their internally experience fear of salient emotional faces. Furthermore, both a decrease in symptoms across treatment course and posttreatment anxiety symptom severity were associated with this pattern. Nonetheless, it is important to consider that the documented amygdala perturbations may be present in a portion of pediatric anxiety cases that respond effectively to CBT or psychopharmacological treatment, whereas other cases who are more treatment resistant may react more positively to treatments that elicit input from other brain regions.

Another study focused on treatment-related brain response changes in association with attention orienting using a dot-probe task. Here, adolescents with GAD exhibited a significant increase in right vlPFC activation in response to angry versus neutral faces following effective treatment with either CBT or an SSRI [140]. As in past neuroimaging results comparing pediatric anxiety patients and controls, these treatment-related results also suggest the vlPFC may facilitate effective neural and affective responding via other brain regions (e.g., amygdala), perhaps through regulating overwhelming emotions or reframing biased cognitions. Thus, targeting the ventral regions of the PFC may offer one mechanism by which negative emotions such as anxiety can be reduced.

Striatal responses to reward have also been examined in the context of treatment for adolescent depression [141]. In this study, a monetary reward task was administered to assess striatal response during the anticipation of reward outcomes prior to the start of 8-week open label treatment with either CBT or CBT plus an SSRI. During each of the eight weeks of treatment, clinician ratings of symptom severity and improvement and self-reported anxiety and depressive symptoms were obtained. Greater pre-treatment striatal response to reward anticipation was associated with lower clinician-rated severity and lower anxiety symptom levels after the course of treatment. Interestingly, greater striatal response was associated with a faster reduction in anxiety symptom levels. These results suggest that a typical striatal response (increased rather than reduced as seen in depression) is associated with a better response to treatment, in terms of anxiety symptoms. It also suggests a

role of anxiety in the reward-related pathophysiology of adolescent depression, which underscores recent findings showing elevated striatal response to monetary incentives in adolescents with diagnosed anxiety disorders [52].

Conclusions and Future Directions

Clinical cognitive neuroscience provides an exciting bridge between basic and clinical domains of psychiatric and psychological research, particularly in the area of anxiety. Our current understanding of brain-behavior relationships is possible because of the applicability of animal models of fear responses to humans. As this chapter described, neurobiological research using tools such as fMRI has allowed for the testing of hypotheses about how specific neural circuits underlie psychological processes that shape behavior. Adding a developmental component to this approach has further deepened our understanding of the nature of neural structures and circuits and their connections in relation to pediatric anxiety.

Future work in this area will benefit from the inclusion of larger samples as well as of pure patient groups for cross-comparisons where possible. In addition, although the normative, longitudinal progression of brain structure has been fairly well characterized [21, 28, 79, 142–144], studies mapping longitudinal trajectories of brain function in response to the types of tasks described in this chapter need to be conducted in both pediatric health and anxiety. It would also be beneficial to chart longitudinal changes in anatomy among anxiety-disordered youth to pinpoint whether anxiety has long-term influences on neural structures such as the amygdala, striatum, or vPFC or whether these structures drive anxiety over time. More research that employs techniques such as diffusion tensor imaging would be beneficial for understanding anatomical connections within pediatric anxiety samples as well as work that focuses on the relationships between function and structure. Finally, additional work is necessary to determine the stability of neural functional change due to the effects of treatment once it has been completed.

In sum, we have described work that aims to pinpoint what psychological processes are at play in modulating and mapping neural structure and function in clinical pediatric anxiety. We hope that in the next generation of research of this kind, the information gathered to date will be translated into the development of effective, targeted treatments for pediatric anxiety.

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Temperamental Risk Factors for Pediatric Anxiety Disorders

Kristin A. Buss and Elizabeth J. Kiel

Abstract Fearful temperament, most often conceptualized as behavioral inhibition, has been found to be a robust predictor for the development of pediatric anxiety disorders, with most evidence suggesting a link with social anxiety disorder. In addition to a detailed review of behavioral inhibition, recent work that supports a new construct, dysregulated fear, is also reviewed in this chapter. New evidence is presented that demonstrates that dysregulated fear is conceptually and methodologically distinct from behavioral inhibition and improves the prediction of which fearful toddlers are at risk for pediatric anxiety disorders. The following review will summarize the empirical bases for these two approaches and their role in the development of anxiety disorders, as well as evidence for biomarkers, executive processes, and parenting environment that exacerbate or ameliorate this early temperament risk. Specifically, research on fearful temperament has identified multiple trajectories and outcomes for children with the same underlying temperamental biases. That is, not all young children who display fearful temperament maintain this behavioral profile or develop anxiety symptoms. Therefore, this chapter summarizes evidence for biological, regulatory, and parental processes that account for these divergent trajectories and addresses the question of which fearful children are at highest risk for developing anxiety disorders.

Keywords Fearful temperament • Behavioral inhibition • Dysregulated fear • Maternal overprotection • Pediatric anxiety disorders • Development • Biomarkers • Executive processes

Over the past 25 years, a great deal of research has focused on fearful temperament as a putative risk factor for the development of pediatric anxiety disorders, with most evidence suggesting a link with social anxiety disorder [1–8]. The bulk of the literature on fearful temperament has been framed by the prominent approach of behavioral inhibition; thus, this will be discussed in detail in this chapter. However, we also include recent work that supports a new construct, dysregulated fear, which is conceptually and methodologically distinct from behavioral inhibition and improves the prediction of which fearful toddlers are at risk for pediatric anxiety disorders [9]. The following review will summarize the empirical bases for these two approaches and their role in the development of anxiety disorders, as well as evidence for biomarkers, executive processes, and parenting environment that

K.A. Buss (✉)
Department of Psychology, The Pennsylvania State University, University Park, PA, USA
e-mail: kab37@psu.edu

E.J. Kiel
Psychology Department, Miami University, Oxford, OH, USA

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exacerbate or ameliorate this early temperament risk. Throughout this chapter, the broader term of fearful temperament will be used if neither behavioral inhibition nor dysregulated fear is specified.

Research on fearful temperament has been influenced by two theoretical traditions in developmental science: temperament theory and developmental psychopathology. Most researchers agree that temperament refers to individual differences in behavioral tendencies that appear in infancy, are relatively stable across the lifespan and across situations, and involve biological and heritable underpinnings [10, 11]. More specifically, dimensions of temperament reflect individual differences in the reactivity and regulation of behavioral and biological expressions of *basic* affective processes, such as fear [12, 13]. Given the complexity of temperamental variation, no single measure of behavior is believed sufficient to characterize these individual differences. Thus, it is best captured by measuring several response parameters such as behavioral frequency, intensity, and duration of responses across multiple contexts, raters, and systems of response (e.g., behavioral and biological) [12, 14, 15]. Unlike other temperament constructs or dimensions (e.g., activity level, positivity), research on fearful temperament has always focused on integrating across multiple systems, helping to push the temperament field into an ever-growing interdisciplinary science, for instance, with the integration of biological measures [16, 17].

Despite theoretical emphasis on the stability of temperament traits, work on fearful temperament has identified multiple trajectories and outcomes for children with the same underlying temperamental biases. That is, not all young children who display fearful temperament maintain this behavioral profile or develop anxiety symptoms [1–8]. The developmental psychopathology perspective acknowledges this complexity, emphasizing the interaction between a child and the environment that influences adaptive and maladaptive developmental trajectories [18–20]. For instance, deviations from normal development that put a child at risk for anxiety may exist not only in individual characteristics of the temperamentally fearful child but also in relationship factors (e.g., parenting) that disrupt the achievement of age-related tasks [6]. In line with the developmental psychopathology perspective, it is also possible that, in addition to risk for developing classifiable disorders, temperamentally fearful children may show failures in typical developmental tasks or adaptation at important milestones, such as the transition to kindergarten, that would increase their risk for later disorder [19, 21]. For example, temperamentally fearful children are likely to exhibit social withdrawal [22–24] and lack of peer competence [25, 26], which interfere with the formation of friendships and perhaps lead to peer rejection. These social vulnerabilities may put children at increased risk for later social anxiety disorder and other internalizing symptoms.

Before proceeding, some discussion of conceptual and methodological issues is warranted in order to interpret the predictive validity of early temperamental fearfulness on the development of anxiety disorders. A nontrivial amount of conceptual and methodological overlap exists in the broader literature on fearful temperament and in the literature on social wariness (e.g., shyness, reticence). Whether behavioral inhibition, dysregulated fear, social withdrawal, anxious solitude, shyness, and social anxiety are different manifestations of the same underlying temperamental bias, partially overlapping constructs that just differ in how and when they are measured, or orthogonal constructs remains an open question in the literature. It is important to point out that extreme fearful temperament and social withdrawal share common features such as avoidance of novelty, fearfulness, and physiological and neural activity profiles [27, 28]. Much of this overlap may be an artifact of similar assessment methods as all of these constructs can be objectively observed [29]. However, they can also be distinguished [28]. For instance, behavioral inhibition is characterized as fearful/wary behavior to *novelty,* while social withdrawal is typically in response to familiar social situations (i.e., with peers), and anxiety symptoms and diagnosis require subjective reports of distress. Another issue to consider is that variation in fearful temperament, especially in observational contexts, is more readily assessed in infants and toddlers, and it is ever more challenging to attribute variation in inhibited or withdrawn behavior solely to temperamental characteristics as children develop and encounter an ever-expanding social network.

Overview of the Fearful Temperament Literature

In this section, we review the literature on fearful temperament, with specific focus on the constructs of behavioral inhibition and dysregulated fear. Given the specific goals of this chapter to present a broad overview of the role of fearful temperament in the development of pediatric anxiety problems, the current review of behavioral inhibition will not be as comprehensive as other published reviews (see [30–32]).

Behavioral Inhibition

There are a variety of conceptualizations of fearful and extremely shy behavior in the temperament literature including treating fear as synonymous with other types of negative affectivity [33], fear as one component of a higher-order factor of negative affect [34, 35], fear as multidimensional with distinctions between object fear and social fear [36], and fear as shy behavior manifesting in peer interactions [22]. However, the approach forwarded by Kagan has received the most attention. Strongly rooted in biological perspectives on individual differences, Kagan's approach to temperament highlights qualitatively distinct types. This pioneering work began with observations of toddlers (~14–24 months of age) in a series of novel situations such as playing with a robot and adult stranger interactions. Behaviors coded across these episodes were used to differentiate two temperament types: inhibited children who were characteristically shy, fearful, and withdrawn, and showed signs of decreased activity and approach [37–40], and uninhibited children who were characteristically bold showing high activity and approach in these same situations. Identification of these two distinct groups has been replicated across several different samples and laboratories [37–42]. In addition, studies have examined behavioral inhibition characterized by similar sets of behaviors using a continuous composite of fear behavior rather than a dichotomous group approach [1, 43–45].

These patterns of inhibited and uninhibited behavior have been predicted from reactivity to stimuli early in infancy, supporting a biological and/or genetic basis. At 4 months, infants were exposed to a variety of mobiles and other sensory experiences [46]. Four types of reactivity groups were created based on infants' responses to these stimuli: high motor–high cry, high motor–low cry, low motor–low cry, and low motor–high cry. Infants who displayed high-motor and high-cry behavior in response to the stimuli were labeled high reactive, while infants displaying low-motor and low-cry behavior were labeled low reactive. Two years later, the high and low reactivity profiles predicted inhibited and uninhibited behavior, respectively [43, 46]. These infant profiles, their association with later toddler behavior, and longitudinal outcomes have been replicated across other samples [43, 47–53].

The stability of behavioral inhibition has been well documented [1, 37–39, 43–53]. This has been demonstrated in longitudinal studies of behavioral inhibition across the lifespan [15, 32, 46] including development of social wariness later in childhood (see [31] for detailed review) [37–39, 49]. Despite this consistency in reported stability, it is important to note that stability of behavioral inhibition is fairly modest with not all inhibited children retaining their inhibited status across development or becoming socially wary. In particular, some studies have reported stability for only a subset of children, such as those who were most extreme in their behavior [42, 52, 53]. This observed instability may be due to several factors. First, measuring behavioral expression of the same construct at different developmental periods can be difficult (i.e., heterotypic continuity). Second, the observed lack of stability may be an artifact of attempting to aggregate across different developmental pathways of fearful children. Most studies have used statistical approaches that examine linear predictions and focus on between-person differences rather than focusing on within-person stability and nonlinear models of change

[54–57]. Third, across studies, indices of inhibition or fearful temperament may differ. Thus, it cannot be assumed that any two groups of temperamentally fearful children are the same. Further, each of these indices of "fear" may have unique associations with physiology and risk for anxiety symptoms [58–61]. As a result, this heterogeneity in identification of behavioral inhibition may limit the ability to accurately predict stability.

Despite these limitations in understanding the stability of behavioral inhibition, there is significant evidence suggesting that children who are behaviorally inhibited are particularly at risk for social withdrawal (e.g., reticent behavior with peers) [27, 49] and the development of social anxiety symptoms in middle childhood [3, 62–66]. Children who show the most stable inhibition throughout childhood appear to be at greatest risk for developing anxiety disorders in adolescence, particularly social anxiety disorder [8, 32]. In light of evidence that social anxiety may be a mechanism by which fearful temperament is linked to other anxiety and internalizing disorders (e.g., generalized anxiety disorder, depression) [5, 21, 32, 64–68], middle childhood is a key period to examine the development of social anxiety among extremely fearful or inhibited children.

Dysregulated Fear

Now we turn to discussion of the dysregulated fear construct, which is a new advance in the identification of fearful children that builds upon the behavioral inhibition tradition. Individual differences in behavioral inhibition are most often identified by aggregating (i.e., averaging) behavioral measures across situations. Thus, the consistency in behavior across situations is the hallmark of characterizing children as fearful/inhibited. However, upon closer examination of the correlations across situations, the behavioral indicators of inhibition are only modestly correlated and low in many cases [9, 37]. Thus, it can be argued that simply averaging behavior across multiple situations is not enough to capture the complexity of fear because it obscures meaningful individual differences and may cause us to miss children who show extreme fear only in specific contexts [9]. Based on this, the dysregulated fear theory postulates that it is not only how much fear is exhibited but also when and what type of fear is exhibited that is critical to identifying a more homogeneous pattern of behavior [9]. This is consistent with other literature that suggests that expression of behavior with respect to the eliciting context may be a key feature of individual differences in emotion regulation [67, 68], specifically anxious behavior [69, 70]. Moreover, levels of distress that are not predictably matched to a situation (i.e., being fearful in typically safe situations) are a key defining feature of most of the anxiety disorders. Thus, dysregulated fear has been defined as behavioral responses that are not matched to the incentive properties of the eliciting context or the availability of coping resources (e.g., high fear in low-threat, controllable contexts). It was hypothesized that focusing on fear responses in low-threat situations would yield a more homogeneous type of fearful child that would be empirically distinct from behaviorally inhibited children.

In an initial study of this construct [59], 24-month-old toddlers participated in three versions of a male stranger approach episode that varied in level of threat: (1) toddler was playing on the floor with toys (least threatening), (2) toddler was sitting in a highchair, and (3) toddler was in a highchair and cardiac physiology was recorded (most threatening). As predicted, mean levels of fear behaviors (e.g., facial fear, distress), and duration of freezing in particular, varied across the three versions with the toy play version of the stranger approach resulting in less fear and freezing compared to the other versions. More interesting, however, was the identification of a group of toddlers who displayed long durations of freezing behavior in the putatively lowest-threat situation (toy play version). These toddlers had the highest cortisol levels and more sympathetic cardiac reactivity at baseline [measured by pre-ejection period (PEP); see later section of this chapter for more detail on this work]. These data

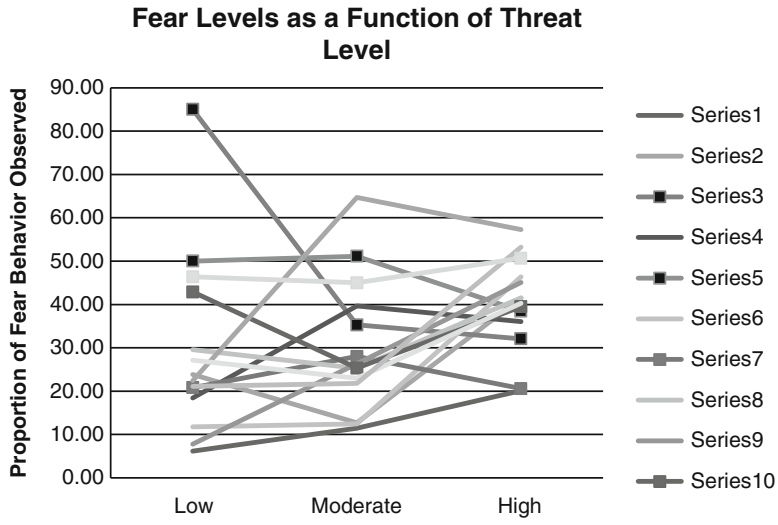

Fig. 1 Graph of ten randomly selected cases from age 2 observational data. The proportion of time fear was observed is plotted against the level of threat of the episodes. Cases appearing with square markers at data points represent examples of dysregulated fear patterns, high fear in low-threat situations relative to high-threat situations; cases without markers represent the typical fear pattern of increasing fear as threat increases

suggested that displaying high levels of fear in situations observed to be nonthreatening for most children may reflect a type of dysregulation of fear that would put children at risk for a variety of negative outcomes. Specifically, this approach to the characterization of fearful temperament had potential to improve our prediction of which children are most at risk for developing anxiety [59].

A subsequent longitudinal study was conducted to replicate and extend these original findings [51]. Toddlers (24 months old) participated in six episodes all designed to be novel, either engaging or fear eliciting and varying putatively in threat level [71, 72]. Two episodes were engaging and low in threat: playing games with two friendly puppets behind a puppet theater and a female clown with a bag of toys. Two episodes were designed to capture fear of strangers and to be moderately threatening: one involving an interaction with a male stranger and one with a female stranger doing paperwork in the corner of the room. Finally, two episodes were designed to be high in threat and novelty: these involved a remote-controlled robot that lit up, made noises, and moved around on a platform and a remote-controlled spider (i.e., toy spider placed on a hidden vehicle) that moved toward the toddlers. The episodes used are largely similar but expand on those previously used to measure behavioral inhibition, with the important addition of the low-threat episodes. In the first cohort, episode order was counterbalanced in order to investigate differences in fear behavior as a function of episode type.

Based on a composite of several different behaviors indicating fear (e.g., facial fear, freezing, proximity to mother), the average duration of fearful behavior increased as level of threat increased with the lowest duration of fear behavior exhibited during the puppet show and clown conditions and the highest during the robot and spider episodes [9]. Multilevel modeling was used to capture individual patterns of change in fear from low to high threat, creating a slope measure for each toddler. What is particularly relevant to a fearful temperament perspective is that significant variability in these slopes was identified. For example, Fig. 1 shows plots of several cases showing different patterns of fear across the three levels of threat. The typical pattern is characterized by the highest levels of fear observed during the higher-threat episodes. In contrast, there are a few children who show

higher or equivalent levels of fear to the low- and high-threat contexts (lines marked with squares). It is this pattern that we label dysregulated. Moreover, there was evidence that the toddlers showing the highest levels of fear in the lowest-threat episodes were not always the same as those toddlers showing high levels of fear in the high-threat episodes—these latter types of children would likely be categorized as behaviorally inhibited. Overall, less than one-third of the children showed consistently high fear behavior across episodes, thus highlighting the problem with creating averages across episodes. We also compared the two fearful temperament constructs: dysregulated fear and behavioral inhibition (measured as the average of avoidant, wary, and fearful behavior across tasks). Although highly correlated ($r = 0.60$), this correlation was carried mainly by the children low in both behavioral inhibition and dysregulated fear. Dysregulated fear predicted unique variance in social wariness at age 3, age 4, and during the fall of kindergarten [9]. In addition, there is evidence that this pattern of displaying higher levels of fear in putatively lower-threat situations is stable across a 3-year period [73]. In sum, using a dysregulated fear approach provides a unique way to identify extremely fearful children by focusing on high fear in *lower-threat situations*.

Similar to the behavioral inhibition literature, dysregulated fear has been associated with subsequent development of social anxiety. In a recent study, children who showed a pattern of fear consistent with a dysregulated fear profile were nearly four times as likely to show symptoms of social anxiety disorder compared to children characterized as fearful or shy at age 5 (but not dysregulated at age 2) [73]. Further, dysregulated fear is associated with higher maternal-reported anxiety and/or social withdrawal concurrently, at ages 3 and 4, and with teachers reporting anxiety in the child at the transition to kindergarten [9]. This effect of dysregulated fear on social withdrawal and anxious behavior was still significant after controlling for behavioral inhibition, highlighting the specific trajectory associated with a dysregulated fear pattern. In a follow-up study with observations through the summer after the kindergarten year, children with a history of dysregulated fear were more likely to be reticent with unfamiliar peers at age 5 [73].

In summary, decades of research have established that fearful temperament is a robust individual difference characterized by wariness, fear, and avoidance of novel situations. These behaviors can be reliably measured early in development (14 months) and predicted from distress and activity at 4 months of age. Although this literature has been dominated by behavioral inhibition, the new construct of dysregulated fear is distinguishable from behavioral inhibition and has been shown to improve on the prediction of social wariness across early childhood by identifying a more homogeneous subtype of fearful children [9].

How Does Fearful Temperament Become a Disorder?

Not all inhibited/fearful children develop anxiety, either at subclinical or clinical levels, and some even appear to grow out of this inhibited behavior. Perez-Edgar and Fox [29] suggest that a one-to-one correspondence between early temperamental variation and anxious behaviors that appear later in development will not be found because development does not occur as a simple unfolding of a single trait or even set of traits. Development occurs via transactional processes involving interactions between the child and his/her environment. In addition, biological processes also contribute to developmental trajectories in ways we are only beginning to understand [74, 75]. In this section, we will address the following question: What factors account for the stability of inhibition/fear and also for the trajectories toward maladjustment? That is, which of these children should we be worried about and what are the processes linking this early-emerging behavioral style to development of maladaptive outcomes. Biological, cognitive (attentional), genetic, and environmental (specifically, parenting) influences will be discussed.

Biological Correlates and Mechanisms

In the previous sections, we have focused on the behavioral aspects of fearful temperament and development of risk for anxiety disorders. Recently, there have been calls to integrate empirical findings on the development of internalizing disorders (e.g., anxiety) across biological and psychological (i.e., behavioral) domains [76]. Physiological measures implicate multiple systems (e.g., amygdala, prefrontal cortex, autonomic nervous system, and neuroendocrine) in the neural circuitry of fear [58]. Dysregulation of physiological systems is common among children with internalizing disorders [77], and numerous studies have documented physiological patterns associated with fearful behavior [60]. Many temperament researchers argue that the early emergence of individual differences in this and other domains suggests a biological basis [10, 16, 78]. Specifically, Kagan has suggested that a proximal cause of behavioral inhibition is a biological diathesis that gives rise to a pattern of fearful and anxious behavior [15, 79]. However, we still lack a complete understanding of the biological–behavioral link. This section provides a brief overview of this work; for more information on this topic, the reader is referred to reviews elsewhere [17, 60].

Cortisol

A primary area of study has been the neuroendocrine responses of the hypothalamic–pituitary–adrenocortical (HPA) system to stress and novelty, as indexed by cortisol production [79]. Atypical cortisol patterns (e.g., high basal, altered diurnal, high reactivity) have been associated with fear, extreme shyness, and social withdrawal in children [59, 80–84]. In a recent study, in contrast to a pattern of lower levels of cortisol across the school year for the majority of children, Tarullo and colleagues reported increasing cortisol levels across the school year for inhibited preschoolers [85]. This finding was most evident for inhibited children who were more popular and dominant with peers compared to other inhibited preschoolers. However, other work only reports higher cortisol reactivity for fearful, withdrawn behavior when other risk factors (e.g., insecure attachment, early maternal stress) are present [72, 86], suggesting the complexity of the link between behavior and the HPA system [87].

Autonomic Reactivity

Autonomic reactivity, including both the sympathetic (SNS) and parasympathetic (PNS) branches, has been a central focus of research on stress sensitivity and the development of anxious/internalizing problems [88, 89]. Physiological response patterns, such as increased heart rate or low heart rate variability, of extremely inhibited children are believed to reflect an overall increase in SNS activity [15, 39, 48, 90, 91]. However, changes in heart rate are influenced by both the SNS and PNS, so measures specifically linked to these two branches have been the focus of the most recent research. The SNS modulates PEP [92], which is the period between ventricular contraction and the semilunar valves opening to eject blood into the aorta, such that increased sympathetic influence on the heart results in a faster PEP due to increased contractility. PEP can be reliably measured in children making it a useful noninvasive measure of SNS activity [93–95]. There have been only a few studies of temperament and PEP associations in children. In a study of 24-month-olds, faster resting PEP was related to task-specific freezing behavior, a measure of dysregulated fear [59]. For children high in temperamental surgency (i.e., the opposite of fearful or inhibited), a lack of PEP reactivity to a stranger interaction was associated with poorer emotion regulation [96], suggesting that for non-fearful children, SNS reactivity has a positive influence on behavior. However, others have failed to find an association

between fear and PEP [97], suggesting that the type of fear or eliciting context may be important for a full understanding of behavioral–biological associations.

Turning to PNS activity, decreases in respiratory sinus arrhythmia (RSA) (i.e., RSA suppression, vagal withdrawal) are thought to represent the physiological underpinnings of emotion regulation [89, 98, 99]. This interpretation relies on the assumption that decreases in RSA, across all contexts, are indicative of good social–emotional outcomes [89]. Consistent with this interpretation, we have found evidence that the dysregulated fear profile is associated with a pattern of RSA across tasks that may reflect an additional risk factor [100]. In the toddler study described earlier, RSA was collected at baseline and during each of the novel tasks, allowing for measures of RSA suppression across conditions. Failure to suppress RSA across tasks was associated with the dysregulated fear profile and more maternal-reported child anxiety symptoms [100].

Neural Correlates

As stated at the outset of this section, behavioral inhibition (and fear more broadly) is hypothesized to develop from underlying biological vulnerabilities. In particular, it has been suggested that greater stress and peripheral physiological reactivity (e.g., SNS reactivity) results from reactivity of the amygdala and related circuitry including the frontal cortex [15, 101]. From the earliest studies of frontal EEG asymmetry (where relative contribution of right and left hemisphere activation is inferred from a difference score), fearful and inhibited behaviors have been associated with greater relative right frontal activity [102, 103]. This pattern of activity has been found using baseline activity in infants and children [41, 43, 51, 104, 105] and during tasks designed to elicit fearful behaviors and withdrawal [84, 106, 107]. An association between relative right frontal activity and maternal-reported fear for an unselected sample of infants has also been observed in a second-by-second analysis of EEG asymmetry [108]. From recent research using source modeling analyses, evidence is emerging that this relative difference in neural activity has been located in the right dorsolateral cortex in humans [109] and nonhuman primates [70]. Finally, stability in frontal EEG asymmetry from 3 to 10 years of age accounted for stability in inhibited behavioral profiles for the most extreme group of children [53]; and in another sample, 9-month right frontal asymmetry was associated with stability in behavioral inhibition from infancy to age 4 [50]. Collectively, these data suggest that this pattern of EEG asymmetry is a valid and sensitive neural marker for fearful temperament that can be used to better characterize developmental trajectories and risk for anxiety disorders.

Neuroimaging studies provide further evidence of the neural circuitry of inhibited behavior. The amygdala was first hypothesized by Kagan to be central to the development of inhibited behavior [39]. Consistent with this, Schwartz and colleagues reported the first fMRI evidence of differences in amygdala activity during novel stimuli presentation between adults with a history of behavioral inhibition as toddlers and to those who were identified as uninhibited [110]. This finding has been replicated and extended in a handful of informative studies that highlight the neural circuitry which includes but is not limited to the amygdala and expand the contexts under which these associations are observed [111–114]. For example, adolescents characterized as behaviorally inhibited as young children show exaggerated amygdala activity while viewing emotion faces when asked to subjectively report their fear level (vs. passive viewing) compared to uninhibited adolescents [111]. In other words, passive viewing alone does not reveal a difference between inhibited and uninhibited adolescents, and only during the putatively more stressful context of reporting on their own fear do the inhibited and uninhibited adolescents differ in amygdala activity.

A series of three studies examining the circuitry of reward and punishment in inhibited adolescents implicate the striatum and ventromedial prefrontal cortex but also highlight the importance of eliciting context. Using the same sample as Perez-Edgar but a different task that contained cues for

potential reward and loss, Guyer and colleagues demonstrated differences between inhibited and uninhibited adolescents in the striatal regions of the brain with greater activation for inhibited relative to uninhibited adolescents even though there were no differences in performance [112]. The authors interpret these findings as increased sensitivity to incentives (both rewarding and punishing) for inhibited adolescents reflecting a potential vulnerability for developing anxiety disorders. In a separate replication sample using a similar incentive task, when adolescents were lead to believe that their performance was directly tied (contingent) to the incentives (reward or punishment) versus noncontingent trials, behaviorally inhibited adolescents had greater striatal activity than uninhibited adolescents [113]. Finally, when reward feedback was introduced into the design, greater differentiation between the inhibited and uninhibited adolescents was observed, suggesting that inhibited adolescents were more sensitive to feedback indicating no reward (i.e., negative feedback condition) [114].

In summary, biological dysregulation occurring across multiple systems characterizes children who are temperamentally fearful. Although the bulk of this work has been with behaviorally inhibited children (especially at the neural level), there is emerging evidence for altered physiology in children with dysregulated fear as well. Collectively this work is consistent with the hypothesis put forth by Kagan that this pattern of fearful and anxious behavior is the result of a biological diathesis [15, 79] and with biologically based models of anxiety disorders [77].

Attentional Bias to Threat

The control of attention has long been hypothesized to be important in the maintenance of inhibited behavior across development [115]. Evidence suggests that fearful children who are at risk for anxiety have heightened vigilance to, and increased monitoring of, their surroundings compared to those not at risk [115, 116]. For instance, anxious individuals show an attentional bias toward threat-relevant stimuli (e.g., angry faces) that non-anxious individuals do not exhibit [117]. See chapter "Neurobiology of Pediatric Anxiety Disorders" for a more thorough review of attentional bias to threat and pediatric anxiety disorders.

Control of attention away from putatively threatening novel stimuli in infants is associated with reductions in distress [118, 119], while sustained attention toward novelty has been associated with fearful behavior, anxiety [120, 121], and greater social wariness/anxiety in kindergarten [120]. Fox and colleagues have contributed to this literature by demonstrating that this type of attention bias, and the control of attention more broadly, interacts with fearful temperament to predict anxiety development in adolescents [122–125]. In a longitudinal study, from toddlerhood to adolescence, Perez-Edgar and colleagues [123] demonstrated that a pattern of vigilance (i.e., low sustained attention to fixation and high attention to distractor) in 9-month-olds was associated with greater behavioral inhibition as toddlers and during middle childhood. In addition, the association between behavioral inhibition and adolescent social discomfort (nervous behavior with peers) was significant only for the vigilant infant group. Recent findings have extended this literature to a large sample of low-risk adolescents demonstrating that attentional control moderated the relation between self-reported behavioral inhibition and internalizing symptoms [126].

This is an exciting new area of research because of obvious connections to neurophysiology and circuitry reviewed above. By examining neural processes underlying attentional biases, earlier identification of risk may be revealed [127–129].

Genetics

Like many dimensions of temperament, fearful temperament and related anxious behavior have been shown to be moderately heritable [130, 131]. Several twin studies have found significant heritability for observed behavioral inhibition and inhibited behavior and parent-reported inhibited temperament

[132–136]. For example, Matheny [134] found evidence for genetic influences on the stability of behavioral inhibition over time. However, other work suggests that genetic influences (i.e., heritability) on behavioral inhibition decrease across the preschool years [137], indicating that environmental influences may begin to shape this temperamental vulnerability. Other studies have found low heritability estimates [138, 139]. Adoption studies have similarly yielded mixed results, with some finding significant genetic influences [140], and others [141] finding low estimates of genetic influence on parent-reported infant shyness. How genetic and environmental factors impact the trajectory from fearful temperament to anxiety is still an open question [142]. In an adoption study, child social inhibition was not directly associated with birth or adoptive parent anxiety [142]. However, for children whose birth mothers met criteria for social phobia, social inhibition was associated with attentional control when adoptive parents were also anxious. These results are consistent with differential susceptibility and biological sensitivity to context models [143, 144] which suggest that genetic vulnerability is not deterministic but imparts a sensitivity to environmental influence.

Given that, overall, there seem to be at least moderate genetic influences on behavioral inhibition, it is not surprising that children are more likely to be behaviorally inhibited when their parents have an anxiety disorder. Behavioral inhibition has been found to be more common among parents with panic disorder [145–148] and trait anxiety [149], although these associations are not always found [150]. Although there is evidence for a direct relation between parental anxiety and children's proneness to anxiety, it is also likely that this link is facilitated by anxious parents' actions with their fearful/inhibited children. These include behaviors listed below, although it should be noted that these behaviors may be displayed by non-anxious parents as well.

Parenting

Several types of parenting are relevant to the relation between fearful temperament and later anxiety outcomes. The following section discusses sensitive versus insensitive parenting in general, as well as intrusive and protective parenting, specifically. The attachment relationship may also be considered a context that influences anxiety development. Finally, influences on parenting behavior with temperamentally fearful children are discussed.

Sensitive Parenting

Sensitive versus insensitive parenting is an important determinant of the outcomes of behaviorally inhibited children. Defined by behaviors such as physical comfort, responsiveness to children's cues, and consideration of the child's pacing during activities, the connotation of "sensitivity" is positive: sensitive behaviors lead to adaptive outcomes for children. When examining outcomes of children broadly, this notion is supported [151–153]. In the case of behaviorally inhibited children and anxiety-spectrum outcomes, sensitive parenting has been found to alter the trajectory of inhibited behavior, such that toddlers who were inhibited or shy and had mothers who were sensitive were less inhibited as school-aged children than those whose mothers displayed lower sensitivity [154, 155]. Infants, especially boys, with "difficult temperament" (similar to inhibited temperament in that it includes negative mood and high withdrawal) were less likely to develop anxiety/depression symptoms as preschoolers if their mothers displayed sensitive behavior than those whose mothers displayed lower sensitivity [156].

There are several mechanisms by which maternal sensitivity may protect behaviorally inhibited children from developing increased anxiety. Maternal sensitivity may facilitate toddlers' development of effective regulation of fear (e.g., by regulating attention, using behavioral distraction, or getting appropriate support from a caregiver). For example, Glöggler and Pauli-Pott [157] found that children

whose mothers displayed higher sensitivity used more active regulation during a fear-eliciting situation than children of less sensitive mothers. Sensitive parenting may also protect inhibited toddlers from developing poor peer relations, which has been found to be a common outcome for inhibited children and a precursor to anxiety problems. Toddlers displaying anxious solitude, a similar construct to behavioral inhibition, were found to contribute more positive and fewer negative interactions with peers and to be more accepted and less rejected by their peers as older children when their mothers had displayed sensitive parenting [158].

In contrast to these findings, other studies have found that maternal sensitivity maintains or exacerbates behavioral inhibition or increases the association between inhibition and later anxiety problems. For example, Arcus [159] found that infants showing early signs of inhibited behavior were more likely to be inhibited as toddlers if mothers were consistently responsive to their distress, which by some definitions would be considered "sensitive," and less likely to be inhibited if their mothers set firm limits, which may be seen as less sensitive. Similarly, Mount et al. [160] found that very high levels of maternal sensitivity related to more anxiety for inhibited toddlers. Park et al. [44] found that infants high in negative emotionality showed increased inhibition as preschoolers if parents showed high sensitivity and low intrusiveness. In these cases, "sensitivity" may have indicated a "coddling" parenting style that prevented inhibited toddlers from developing more independent regulation skills [159].

The positive relation between highly sensitive parenting behavior and inhibition may be specific to children already displaying highly inhibited behavior, as indicated by moderations by child temperament in the above studies. Specifically, Mount et al. [160] found that the relation between highly sensitive parenting and toddler anxiety mentioned above did not hold for children who were less inhibited; rather, maternal sensitivity related to lower anxiety for toddlers displaying low levels of inhibition. Park and colleagues [44] found that the association between high sensitivity/low intrusiveness and inhibition was especially salient for more highly negative infants. Inhibited children may require stronger (although still gentle) encouragement to interact with novelty and practice independent coping skills than less inhibited children to avoid later anxiety problems.

These disparate findings cause some confusion about the precise nature of the relation between parental sensitivity and inhibited temperament. Although the terminology may be inconsistently used, we believe the results of these various studies can be summarized as a curvilinear relation between parental "encouragement to approach/engage with novelty" and children's inhibition and anxiety (Fig. 2). At the extreme end of encouragement to approach/engage is parental behavior that pushes the child towards novelty with so much force that it overwhelms his/her capacity for independent coping. Most would agree that this constitutes "insensitive" behavior (and others have labeled this more specifically as "intrusiveness," described subsequently). At the opposite extreme resides parenting behavior that actively prevents the child from approaching and engaging with novelty, keeping him/her

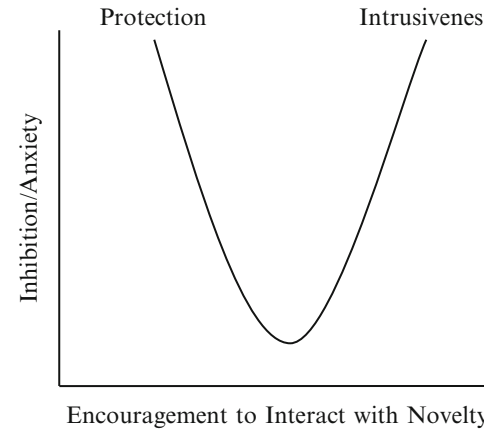

Fig. 2 A conceptual graph of the putative curvilinear relation between encouragement to interact with novelty and inhibition/anxiety over time. Extreme ends of encouragement to interact represent protection, at the low end, and intrusiveness, at the high end, both of which may maintain inhibition and lead to anxiety over the course of development

from practicing and mastering independent coping and regulation in novel and uncertain contexts. Because this type of parenting behavior might also involve displays of warmth and affection, this behavior might have been labeled as "sensitive" in studies finding a positive relation between sensitive parenting and young children's inhibited temperament and anxiety (some would label this "protection" or "overprotection," also discussed below). Both of these extremes seem to relate to maintained or increased inhibition and risk for anxiety problems over time. In the middle of this curve resides what we would call "gentle encouragement." This includes parental behaviors that provide the extra encouragement that inhibited children require to come into contact and cope with novelty but do so in a way that challenges children within their range of coping. These behaviors have been less frequently studied, but we suggest that examples may include modeling interaction with novelty, verbally encouraging approach, and physically coaxing children to approach and engage at a slow pace. Gentle encouragement may include behaviors labeled as "sensitive" in the above studies that find a negative relation between sensitive parenting and children's inhibited temperament or anxiety.

There is some existing evidence for this curvilinear association. Mount et al. [160] found a curvilinear relation between maternal sensitivity and toddler anxiety that existed for more inhibited, but not less inhibited, toddlers. When mothers were very low or very high in sensitivity, inhibited toddlers displayed more anxiety. At moderate levels of sensitivity, inhibited toddlers displayed less anxiety. We suggest that to more clearly understand the relation between parenting and behavioral inhibition and subsequent anxiety, "sensitivity" may be too vague of a term and more specific descriptions of behaviors should be used. To this end, we are currently in the process of examining such a curvilinear relation with parenting behavior that explicitly positions intrusive, gently encouraging (i.e., modeling and slow-paced approach), and protective behavior along a continuum of an "encouragement to approach/engage" variable. A body of research supports the positioning of intrusiveness and protection at the two ends of this continuum and their positive relation to behavioral inhibition and anxiety.

Intrusive Parenting

Intrusive behavior occurs when parents push children to interact with novelty too fast or with too much force or they intrude on and take over children's independent activity. Intrusiveness has been found to moderate the stability of inhibition, such that inhibited toddlers are more likely to continue to show inhibited behavior later in childhood when their parents engage in more intrusive behavior with them [23]. Therefore, intrusiveness is located on the far right side of "encouragement to approach/engage with novelty" in Fig. 2. This may occur because intrusive parenting takes control of the situation away from the child, fostering helplessness and preventing them from being able to build adaptive coping skills during times of uncertainty [161]. Indeed, intrusive parenting behavior has been related to increased stress reactivity for inhibited toddlers [72].

Sometimes related to intrusive behavior are other negative parenting behaviors like derision, criticism, and emotional over-involvement, the latter two comprising the construct of "expressed emotion." Bivariate relations have been found between these constructs and inhibited temperament, although results are somewhat inconsistent across studies [162, 163]. Moreover, negative parenting behaviors have been found to predict and maintain inhibited temperament over time. For example, Rubin et al. [23] found that inhibition shown with peers during toddlerhood predicted continued inhibition (in the form of social reticence) at age 4 only when mothers were highly derisive.

Protective Parenting

Protection and overprotection, along with Rubin's construct of oversolicitousness (all of which we will refer to under the umbrella term of "protection" or "protective behavior" from here forth), have

been conceptualized as restrictions on children's exploration and new experiences as well as excessive physical comfort when these responses are not warranted [23, 120, 160, 161, 164–167], and would thus reside on the far left side of the continuum of "encouragement to approach/engage with novelty" depicted in Fig. 2. Protective behavior has been linked to inhibited temperament [167, 168] and has been found to moderate (i.e., increase) the stability from temperamental inhibition and related constructs (e.g., reticence with peers) to later indices of inhibition (e.g., social wariness, social withdrawal) and anxiety [23, 49]. Edwards et al. [168] found that both preschool temperamental inhibition (measured as parent-reported behavioral wariness with adults and peers and in unfamiliar and challenging situations) and protective parenting predicted children's anxiety symptoms (diagnostic criteria for anxiety disorders) 1 year later, above and beyond stability in anxiety. Protective behavior may maintain inhibited and anxious responses to novelty and uncertainty over time by assuming regulation of the child and situation so that the child does not practice and learn independent coping and regulation. Even within the situation, protective behavior may prevent the alleviation of distress [169].

Attachment

Unlike the above constructs, which are concerned with behavior as a parent characteristic, the quality of the attachment relationship between parent and child is a relational construct that has also been found to influence trajectories of inhibited children. A secure attachment relationship is conceptualized as reflecting the child's experience of a history of warm, responsive parenting [170]. An insecure relationship, particularly the insecure-resistant subtype, which is conceptualized as a history of inconsistent or inadequate responses from the caregiver, seems to be a risk for anxiety problems. According to attachment theory, children who receive inconsistent responses from caregivers maintain anxiety about the availability of their caregivers that is not relieved when they return from a separation [170–172]. Infants in insecure–resistant relationships therefore develop strategies of arousal and vigilance that carry over to other relationships and situations. This is supported by research showing that insecure attachment is related to behavioral inhibition [173] and that behaviorally inhibited children who have an insecure attachment relationship show higher salivary cortisol levels than those who have a secure attachment [72, 174]. Although there has been some debate about whether temperament and attachment represent unique constructs [175], it has generally been found that they make both independent and interactive, rather than redundant, contributions to anxiety outcomes, such that inhibited children who also have insecure–resistant attachment relationships with their primary caregiver are at the highest risk of developing anxiety problems [149, 176–178]. Insecure attachment has also been found to increase the stability of inhibited behavior across the first two years of life [43].

Influences on Parenting Behaviors

Thus far, parenting behavior has been discussed as a determinant of outcomes for inhibited children. Of course, the association between parenting behavior and inhibition is likely bidirectional. A central tenet of the developmental psychopathology perspective is that children play an active role in influencing their environments [19], and evidence is mounting for such a conceptualization in relation to inhibited temperament. Thus, toddlers' temperament and behaviors are important influences on parents' behaviors. Much of the work in this area has focused on the influence of toddler inhibition on protective parenting. For example, parents' perceptions of their children's inhibition (fearfulness, shyness) have been found to predict future protective parenting [179, 180].

Inhibited children may be particularly likely to elicit protective responses when they face feared, novel, and uncertain situations. Thus, some recent work has focused on protective behavior enacted by mothers in response to such solicitations during laboratory novelty tasks. Consistent with the conceptualization that inhibited children elicit protective behavior, which then increases the likelihood of

further inhibition and anxiety, results suggest that solicited maternal protection mediates the relation between toddler inhibition and anxious behavior observed in preschool-aged children [164] and kindergarteners [120]. Furthermore, the context of this solicited maternal protective behavior appears to play an important role in whether it facilitates the relation between toddlers' inhibited temperament and later anxious behavior. Similarly to how inhibited behaviors in low-threat contexts seem to identify toddlers at risk for later anxiety problems [9], protective behavior displayed in low-threat, but not in high-threat, contexts relates to inhibited temperament and mediates the relation between age 2 inhibited temperament and age 3 shyness [181]. These results are consistent with the theoretical notion that the development of independent regulation and coping occurs in situations that are challenging yet not overwhelming and that parental intervention during these situations may disrupt this important learning process [182].

Parents' own characteristics, including anxiety and depression symptoms, cognitions, and emotion processes, also influence whether they engage in particular behaviors. As mentioned previously, parental anxiety relates to children's inhibited temperament, and one mechanism besides shared genetic liability may be the higher likelihood of engaging in anxiogenic parenting. For example, anxious mothers have been found to grant less autonomy and be more critical, and these behaviors subsequently predict child anxiety [183]. Maternal depression has similarly been investigated as an influence on parenting behavior. Some of the aforementioned parenting behaviors, including criticism, protective behavior, and related or other problematic behaviors such as not granting autonomy and disengagement, have been found to be related to maternal anxiety and depression [183–186]. Further, these behaviors have been associated with children's inhibited temperament and anxiety specifically for mothers with anxiety disorders or high levels of trait anxiety, but not (or less so) for mothers with low levels of anxiety [187, 188].

Parents may behave differently with their inhibited children depending on how they understand, think about, and anticipate fearfulness and shyness. Rubin and colleagues have identified parenting beliefs as characteristics that shape subsequent behavior. Mills and Rubin [189] defined parenting beliefs as cognitive/affective processes that direct the strategies parents use to socialize social competence in their children. In the case of inhibited temperament, these processes may consist of attitudes about inhibition, goals for the situation in which inhibition is shown, attributions about causes (i.e., internal or external, stable or unstable) for inhibited behavior, and emotional responses to displays of inhibition. In general, parents tended to respond to inhibited behavior with the emotions of confusion and concern and to attribute inhibition to transient states rather than stable characteristics [189].

Of course, individual differences exist in these beliefs. Beliefs may be different for parents of more temperamentally inhibited children than parents of other children. Compared to mothers of less inhibited boys, mothers of temperamentally inhibited boys have reported being less confused about inhibited behavior and more focused on relational goals (wanting to maintain a positive relationship and help their children develop social skills) [179]. Other studies have found that mothers of temperamentally inhibited or anxiety-prone children were more likely to endorse parent-centered goals (i.e., wanting a "quick fix" for the situations without regards for the child's perspective) than mothers of children who did not exhibit temperamental vulnerability towards anxiety [190]. Beliefs appear to be associated with both parents' subjective perceptions of inhibition and objective measures of children's physiological dysregulation [166, 191]. For example, baseline cardiac vagal tone in 2-year-old children predicted beliefs in restrictive parenting 2 years later [191]. Parenting style has also been found to be related to beliefs, such that more authoritarian mothers endorse fewer relational goals, attribute inhibition to dispositional characteristics, and report more embarrassment in response to shyness [192]. Certainly, the relation between parenting style and beliefs may be bidirectional in nature. Finally, beliefs may be shaped by the perspective of one's culture on inhibition. For example, mothers in Eastern cultures have been found to be more accepting of inhibited behavior, whereas mothers in the Western cultures are less accepting and more negative about inhibition [193, 194]. These beliefs then translate into parenting behavior. Mothers who view their inhibited children as dispositionally inhibited

(attributing inhibition to internal and stable causes rather than situational and unstable causes), and therefore vulnerable, are less likely to encourage independence and more likely to behave punitively, protectively, or in a controlling manner, at least in North American samples [180, 193].

Recent work has focused on a different type of cognition: the accuracy with which parents anticipate their child's inhibited behavior. In an initial study on maternal accuracy, this construct was operationalized as the statistical relation between mothers' predictions about toddlers' reactions to emotion-eliciting stimuli and toddlers' actual reactions [195]. Across several studies, mothers of inhibited toddlers tended to be more accurate in predicting inhibition or fearful distress than mothers of less inhibited toddlers [120, 164, 181]. Maternal accuracy appears to be more than a reflection of toddler inhibition, however. In these studies, maternal accuracy served a moderating role in the relation between inhibited temperament and protective parenting. The more accurately mothers anticipated their children's distress to novel situations, the higher the relation between inhibited temperament and protective behavior. So, when toddlers display inhibited temperament *and* mothers are particularly attuned to impending displays of this behavior, they may be more likely to enact protection. The context of situations in which this relation unfolds appears to be important [181]. Specifically, in situations that are highly stressful for children (i.e., when stimuli more universally elicit fearful responses and are physically intrusive), inhibition and accuracy do not relate to protection. In these situations, protective behavior may be a more universal response by parents and not tied to anxiety processes. In situations that, although novel, are presented in a friendlier manner and allow the toddler more time and space to cope, inhibited temperament and accuracy interact in relation to protective behavior. In this case, protection is less warranted and may depend more on maternal cognitions about the situation than when the characteristics of the situation itself (the universally threatening nature of it) dictate a response.

Conclusion

In this chapter, we have provided a broad overview of the literature on fearful temperament highlighting its identification in children, risk for social and anxiety problems across development, and biological and parenting factors associated with individual differences and risk trajectories. Taken together, the literature reviewed provides compelling evidence that this early-emerging individual temperament is a key risk factor for the development of anxiety disorders later in childhood.

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Part II
Anxiety Disorders

Generalized Anxiety Disorder in Children and Adolescents

Golda S. Ginsburg and Nicholas W. Affrunti

Abstract This chapter presents an overview of pediatric generalized anxiety disorder (GAD). Youth with GAD worry excessively, are unable to control their worry, and experience significant distress and impairment as a result. Previously referred to as overanxious disorder, GAD is common and highly comorbid with other anxiety disorders. The etiology of GAD is multi-determined encompassing biological and environmental influences. If left untreated, the disorder can be chronic and predictive of adulthood anxiety and depression. GAD-specific assessment tools are now available, including those that target unique cognitive aspects of the disorder. Evidence-based treatments for pediatric GAD involve cognitive and behavioral (CBT) and pharmacological interventions. Recent psychosocial interventions have tailored CBT to specifically target worry.

Keywords Worry • Generalized anxiety • Overanxious • Pediatric • Children • Adolescents

Case Scenario

Daniel is a 13-year-old Caucasian male who presented at our clinic with complaints of insomnia and feeling like he could "not turn off his brain." He reported thinking about things over and over again and was unable to control his thoughts when it was time to go to sleep. When asked about the content and nature of these thoughts, he reported thinking about getting bad grades in school, a poor play he made in a baseball game, if his parents had enough money, if he is going to get into a good college, and natural disasters. He stated that these thoughts would bother him both at night and during the day. When these thoughts occurred during the day, he reported feeling "stressed out" and would often lash out at others, even if they did not deserve it and acknowledged getting into frequent arguments at home with his parents and siblings. While Daniel stated that he typically had good friendships and was involved in sports and other activities, he was beginning to dislike school because it was causing him too much stress and his grades had been getting worse over the past year. He also reported getting headaches and stomachaches that had no medical etiology according to his pediatrician.

G.S. Ginsburg (✉)
Division of Child and Adolescent Psychiatry, The Johns Hopkins University School of Medicine, Baltimore, MD, USA
e-mail: gginsbu@jhmi.edu

N.W. Affrunti
Department of Psychological and Brain Sciences, University of Louisville, Louisville, KY, USA

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Description of the Disorder

Daniel has generalized anxiety disorder (GAD). This disorder is characterized by persistent and excessive worries about a number of different issues, coupled with one or more somatic symptoms (refer to Table 1 for full diagnostic criteria). These symptoms cause significant distress and impair daily functioning [1]. Children with GAD are often overly self-critical, evaluating themselves in an all-or-nothing fashion [2]. Frequently, this leads youth to avoid activities where they feel they may not be able to perform perfectly and to seek excessive reassurance from teachers, caregivers, and others about their performance [3]. Children with GAD have relatively few friends when compared to their nonanxious peers but appear comparable to nonanxious peers in the quality of their peer relationships, frequency of contact with friends, and the ability to make new friends [4]. Relative to children with other anxiety disorders, youth with GAD tend to have more somatic symptoms (e.g., headaches, stomachaches, muscle tension, restlessness) and sleep disruptions [5, 6].

Children with this clinical profile were first diagnosed in DSM-III using overanxious disorder (OAD) rather than GAD. However, because the OAD diagnosis had poor reliability and validity [7, 8] and symptoms of OAD overlapped with GAD [9, 10], the diagnosis of OAD was eliminated in DSM-IV and was incorporated into GAD (see Table 1). With the upcoming release of DSM-V, the proposed diagnostic criteria have again been revised. Relevant to diagnosing children, the first change reduces the length of time the worries have to be present from 6 months to 3 months. There is preliminary evidence that this criteria change may have the most pronounced effect on rates of GAD [11]. Another proposed change is the removal of criteria B, "The worry is difficult to control," as this was considered redundant with the "excessive" criterion (see Table 1).

The primary symptom of GAD, worry, is a relatively common phenomenon in typically developing children and adolescents, with 80 % of youth (age 7 years and older) and almost 50 % of younger-aged children (ages 4–6 years) reporting at least one worry [12]. The most common worries reported by normal children were personal harm and/or harm to others, dying, and test performance, all reported by over 13 % of the sample [12]. The most frequently reported worries among clinically referred youth were related to health (self and others), school, personal harm, natural and human-made disasters, and problems with peers [13]. Although children with GAD appear to worry about similar things as their nonanxious peers, they do so in excess [14]. For example, children with GAD (and OAD) endorsed an average of six worries, while those not diagnosed with GAD (or OAD) only endorsed an average of one worry. Furthermore, children with GAD (or OAD) have a higher frequency of worries that are recurrent, are more difficult to control, and result in greater interference in functioning [15].

This pattern is also true when comparing children with GAD to those diagnosed with another anxiety disorder [10, 13, 14]. Pina et al. [16] found that children and adolescents who reported excessive and uncontrollable worry about their own health, family, or school were 10–25 times more likely to receive a GAD diagnosis (relative to another anxiety disorder) than those children who did not report excessive and uncontrollable worry in one of those areas. There is a clear difference between the amount, intensity, uncontrollability, and sometimes even content of the worry reported by children with GAD compared to the worries of nonanxious children or those children with another anxiety disorder.

The diagnosis of GAD is one with a considerable history of controversy, primarily due to the finding of high rates of comorbidity between GAD and other anxiety and mood disorders [17]. Specifically, it has been argued that GAD, rather than a unique psychiatric disorder, is a prodromal condition, a risk factor for other emotional disorders, or a subtype of major depression [18, 19]. However, data is accumulating to contradict this claim. For instance, in a recent study of 3,021 individuals followed for 10 years (age 14–24 years at baseline, 21–34 years at follow-up), GAD was found to be more related to anxiety, than depressive disorders [20], suggesting there are different developmental patterns for GAD and depressive disorders. In an analysis of 5,001 individuals from the National Comorbidity Survey (NCS) and NCS follow-up survey, GAD and major depressive

Table 1 Diagnostic criteria for pediatric generalized anxiety disorder

Overanxious disorder (DSM-III-R)	Generalized anxiety disorder (DSM-IV-TR)	(Proposed) Generalized anxiety disorder (DSM-V)
A. Excessive or unrealistic worry for at least 6 months of 4 or more of the following: 1. Future events 2. Past behavior 3. Competence (school, peers) 4. Somatic complaints 5. Self-consciousness 6. Need for reassurance 7. Tension, inability to relax.	A. Excessive anxiety and worry occurring more days than not about a number of events or activities for at least 6 months. **B. The worry is difficult to control.** **C. Anxiety and worry are associated with at least three (one for children) of the following:** **1. Restlessness or feeling keyed up or on edge** **2. Being easily fatigued** **3. Difficulty concentrating or mind going blank** **4. Irritability** **5. Muscle tension** **6. Sleep Disturbance** **D. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.**	A. Excessive anxiety and worry about two or more domains of activities or events (domains like family, health, finances, and school/work difficulties) B. The excessive anxiety and worry occur on more days than not **for three months or more** C. The anxiety and worry are associated with one or more of the following symptoms: 1. Restlessness or feeling keyed up or on edge 2. Being easily fatigued 3. Difficulty concentrating or mind going blank 4. Irritability 5. Muscle tension 6. Sleep disturbance **D. The anxiety and worry are associated with one or more of the following behaviors:** **1. Marked avoidance of situations in which a negative outcome could occur** **2. Marked time and effort preparing for situations in which a negative outcome could occur** **3. Marked procrastination in behavior or decision-making due to worries** **4. Repeatedly seeking reassurance due to worries**
Generalized Anxiety Disorder (DSM-III-R) A. Excessive or unrealistic anxiety or worry about 2 or more life circumstances for at least 6 months, where the person is bothered by these concerns more days than not. B. At least 6 of the following are present while anxious: Motor tension: 1. Trembling, twitching, feeling shaky 2. Muscle tension, aches, soreness; 3. Restlessness 4. Easy fatigue. Autonomic hyperactivity: 1. Shortness of breath/ smothering sensation 2. Palpitations, tachycardia 3. Sweating or cold, clammy hands; 4. Dry mouth 5. Dizziness or lightheadedness 6. Nausea, diarrhea, other abdominal distress 7. Flushes (hot flashes), chills 8. Frequent urination 9. Trouble swallowing/"lump in throat." Vigilance and scanning: 1. Feeling keyed up, on edge 2. Exaggerated startle response 3. Difficulty concentrating, mind going blank because of anxiety 4. Trouble falling or staying asleep 5. Irritability		

Bolded criteria show additions and changes to the diagnostic criteria of OAD/GAD from DSM-III-R to the proposed DSM-V criteria

episode were found to have distinct determinants, and the stability of these disorders could not be explained by a single underlying internalizing factor [21]. Moreover, data revealing that GAD can either precede or follow other anxiety and mood disorders are inconsistent with classifying it as a prodromal or residual condition [22, 23].

Prevalence

Community Samples

Early epidemiological studies, using OAD criteria, report prevalence rates from community samples ranging from 7 % [24] to 12.4 % [25]. More recent studies, using the DSM-IV criteria for GAD, report lower prevalence rates ranging from 0.1 % [26] to 3.3 % [27]. The lower rates of GAD shown in community samples, compared to those of OAD, may be due to the addition of impairment criteria for GAD in DSM-IV [28]. The wide range of prevalence rates is due to variability in sample characteristics (e.g., age), diagnostic instruments, reporters, degree of severity and impairment required, criteria used for diagnoses (e.g., OAD versus GAD), and setting.

Clinical Samples

Prevalence rates of OAD/GAD in clinical samples also vary widely and for similar reasons as the range published in epidemiological studies. In general, in outpatient clinics, rates of GAD are reported to range from 3 % [29] to as high as 15 % [30]. Prevalence rates of OAD in samples referred to specialized anxiety clinics range between 12 % [8] and 53 % [9]. Prevalence rates of GAD, using DSM-IV criteria, in samples referred to specialized anxiety clinics range between 19 % [31] and 43 % [32]. GAD was the most common anxiety diagnosis in these samples and is generally the most prevalent diagnosis seen at specialized anxiety clinics [33, 34].

Age

The prevalence of both OAD and GAD increases with age. In a community sample of preschoolers (age 4 years), the prevalence rate of GAD, using DSM-IV criteria, was less than 1 % of the sample [35]. Merikangas et al. [26] found a similar rate (0.1 %) in a community sample of children 8–11 years of age. However, that rate grew to 1.1 % for adolescents (ages 12–15 years). Costello et al. [36] reported that the 3-month prevalence rate of GAD dropped from ages 9–10 to 12–13 years, then rose steadily thereafter. Studies using OAD criteria have found similar increases in adolescents. For instance, Kashani and Orvaschel [25] reported a prevalence rate of 8.6 % in a community sample of 8-year-olds and 17.1 % among 17-year-olds.

Consistent with the prevalence of GAD, *symptoms* of GAD or worry also show an overall increase with age [12, 37, 38]. One explanation for the increase in GAD and worries as children age is the change in cognitive skills, which plays a key role in the etiology and maintenance of GAD. Specifically, as children age, they become more aware of future possibilities, deduce the threats that could result, and think of more negative consequences of these threats [39]. Rapee [40] posits that the increase in the prevalence of GAD symptoms over time may also be due to increases in GAD symptoms in girls rather than a general increase.

The content of worry also appears to vary with age. Younger children (under 6 years) are more likely to worry about separation from their parents and burglars, while older children (10–12 years) are more likely to worry about tests and academic performance, death, physical appearance, and social ills [12]. Masi et al. [41] found that children (7–11 years) compared to adolescents (12–18 years) with GAD reported significantly more need for reassurance and significantly less brooding. Pina et al. [16] investigated the symptoms present in 111 children (6–11 years) and adolescents (12–17 years) diagnosed with GAD and found that adolescents endorsed more physical symptoms than children.

Gender

Gender differences in the prevalence of OAD/GAD in children and adolescents are inconsistent. Merikangas et al. [26] reported no gender differences in a sample of 8–15-year-olds, using the DSM-IV criteria for GAD, drawn from a community sample. In other community samples, using the OAD criteria, girls (of all ages) were found to have higher rates than boys (15 % of girls and 9 % of boys; [25]). Clinical samples have reported no gender differences in OAD/GAD in children 9–13 years of age [42, 43]. There remains a lack of conclusive research looking at gender differences in clinic samples in older adolescents.

With respect to symptoms of GAD and/or worry, females report more GAD symptoms than males. In a sample of 1,653 adolescents, 14–18 years, females reported more GAD symptoms than their male counterparts [44]. In a sample of African-American adolescents (12–19 years), females self-reported more GAD symptoms than males [45]. The reason that females report more GAD symptoms than males may be due to their beliefs about worry. A study of 16- to 19-year-old students found that females were significantly higher on their positive beliefs about worry [46]. That is, women may be more likely to worry because they believe that worry is a useful cognitive strategy. More research is necessary to identify and understand gender differences in GAD and worry.

Race/Ethnicity

Though data on the prevalence of OAD/GAD across racial and ethnic groups is sparse, the results are generally consistent. Data from specialized anxiety clinics report similar rates of OAD/GAD in Caucasian and minority children (e.g., [43, 47, 48]). Consistent with the prevalence rates of GAD across racial/ethnic groups, no differences in the manifestation or severity of GAD *symptoms* have been found across racial or ethnic groups [45, 49]. For instance, Austin and Chorpita [50] reported that Caucasian, Chinese American, Filipino American, Native Hawaiian, and Japanese American children, 7–18 years, all showed similar levels of GAD symptoms, as rated by child self-report.

Course

Early studies based on retrospective reports suggested that a significant proportion (44 %) of adults with GAD recalled that the onset of their illness began in childhood [51]. Prospective studies of GAD, though few in number, reveal that GAD is fairly stable over time, suggesting it is a chronic illness if left untreated. This literature, however, is inconsistent due to variations across studies noted earlier (e.g., in the diagnostic criteria used, informants, and samples). For instance, in a community sample

of over 300 children (9–18 years) evaluated over a 2.5-year period, half of the subjects that were diagnosed with OAD/GAD at time 1 were again diagnosed with OAD/GAD at time 2; findings did not vary by age or gender [52]. In contrast, Essau et al. [53] followed a community sample of German adolescents with a broad range of anxiety disorders (AD) and found that 77 % of the adolescents with a current AD at time 1 no longer met diagnostic criteria (using the World Health Organization Composite International Diagnostic Interview; CIDI) at time 2 (average of 15 months later). Factors associated with the stability of anxiety disorders, though not unique to GAD, included older age, more negative life events, and the presence of comorbid somatoform or substance use disorders. In a clinical sample, Carballo et al. [54] found that GAD was less stable relative to other anxiety disorders such as specific and social phobias (SOPs). No significant sex differences were observed on the diagnostic stability of the anxiety disorder categories studied.

In addition to being fairly stable, GAD and worry appear to be risk factors for later anxiety and depressive disorders. For instance, in a community sample of 712 adolescents, OAD was strongly associated with early-adulthood diagnoses of GAD, depression, and SOP [55]. Data from the Great Smoky Mountains Study [56] revealed that childhood OAD was associated with later OAD, panic attacks, depression, and conduct disorder (CD), while childhood GAD was related only to conduct disorder. Beesdo and colleagues [20] followed a community sample ($N = 3{,}021$, 14–24 years at time 1) for 10 years. GAD, phobias, panic disorder, and depressive disorders predicted each other over time, and early-onset GAD was a stronger predictor of later anxiety rather than depressive disorders. Several variables predicted GAD onset over time (and they were similar to those found for other anxiety disorders) including parental GAD and depression, childhood behavioral inhibition, childhood separation events, and parental overprotection. Uniquely, GAD was associated with the personality trait "reward dependence" (based on self-reported personality) and dysfunctional family functioning. In sum, GAD and associated worry appears stable and is associated with a broad range of downstream disorders.

Differential Diagnosis

Distinguishing GAD from other anxiety disorders can be difficult because many of the symptoms overlap with other anxiety disorders and rates of comorbidity are high. For example, children with OCD and GAD may present with complaints of excessive thoughts or worries that can be intrusive. To differentiate between the two disorders, determining the nature of the thoughts or worries is critical. Youth with GAD generally worry about everyday or real-life problems (e.g., test performance, school, friendships), while youth with OCD have thoughts that are typically not connected to everyday events and have a more unrealistic quality (e.g., contamination by germs) [1]. For a child experiencing worry about social situations, differentiating between SOP and GAD is key. Youth with GAD tend to worry more chronically and across several situations (social and nonsocial), whereas youth with SOP generally experience social anxiety only and in the context of social evaluative cues. For those already diagnosed with a different Axis I disorder (e.g., panic disorder), the excessive worry must be unrelated to that disorder (e.g., cannot be worried about having a panic attack) for it to be considered a symptom of GAD.

Etiology

Several etiological models of pediatric GAD have been proposed [40, 57]. The most recent, by Kertz and Woodruff-Borden [57], is presented in Fig. 1. Briefly, according to these developmental models, a child with GAD is born with a vulnerability to anxiety (manifested by heightened arousal

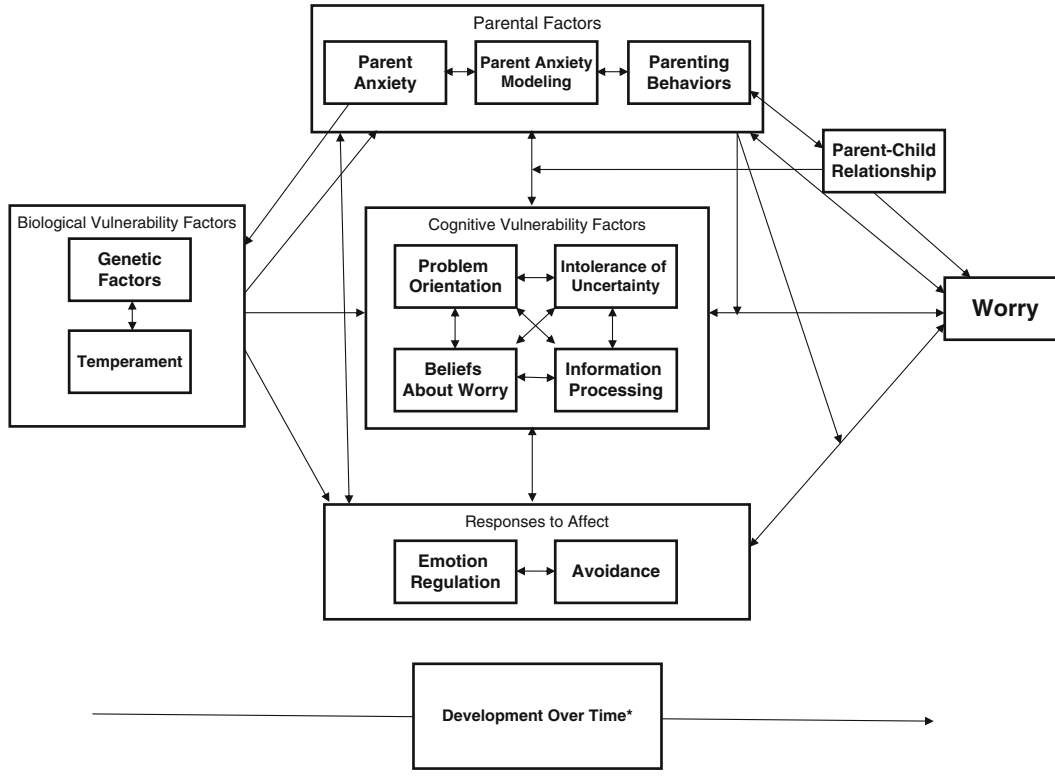

Fig. 1 Etiological model of pediatric generalized anxiety disorder (GAD). From Kertz et al. [57] used with permission

and emotional reactivity). This vulnerability may be inherited from an anxious parent or other family member. Children's biological vulnerability, such as deficits in cognitive (e.g., information processing) and affective (e.g., emotion regulation) functioning, increases their behavioral avoidance, ultimately maintains and/or exacerbates worry and anxiety, and leads to considerable distress and impairment. Parents of these youth, either due to their own anxiety or in response to their child's temperament, respond with greater overprotection and other anxiety-enhancing parenting behaviors (e.g., criticism) that also perpetuate the child's anxiety.

Despite the empirical advances that have informed these models, it should be noted that not all components have empirical support, the magnitude of each component's contribution is unclear, and unknown etiological factors likely exist. Some aspects of this model have support in adults (e.g., cognitive factors) but not children, and most of the factors proposed in the etiology of GAD also play a role in the development of other pediatric anxiety disorders. Data determining the specificity of these etiological factors for GAD awaits future investigation. Despite these limitations, there is a consensus that GAD is multi-determined with both biological and environmental factors playing key roles that influence each other in a transactional manner over a child's development. The evidence for key components of etiological models is briefly discussed below.

Heritability

Research based on family aggregation and twin studies support claims that anxiety runs in families. Studies that have focused on GAD, using adult twins, have found that genes accounted for approximately 30 % of the variance in GAD symptoms [58–60] and similar results have been found with child samples [61]. However, it has been hypothesized that the genetic link is likely to be for anxiety as a broad construct and/or emotional reactivity rather than for a specific disorder [59, 62]. More recently, researchers have focused on identifying candidate genes, with preliminary data suggesting that anxiety disorders are associated with serotonin genes (see [63] for a review), though again the specificity of these findings for GAD are not clear.

A related area of research supporting the heritability of anxiety comes from studies examining the genetic basis of temperamental and cognitive vulnerabilities that purportedly mediate the relationship between genes and anxiety disorders. Behavioral inhibition (BI) is the temperamental style most highly linked with anxiety and is characterized by increased physiological arousal and fear of novel stimuli [64]. However, the presence of BI has been associated with a broad range of anxiety disorders, especially social fears and SOP, and the majority of youth with BI do not go on to develop an anxiety disorder [65–67]. Thus, the association of BI with GAD specifically is insufficient at this time.

Cognitive Factors

A large body of data confirms that youth with GAD display problematic cognitive processes. Relative to their nonanxious peers, youth with GAD are more likely to overestimate the negative consequences of their actions, expect negative consequences to occur with greater frequency, overestimate the likelihood of threatening situations, interpret ambiguity as threatening, and have impaired problem-solving skills [68–70]. Recently some adult-based cognitive models and concepts have been explored in youth (see [57, 71] for reviews). These adult cognitive models include the avoidance model [72, 73], metacognitive models (e.g., [74, 75]), the role of intolerance of uncertainty [76], and problem-solving or problem-orientation deficits [77]. Literature testing these adult models in youth, however, has only indicated partial support. For instance, metacognitive models [74, 75] suggest that positive beliefs about the usefulness of worry (i.e., worry superstitiously allows control over events) and negative beliefs about worry (i.e., worry is dangerous and uncontrollable) play a role in the development of GAD. Recent research has found that youth do endorse positive and negative beliefs about worry and there is some support among both clinical (i.e., youth meeting criteria for OAD/GAD) and nonclinical youth indicating that positive beliefs about worry are associated with greater worry severity [46, 78, 79]. Yet, several studies have failed to find a unique relation between positive beliefs about worry and OAD/GAD [15, 80, 81]. A similar pattern of inconsistencies has been reported between negative beliefs about worry and OAD/GAD [15, 81]. Thus, the relevance of this and other "adult" cognitive models awaits empirical examination and validation among youth.

More consistent data supports the role of disturbances in information processing that cause and/or maintain GAD (and other anxiety disorders). This body of work contends that youth with GAD are more likely to interpret ambiguous information as threatening and have an attentional bias toward threatening stimuli. Data from studies using experimental threat tasks such as the dot probe and the emotional Stroop tasks indicate that children with GAD, versus nonanxious peers, show a faster reaction time to threatening, compared to nonthreatening stimuli [82–86]. For instance, Waters et al. [87] examined the attentional bias for angry and happy faces in 7- to 12-year-old children with GAD ($N=23$) and nonanxious controls ($N=25$) and found that GAD severity was associated with greater attentional bias toward angry faces. It is hypothesized that vigilance for threat involves interactions between the amygdala and the ventrolateral prefrontal cortex, which constitute a neural circuit that is

responsible for threat, and that disturbed interactions between these structures may result in hypervigilance and anxiety [88] (see chapter "Neurobiology of Pediatric Anxiety Disorders" for a more detailed discussion).

Parenting and the Parent–Child Relationship

Several reviews and meta-analyses have confirmed a relation between specific parenting behaviors and anxiety symptoms/disorders in youth [89–93]. Though inconsistent findings across studies exist, parental behaviors such as overcontrol (including overinvolvement and less autonomy granting), modeling of anxiety, low acceptance and warmth, as well as high catastrophizing and criticism have been linked to high levels of child anxiety overall. The amount of variance accounted for by these parenting variables is small (collectively likely to be less than 20 %). The impact of parental behaviors is also believed to be moderated by child gender, child age, socioeconomic status, and type of interaction task used to measure parenting [94, 95]. Interventions targeting parents and parent behaviors have shown evidence of reducing anxiety symptoms in their children [96]. Additional research is clearly needed in this area. Few studies linking parenting behaviors and child anxiety are longitudinal; thus, the direction of effects and long-term impact is uncertain. Evidence from longitudinal studies has concluded that a reciprocal relationship exists: parental behaviors affect child anxiety and child anxiety symptoms affect parental behaviors (e.g., [95, 97]).

Studies examining the relation between parenting and GAD or worry symptoms specifically are sparse, though the pattern of findings parallels those in studies examining the link between parenting and a broad range of anxiety symptoms/disorders. For instance, several studies using community samples and child self-report measures report that perceived parental overprotection, anxious rearing, overcontrol, warmth, and rejection are associated with higher levels of worry [98]. Findings, however, varied by parent (mother, father) and child gender [99, 100]. Hale et al. [101], also using a community sample, examined the relation between perceived parental alienation and GAD symptoms among adolescents (ages 12–19 years; $N = 1{,}106$). Based only on adolescent reports of both constructs, the authors found that higher perceived parental alienation, rejection, and control were associated with higher GAD symptoms. Parental alienation and rejection made unique contributions to worry symptoms when all parenting variables were entered into a single model, and slight variations were noted based on child age and gender.

In addition to specific parenting behaviors, parental attachment has been examined in relation to worry and/or GAD. The construct of attachment, based on the work of Bowlby [102] refers to the quality of the parent–child bond. Individuals with an insecure attachment (theorized to be the result of early experiences with unpredictable caregiver responsiveness) are predicted to be at greater risk for developing excessive anxiety and worry. With respect to worry, retrospective studies with adults [103, 104] have found that individuals with GAD are more likely to report an insecure attachment with their mothers compared to their nonanxious peers (no comparisons between GAD and other anxiety disorders were included). This relation is also present in child samples using cross-sectional designs. For instance, Muris et al. [12] reported that an insecure attachment (avoidant or ambivalent), along with perceived parental rejection and anxious rearing, was associated with higher levels of worry in a community sample of children ($N = 159$; ages 9–13). Brown and Whiteside [105] replicated and extended this finding with a clinical sample of anxious youth ($N = 64$; 7–18 years). In this study, youth completed measures of parenting behaviors, a single-item measure of attachment style, and the Penn State Worry Questionnaire (PSWQ). Parental attachment as well as parental rejection were positively related to worry. Specifically, youth who classified themselves as ambivalently attached reported higher levels of worry than did children who classified themselves as securely attached. Parental rejection and insecure attachment were both found to make unique contributions to worry [105].

Prospective studies, though few in number, also suggest that specific parenting behaviors and attachment have long-term consequences with respect to child anxiety [106, 107]. For instance, Ginsburg et al. [106] found that higher levels of parental criticism and lower levels of granting of autonomy, assessed when children were in first grade, were associated with higher GAD symptoms in sixth grade. Warren et al. [107] conducted a 16-year follow-up study of children ($N=172$) classified at 12 months of age on attachment style (i.e., secure, avoidant, ambivalent). At follow-up, among the 26 children (out of the total sample) that had at least one current or past anxiety disorder, a greater number had an ambivalent compared to secure attachment. Furthermore, an ambivalent attachment predicted childhood anxiety disorders even after accounting for maternal anxiety and temperamental variables. Notably, the majority of youth classified as insecurely attached (i.e., 70 %) did not develop an anxiety disorder and the relation of attachment to GAD specifically remains unclear.

Finally, a critical question remaining for future research is to identify the mechanisms by which parental behavior or attachment style influences child anxiety and worry. In one of the few studies to address this issue, Affrunti and Ginsburg [108] tested the hypothesis that greater levels of parental overcontrol reduce children's perceived competence, which in turn increases child anxiety levels. Using a sample of 89 mother–child dyads (children aged 6–13), the authors conducted a mediation analysis and found support for this model, i.e., child-perceived competence fully mediated the relationship between maternal overcontrol and child-reported worry symptoms. These data fit with the theory that mothers perceived as using higher levels of overcontrolling behaviors (e.g., demanding to know what the child is doing, not allowing the child to decide what they want to do) reduces children's perceived competence, which in turn increases their level of anxiety. Thus, overcontrolling parents may increase levels of worry in their children through communicating that they do not have the skills to successfully navigate challenges in their environment, which increases children's tendency to worry about their abilities. This increased worry likely leads to greater avoidance and subsequently reduced opportunities for developing effective problem-solving skills. Future research into additional pathways through which parental behaviors or attachment styles impact worry is needed.

Assessment

Although there are many assessment tools for assessing the broad range of pediatric anxiety disorders, few instruments focus exclusively on pediatric GAD. To date, seven measures designed to assess worry and other symptoms of GAD have been published. Table 2 presents a description of each measure [15, 37, 39, 109–112].

The most widely used measure of child and adolescent worry is the Penn State Worry Questionnaire for children PSWQ-C [37], a downward extension of the adult PSWQ [113]. The PSWQ-C assesses the severity, excessiveness, and uncontrollability of worry in children and adolescents. Higher scores reflect a greater degree of worry. Chorpita et al. [37] evaluated the psychometrics of the PSWQ-C in a community sample of 199 and a clinical sample of 35 children and adolescents. They found that the PSWQ-C consisted of a unitary factor (worry) and had high internal consistency with $\alpha=0.89$ when samples were combined. High correlations with the worry scores of the Revised Children's Manifest Anxiety Scale (RCMAS; $r=0.71$) and moderate correlations with the Children's Depression Inventory (CDI; $r=0.52$) provided support for convergent validity. Further support comes from moderate to high correlations with GAD items from the Anxiety Disorder Interview Schedule for DSM-IV Child/Parent Version (ADIS-C/P), such as the number of worries ($r=0.56$), intensity of worries ($r=0.72$), and disorder severity ratings ($r=0.36$). Chorpita et al. [37] reported a 1-week test–retest reliability for the PSWQ-C of 0.92 in a clinical sample. Scores on the PSWQ-C have been shown to discriminate between those children who meet criteria for a diagnosis of GAD and those meeting criteria for any other anxiety or mood disorder [37].

Table 2 Assessment of pediatric GAD

Name of measure	Reporter	Age range (years)	# of Items	Response format	Scoring/range	Psychometrics
Penn State Worry Questionnaire for Children (PSWQ-C) [37]	Child (self-report)	6–18	14 Statements	0 (not true) to 3 (always true)	Total score: 0–42	α=0.89
The Worry Scale [109]	Child (self-report)	5–18	31 Items	0 (never) to 2 (often)	Total score: 0–62	α=0.93
Why Worry Questionnaire (WWQ) [110]	Child (self-report)	12–19	19 Items	1 (strongly disagree) to 5 (strongly agree)	Total score: 19–95	α=0.88
Intolerance of Uncertainty Scale for Children (IUSC) [111]	Parent and child (self-report and parent report)	7–17	27 Items	1 (not at all) to 5 (very much)	Total score: 27–135	α=0.92 (child report), 0.96 (parent report)
The Worry Scale for Children (WCS) [14]	Child (self-report)	8–18	40 Items	1 (almost never) to 3 (often)	Total score: 40–120	α=0.88
Worry Interview [39]	Child (interview)	5–12	3 Vignettes	Open-ended	Qualitative scoring	α=0.70, κ=0.93
The Worry Interview for Children (WIC) [112]	Child (interview)	6–16	14 Areas of worry	Open-ended Intensity of worry: 0 (none) to 4 (very, very much) Frequency of worry: 0 (none) to 2 (a lot)	Qualitative scoring	κ>0.80, test–retest reliability=0.78

The Worry Scale [109] assesses worries involving separation anxiety, contact with strangers, meeting new people, future events, past events, physical symptoms, competency in school, social relationships and social evaluation. Unlike the PSWQ-C, the Worry Scale inquires about specific domains of worry and examines the frequency of those worries (never, often or always), not about the excessiveness or uncontrollability of worry in general. The measure was developed and tested on youth with anxiety, attention deficit hyperactivity disorder, and no disorders. The Worry Scale was shown to have high internal consistency (α=0.93) and good convergent validity, exemplified by positive correlations with self-report measures of child anxiety like the Revised Children's Manifest Anxiety Scale, especially the worry score (r=0.72), State Trait Anxiety Inventory for children, especially trait anxiety (r=0.66), and Fear Survey Schedule for Children-Revised version (r=0.54). The Worry Scale has been shown to differentiate between those children with an anxiety disorder and those without. However, there is no evidence to conclude that the Worry Scale is able to differentiate those children with GAD from those with other anxiety disorders.

Another self-report measure is the *Why Worry Questionnaire* (WWQ; [110]). It assesses erroneous beliefs associated with worry. This questionnaire was created to investigate why, despite worrying being a negative experience causing unpleasant effects, people continue to worry. Specific beliefs associated with worry include, but are not limited to, guilt, distraction, psychological safety or protection, control, learning, and disappointment. Freeston et al. [110] found that these mapped onto two factors: worries that help prevent negative events or avoid the worst outcome and worries that allowed one to increase problem solving and to help find solutions. Unlike the previous self-report measures, the WWQ does not inquire about specific worries or the intensity of those worries. The WWQ showed good internal consistency (α=0.88) in a sample of nonclinical youths (N=777; 12–19 years of age) and high convergent validity in being correlated with the PSWQ-C [78]. A revised version of the WWQ, the WWQ-II, showed good internal consistency (α=0.90) and high correlations with the PSWQ-C in a sample of nonclinical students (N=528; 79).

The Intolerance of Uncertainty Scale for Children (IUSC; [111]) was developed to measure a child's inability to cope with ambiguous and uncertain situations. It assesses a child's tendency to react negatively to uncertain situations across emotional, cognitive, and behavioral domains. Unlike other measures, this questionnaire does not investigate worry itself, but a cognitive factor associated with worry. In adult studies, the concept of intolerance of uncertainty (IU) has been proposed as a cognitive vulnerability factor for excessive worry and GAD [114]. However less is known about the relation between IU, worry, and GAD in children and adolescents. The IUSC comes as both a child self-report and a parent report about child questionnaire. Both the child-report and the parent-report versions show high internal consistencies (α=0.92 and 0.96, respectively) and high convergent validity in being correlated with the PSWQ-C, Multidimensional Anxiety Scale for Children (MASC), and Reassurance-Seeking Scale for Children (RSSC) in a sample of both nonreferred community children (N=124) and treatment-seeking anxiety-disordered children (N=73). The IUSC is able to distinguish anxiety-disordered youth from community youth, but there is no data to suggest it can differentiate those youth with GAD from those youth with another anxiety disorder.

The final self-report measure is the *Worry Scale for Children* (WSC; [15]). Similar to the Worry Scale, the WSC assesses the frequency of specific types of worries. Unlike the PSWQ-C and the WWQ, it does not examine any accompanying cognitions or beliefs, or the severity and excessiveness of such worries. Higher scores indicate greater levels of worry. The measure has shown high internal consistency (α=0.88) and convergent validity in a sample of 193 nonanxious children, but has not been used with clinical samples.

In addition to child self-report questionnaires, two interview measures have been developed. The first was developed by Vasey et al. [39]. During this interview, children read three vignettes depicting worried children in typical situations. Children are then asked to provide items that the child in the story could be worried about and then asked to elaborate on why that child would be worried about that item. The responses are coded and yield scores relating to the frequency of worrisome thoughts

in each vignette, length of worrisome statements, and content of the worry. Content is coded as either (1) relating to self, (2) relating to significant others, or (3) miscellaneous. Self-referential worries are then broken down into (a) threats to physical well-being (e.g., injury, sickness, and kidnapping), (b) threats to behavioral competence (e.g., not being able to complete one's work), or (c) threats to social evaluation (e.g., being teased or embarrassed) or psychological well-being (e.g., feelings of incompetence). The measure was developed as a way to relate children's worry to their social–cognitive developmental status. The measure has only been used with a community sample, and no data is available determining whether this interview would be effective at screening worries of children with GAD.

Another interview, developed by Silverman et al. [112], the *Worry Interview for Children* (WIC) is a semi-structured interview designed to assess worries in 14 areas: health, war, disasters, school, performance, future events, personal harm, little things, family, friends, classmates, money, appearance, and other worries not covered by the categories above. For each worry, children are asked to rate the intensity of the worry on a five-point scale. Children are then asked to rate the frequency with which they worry about that item. Each interview takes approximately 10 min to complete. The WIC has shown to be a reliable interview (e.g., 1-week test–retest reliability was 0.78) and was able to discriminate children with GAD from those with another anxiety disorder [13, 112].

Taken together, the above measures provide some options for assessing worry in children and adolescents. Since not all measures of worry assess the same construct, the "best" instrument depends largely on the goal of the assessment. For instance, if a measure is needed to screen for the diagnosis of GAD, the best tool would be the PSWQ-C or the WIC. The WIC's format provides in-depth information about worry that cannot be gained from the use of a self-report questionnaire. For the purposes of gathering data on the content of children's worry (but not impairment, severity, or associated physical symptoms), the WIC, the Worry Scale, or the WSC would be appropriate.

Treatment

Evidence-based treatments for pediatric GAD parallel those for youth with other anxiety disorders, discussed in the chapter "Cognitive-Behavioral Treatment for Pediatric Anxiety Disorders," and include cognitive behavioral therapy (CBT), selective serotonin reuptake inhibitors (SSRIs), or their combination [115]. Data on the efficacy of CBT and medication are based on treatment studies that have included samples of youth with any combination of GAD, SAD, and SOP rather than on youth who present exclusively with GAD. The inclusion of these three anxiety disorders in most treatment studies is due to the high rates of comorbidity both at the symptom and diagnostic level. Evidence suggests that youth with each of these disorders respond to similar treatment strategies and the presence of GAD does not predict poorer treatment response or remission [116]. Only a small number of randomized controlled medication trials have focused exclusively on youth with GAD. Recently, preliminary data have been published on a pediatric adaptation of a GAD-specific CBT. These GAD-specific treatment studies are briefly summarized below.

Pharmacological Studies

Initial trials for youth with GAD were small and evaluated sertraline [117]. Specifically, in a 9-week double-blind placebo-controlled trial, 22 children, ages 5–17 years, were randomized to sertraline (25–50 mg/day) or placebo. Youth receiving sertraline relative to placebo had significantly larger reductions in anxiety symptoms (based on the Hamilton Anxiety Scale and the Clinical Global Impression Improvement scales).

In a larger report, Rynn and colleagues [118] reported findings from two randomized, double-blind, placebo-controlled trials with youth 6–17 years of age who met DSM-IV criteria for GAD. Youth received a flexible dosage of extended-release venlafaxine ($N = 157$, 37.5–225 mg/day), a serotonin-norepinephrine reuptake inhibitor or placebo ($N = 163$) for 8 weeks. Results were inconsistent across the two studies with extended-release venlafaxine group showing statistically significant improvements on the primary outcome (i.e., change in a composite score based on nine items from the GAD section of a modified version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children) in study 1 but not in study 2. In a pooled analysis across the two studies, the response rates, based on a CGI-I score of <3, were significantly greater with extended-release venlafaxine than placebo (69 % versus 48 %). Treatment-emergent adverse events for venlafaxine that were twice that of the placebo group included asthenia, pain, anorexia, and somnolence. Statistically significant changes in height, weight, blood pressure, pulse, and cholesterol levels were observed in the extended-release venlafaxine group. The authors concluded that the high placebo response rate, particularly evident in study 2, contributed to its failure to show a statistical separation between extended- release venlafaxine and placebo.

Hidalgo et al. [119] reviewed the pharmacological literature for both adults and children with GAD. A total of 21 studies were found but only 2 were with youth and included SSRIs. The results indicated that the average effect size (generally using the HAM-A) across all studies was 0.39 and significantly higher effect sizes were found for children/adolescents than adults, i.e., the ES for youth was 1.38 based on the findings of the two studies. Currently, SSRIs are considered the first-line pharmacological treatment, as these medications have the fewest side effects and laboratory testing is not indicated (see [120] for review).

CBT Studies

Few studies have examined a GAD-specific CBT protocol. Early reports of psychotherapy for youth with GAD involved case studies [121, 122], and the treatment involved standard CBT strategies such as those found in the Coping Cat [123]. Response rates were similar to those found in larger efficacy trials examining CBT for other pediatric anxiety disorders. However, given that only 60 % of youth respond to CBT, efforts at optimizing CBT are needed.

Toward this end, recent efforts aimed at adapting CBT specifically for GAD have been reported. Leger et al. [70] modified a GAD-specific CBT treatment by Dugas et al. [124] and examined its effect on older adolescents (16–18 years) with a primary diagnosis of DSM-IV GAD. The Dugas et al. model of GAD [125] assumes that GAD is maintained by a number of cognitive factors including a low tolerance for uncertainty, dysfunctional beliefs about worry, negative problem orientation, and dysfunctional strategies to reduce distress (i.e., thought/image suppression, ruminating). Their GAD-specific treatment, therefore, targets these factors and includes worry awareness training, planned exposure to uncertainty, modification of dysfunctional beliefs about worry, and at post treatment problem-solving training and relapse prevention. In an open trial of this treatment with a sample of 7 youth (an average of 13 sessions), 43 % no longer met diagnostic criteria for GAD at post treatment [70]. Payne et al. [126] further modified this treatment, based on the work and recommendations of Leger and colleagues [70]. The modification involved decreasing the didactic and increasing the experiential components (via in session exposures), individualizing aspects of the treatment to age and maturity level, and applying the treatment to younger ages. According to the authors, the treatment proceeded in six stages: (1) worry awareness training, (2) planned exposure to uncertainty, (3) modification of dysfunctional beliefs about worry, (4) modified problem-solving training, (5) imaginal exposure to unpleasant images or worries, and (6) relapse prevention. In an open trial, 16 youths (7–17 years) with a primary diagnosis of DSM-IV GAD were treated (average of 10 sessions, range was 5–15). All

participants who entered the study completed treatment and 13 (81 %) lost their GAD diagnosis (not blindly assessed). Results were encouraging and await more rigorous scientific evaluation. In addition, comparisons between GAD-specific and "generic" CBT will be needed.

Case Follow-Up

*Daniel's treatment involved a combination of an SSRI and CBT. Specifically, he was started on a low dose of sertraline (25 mg/day) that was titrated up to 200 mg/day over the course of 12 weeks without side effects. Simultaneously, he completed a 12-week course of CBT. His CBT treatment began with an overview of the CBT model (*i.e.*, how anxiety can manifest itself somatically, behaviorally, and cognitively), and he was asked to monitor these symptoms of anxiety and worry daily using a structured diary. He and his parents generated a list of situations that evoked worry and caused distress and then developed a plan to begin both imaginal (initially) and in vivo exposures. To facilitate exposure to these worry-provoking situations, he was taught how to examine and modify his worry thoughts (to ones that are more realistic and helpful), to use relaxation strategies, and to employ problem-solving skills. He applied these skills at night, at school, and while playing sports. His parents were also informed about ways they could support his treatment and reduce anxiety-enhancing parenting behaviors (*e.g.*, providing excessive reassurance, accommodating avoidance). Over time, Daniel experienced fewer somatic symptoms, was better able to "turn off" his worry, and improved relations with his parents.*

Summary

Though pediatric GAD is a relatively new diagnosis, the hallmark symptoms of the disorder (i.e., worry, somatic symptoms) have remained unchanged since DSM-III and the diagnosis of OAD. Research on pediatric GAD has produced significant advances in our understanding of its prevalence, presentation, and course. Assessment tools focused specifically on worry have facilitated this research. Findings indicate that GAD is prevalent in about 3 % of the general population of youth, increases with age, and presents similarly across gender and races/ethnicities. Early-onset GAD appears chronic and confers risk for downstream disorders, most notable other anxiety disorders. Developmental models of GAD highlight that both biological and environmental factors contribute to illness onset and maintenance. Future research evaluating additional components of these models is still needed. Effective pharmacological and psychosocial treatments are available; however, there remains a dearth of research examining psychosocial treatment options that specifically target worry and GAD.

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Pediatric Social Phobia

Vasco M. Lopes and Anne Marie Albano

Abstract Social phobia (SP) is a common psychological disorder characterized by excessive fear and avoidance of social situations. With a typical onset in late childhood/early adolescence, its course is chronic and unremitting if left untreated. SP has shown to have high psychiatric comorbidity, particularly with depression and other anxiety disorders. Neuroimaging studies show hyperactivity in the amygdala and prefrontal regions in response to social threat in children with social phobia. The past decade has seen a significant increase in validated measures used to screen for and diagnose SP. Effective treatments for pediatric SP include cognitive-behavioral therapy (CBT) and SSRI pharmacotherapy, either alone or in combination.

Keywords Social phobia • Social anxiety • Generalized social phobia • Performance anxiety • Shyness • CBGT-A • SET-C

Case Scenario

Michael D., a 14-year-old high school sophomore, was brought to the clinic by his parents, mostly against his wishes. The D's sought treatment for Mike when he began refusing to attend school because of a group presentation that was assigned in his social studies class. At the time of the intake, Mike had missed 3 weeks of school. The D's recognized that Mike's school refusal was just a new way of avoiding social attention, but were concerned that his behavior was now at a significant level of dysfunction that required intervention.

Mrs. D. described a long history of "shyness" with Mike. As a baby, he was always attached to one of his parents whenever there were visitors in the house or when the family went on outings. It took Mike until he was nearly 4 years of age to warm up to and interact comfortably with relatives. He had difficulty attending kindergarten and would often refuse to play with other children, although he did make two good friends by second grade. As the boys grew older and enlarged their social circles through middle school, Mike would drop out of activities and avoid social gatherings such as

V.M. Lopes
Department of Psychology, Fordham University, New York, NY, USA

A.M. Albano (✉)
Department of Psychiatry, Columbia University Clinic for Anxiety and Related Disorders, Columbia University, New York, NY, USA
e-mail: albanoa@nyspi.columbia.edu

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parties. Mike was always a good student, although he never volunteered to answer questions or participate in class.

During the interview of Mike and his parents, it was evident that he had long-standing social phobia, along with dysthymia, as he was acutely aware that "my life is passing me by." In describing his school refusal, Mike admitted to having intense fears of looking foolish in front of others, and despite his good school performance, he felt the other kids were smarter than he. He admitted to feeling intense fear in a number of social contexts, from informal conversation to performance situations, such as oral reports. Mike's interaction fears were affecting his ability to engage in conversation, answer the telephone, and engage in typical teenage situations, such as dating.

Description of the Disorder

According to the DSM-IV, social phobia (social anxiety disorder) is a marked fear of one or more social or performance situations, where the person is exposed to unfamiliar people or evaluation from others. The term "social anxiety" was added to the DSM-IV nomenclature to underscore the distinction between *social phobia*, which can produce fear of one or many social situations, and *specific phobias*, in which the child or adolescent has excessive fear of only one particular stimulus. Commonly feared situations in social phobia include initiating conversation with peers, speaking or performing in front of the class, and attending social gatherings, such as play dates, dances, or parties, in which the child is expected to interact with others.

Upon exposure to the feared social or performance situation, the child with social phobia (SP) may exhibit physiological symptoms of anxiety, such as increased heart rate, blushing, lightheadedness, gastrointestinal distress, or trembling. At times, these symptoms may result in full or limited symptom cued panic attacks. In children specifically, anxiety reactions may also manifest in the form of crying, tantrums, shrinking away from others, or refusing to speak. Whenever possible, the child will attempt to avoid the social or performance situation that prompts the anxiety, and if unavoidable, the situation may be endured with intense distress (e.g., "Let me just get through this!"). The avoidance, anxious anticipation, and/or emotional distress experienced during the social or performance situation significantly disrupts academic, family, occupational, and social functioning.

Generalized Versus Non-generalized Subtypes

Currently, in DSM-IV, generalized subtype is designated if the child fears "most social situations"; otherwise, a diagnosis of SP is assigned with no subtype indicated. However, it has become common practice in the literature to indicate non-generalized when the child fears only one social situation (e.g., public speaking), or a few contextually similar social situations (e.g., test taking, other evaluative situations such as performing in gym class). Of note, this dichotomous conceptualization of SP as "generalized" versus "non-generalized" has been heavily debated and scrutinized. Some argue that the generalized subtype has significant value and utility since these children usually have greater severity and impairment, higher likelihood of comorbidity, and worse prognosis than those with non-generalized SP [1–5]. Others suggest that this specification has poor reliability and an unclear operational definition since the DSM does not specify *how many* social fears must be present in order to reach the threshold of generalized subtype [6]. Despite this controversy, and the fact that a non-generalized subtype is not specified in DSM-IV, these subtypes will be noted throughout this chapter when necessary to accurately reflect research findings.

DSM-5 Proposed Description

The proposed DSM-5 criteria for social phobia are not expected to deviate much from the DSM-IV. One proposed change, however, lies in the name of the disorder, itself. Whereas the disorder was termed "Social Phobia (Social Anxiety Disorder)" in DSM-IV, it will be called "Social Anxiety Disorder (Social Phobia)" in DSM-5. This semantic change is proposed to reflect the evidence that most individuals with this disorder exhibit anxiety that is generalized to many social situations, and not to one specific situation, as the name *phobia* implies.

In DSM-5, SP will continue to be characterized by the marked fear of one or more social situations in which the person may be evaluated or scrutinized by others. According to Bogels et al. [6], in effort to better organize the Criterion A symptom of "fear or anxiety in social situations," social situations will be classified into one of three categories: *interacting* with others (i.e., having a conversation), being *observed* by others (i.e., eating), or *performing* in front of others (i.e., giving a speech). Additionally, whereas DSM-IV only contains one specification (generalized subtype), DSM-5 will likely carry three specifications: *generalized, performance only, and selective mutism* (*SM*). The specification of *performance only* has been added to reflect evidence that performance anxiety, the excessive fear of performing in front of an audience (i.e., giving public speeches, an artistic performance, or presentation), is a qualitatively distinct type of SP [6]. Selective mutism (SM), formerly its own diagnosis under DSM-IV, will be designated as a subtype of SP in DSM-5. Typically diagnosed in young children, SM is described as the failure to speak in settings where speech is socially expected (i.e., school), despite normal language ability. The rationale for including SM as a specific type of SP comes from research indicating significant comorbidity and conceptual overlap between the two disorders [7–9] (see Chap. 11 for more information on SM). Additional changes to the DSM-IV social phobia criteria have been proposed that only impact adults with the disorder; therefore, they will not be discussed here.

Prevalence

Epidemiological surveys consistently find that SP is one of the most commonly occurring mental disorders [2], with child and adolescent prevalence ranging from 5 % to 13 % [10, 11]. According to the National Comorbidity Survey Replication-Adolescent (NCSR-A; 3), 8.6 % of children, ages 13–18 years, meet criteria for SP at some point during their lifetime. Adult prevalence rates are similar [4, 5, 12], suggesting that SP is a chronic and unremitting disorder if not treated [2]. Research consistently demonstrates that the majority of individuals with SP are diagnosed with the *generalized* subtype [5]. In an epidemiological study, Burstein et al. [3] showed that 55.8 % of children and adolescents diagnosed with SP met criteria for the generalized subtype, while 44.2 % met criteria for non-generalized, and only 0.7 % met criteria for the proposed DSM-5 performance-only subtype. This proportion of generalized subtype is similar to that of adults [4]. Across studies, subtype prevalence estimates vary, however, depending on how generalized SP is operationally defined and the assessment instruments used [4].

In children and adolescents, female prevalence of SP is nearly twice that of males [13]. Age of onset is typically in adolescence, with studies reporting an age range of 12–16 years [5, 13–15]. Age of onset is dependent on several factors, however, such as gender and subtype. Females are more likely to develop the disorder in childhood or adolescence than males (9.2 % and 7.9 % lifetime prevalence, respectively) [3]. Further, within the adolescent period, onset is significantly earlier for females, with an average age of onset being 11.5 years, compared to 14 years of age for males [5]. Children diagnosed with the generalized subtype are more likely to have an earlier age of onset [3, 4]. Roughly 50 % of generalized SP children are diagnosed before age 12, compared to only 19 % of non-generalized SP [5].

Course

The risk for being diagnosed with SP increases dramatically during late childhood and early adolescence. Throughout adolescent development, this risk continues to rise, although not nearly at the same rate as observed during late childhood. Once the individual reaches young adulthood (age 25), the risk of developing SP decreases dramatically [5]. In other words, if the child has not shown significant social anxiety during adolescence, his/her odds of developing symptoms in early adulthood are low.

When SP symptoms emerge during adolescence, they are typically chronic and unabated [2]. If left untreated, an adolescent's anxiety and avoidance of social situations will typically maintain or exacerbate throughout their development into early adulthood in an unremitting manner. Evidence suggests that only 20–40 % of individuals with SP will show remission within 20 years of onset [16]. This chronic nature is compounded by the fact that few adolescents seek treatment for SP. Research shows that only 12.1 % of adolescents diagnosed with SP receive treatment for the disorder [17]. This rate is much lower than the 68 % of adults with lifetime SP who eventually seek treatment [4]. This failure to seek treatment for adolescents with social phobia may be partially due to an unwise and unwarranted idea that social phobia is a "medicalization" of shyness geared towards promoting treatment with pharmaceutical agents, an idea often portrayed in the popular press and media [e.g., 18]. Across development, the likelihood of receiving treatment increases with severity as well as comorbidity [4, 17]. However, although individuals with high severity and comorbidity are more inclined to receive general treatment, they are less likely to receive treatment specific to SP. In fact, retrospective analysis of SP treatment utilization demonstrates that SP adults show an inverse relationship between number of social fears and SP-specific treatment—those with a greater number of fears, severity, and comorbidity were less likely in their lifetime to receive therapy specific to their SP symptoms than those with a smaller number of fears and lower severity [4]. The authors discuss the possibility that those with severe SP may regard their social anxiety as a fixed part of their personality (i.e., shyness) that cannot be changed. Although it is unclear whether these treatment-utilization patterns apply to adolescents, the authors recommend that health care providers screen for possible SP when other anxiety, depressive, or substance abuse symptoms are present.

In comparison to adults, adolescents' symptoms are less likely to wax and wane over time, since they have less control over choosing a niche accommodating to their social anxiety (i.e., a job with no public speaking requirements). Children have much less control over their environment and are thus less able to avoid anxiety-provoking social situations without consequence. Also, whereas adults with SP may be beyond a certain social life stage that previously brought on tremendous anxiety (i.e., a person with romantic relationship anxiety gets married and no longer needs to date), late childhood/early adolescence is marked by a tremendous increase in social demands, such as expanding social groups in school, extracurricular activities, and dating. The fact that children cannot control their environmental niches, coupled with the increase in social demands, causes social anxiety to be chronic and stable throughout this life period.

Comorbidity

SP has a high incidence of comorbid psychiatric disorders in children and adolescents, with epidemiological studies showing rates from 59 % [19] to over 71 % [5]. Childhood SP co-occurs most frequently with other anxiety and mood disorders and more moderately with oppositional defiant disorder (ODD) and later substance use [3]. Comorbidity with other anxiety disorders ranges from 20 % to 41 % [3, 19], with agoraphobia, generalized anxiety, and separation anxiety yielding the highest rates of comorbidity (32.4 %, 32 %, and 27.4 %, respectively) [3]. Comorbidity of SP with mood disorders, including depression and dysthymia, ranges from 41 % to just over 50 % [19–22].

Notably, the generalized subtype of SP is associated with significantly higher comorbidity rates than non-generalized [3, 5, 20], with some studies suggesting rates as high as 88 % [10]. Consistent with this, the risk of developing comorbid disorders is more likely with increased number of social fears. For example, Ruscio et al. [8] conducted an epidemiological study with SP adults investigating a number of social fears. Although this is not the standard manner of differentiating generalized versus non-generalized SP in the DSM, the investigators operationally defined non-generalized SP as having four or fewer social fears and generalized SP as eight or more social fears. The investigators indicate that lifetime SP comorbidity with other disorders is 62.9 % for non-generalized and 81.5 % for generalized SP. Their results are consistent with previous findings indicating a linear effect between number of social fears and likelihood of comorbidity—the greater number of social fears, the higher the likelihood of manifesting comorbid disorders [22].

SP has been described as a *temporally primary* condition, since it has consistently been shown to have an earlier age of onset than comorbid conditions [5]. Although the causal mechanism of this developmental trajectory is unclear, it highlights the implications for early identification and treatment of SP in the prevention of secondary disorders [22]. In retrospective studies of SP adult comorbidity, in 59–76 % of cases, onset of SP precedes the initial onset of depression [20]. Longitudinal prospective studies of adolescents and young adults with SP indicate that carrying an SP diagnosis causes a two-fold increase in risk for developing later depression, with those diagnosed with the generalized subtype showing an even greater risk [20]. As a result of this temporal pattern, adolescent comorbidity is typically lower than in adults [5, 19, 21], since SP symptoms, themselves, are starting to manifest during this age range, and comorbid disorders, such as depression, substance use, and other anxiety disorders, typically develop later [4, 5].

The high comorbidity between SP and depression has received considerable research attention [20, 22, 23]. Recent epidemiological research investigating adolescent comorbidity [3] suggests that the risk for depression and alcohol use in adolescents with SP is not nearly as high once other anxiety and behavioral disorders are factored out. This suggests that SP alone does not predict the later onset of depression but, instead, does so along with multiple anxiety disorders and disruptive behaviors in combination. In other words, the greater severity of overall psychopathology, the greater likelihood of manifesting secondary depression and alcohol use. The authors discuss, however, that this new finding may stem from the fact that epidemiological data was being collected on the current functioning of adolescents and not retrospective functioning of adults. This raises the possibility that secondary depression and alcohol use is more likely to occur in late adolescence/early adulthood, meaning that only retrospective studies or studies with early adults would be able to capture this onset.

Differential Diagnosis

In the last decade, much criticism has come from the media and popular press about how the mental health field has pathologized *shyness* [i.e., 18], a normally developing trait, into the psychiatric disorder of social phobia. Recently investigators have been interested in how much overlap occurs between the normative temperamental trait of shyness and social phobia. Research has found that whereas 46.7 % of adolescents and 62.4 % of parents surveyed in the NCSR-A rated the adolescents as "shy," only 10–12 % of parents or self-identified "shy" youth also met criteria for social phobia [24]. Adolescents with social phobia were no more likely than their shy peers to be taking medication for the disorder, despite significantly greater impairment in their ability to function in school, work, or everyday life situations, and the presence of serious psychiatric comorbidities including other anxiety disorders, depression, and substance abuse. Thus, although shy children exhibit difficulty in novel social situations, it is considered normative, and the child's slight difficulty and fears usually subside after a short duration. Social phobia, on the other hand, is associated with much greater distress

and long-standing impairment in various domains of functioning, as well as increased psychiatric comorbidity.

The hallmark of SP is the exaggerated fear and avoidance of social situations in which the person is subject to public evaluation and scrutiny. Several other disorders show similar avoidance responses to social situations—but it is the *reason* for their avoidance that marks the distinction between SP and other DSM conditions.

Separation anxiety disorder involves a developmentally inappropriate fear of being separated from one's parent or caretaker. Children with separation anxiety may present with symptoms in social situations similar to that of SP; however, their underlying fear, avoidance, or tantrums stem from being separated from their caregiver rather than being evaluated by or fearing rejection of others. When the parent or caregiver is present, a child with separation anxiety disorder can function in social situations comfortably. A child with SP, however, will experience discomfort and anxiety in feared social situations, even if the parent is present.

In *panic disorder with agoraphobia* the individual fears the consequences of a panic attack, which mostly are misinterpreted as a heart attack, stroke, or other catastrophic bodily concern. Additionally, it is characterized by a fear of having another panic attack and avoidance of situations where potential panic attacks may occur. Although children with SP may also experience significant physiological symptoms of anxiety (i.e., blushing, sweating, or increased heart rate), they do not misinterpret these symptoms as life-threatening or create catastrophic interpretations of these bodily cues. Thus, although panic attacks may be present in both panic disorder and SP, the ultimate fear and avoidance in panic disorder stem from the fear of being helpless with symptoms or even dying. In SP, on the other hand, the child may avoid situations in which they are likely to blush or have trouble breathing due to fear of embarrassment or negative evaluation from others. In *agoraphobia without history of panic attacks*, the child has a pervasive fear and avoidance of situations where they may develop subthreshold panic-like somatic symptoms (i.e., headache, vomiting, cardiac symptoms, loss of bladder control). The child's main fear is not necessarily the resulting social evaluation of their symptoms but the presumed lack of ability to get help in managing the physiological symptoms.

There is overlap between SP and *avoidant personality disorder* (*APD*). This is evidenced by high comorbidity as well as conceptual similarities. APD has been suggested to be a more severe form of generalized SP, rather than a qualitatively distinct disorder [25, 26]. A key distinction lies in pervasiveness. Adolescents with SP can become highly anxious and avoidant of certain social situations yet have a healthy sense of adequacy in other social domains. Adolescents with APD have an underlying sense of inadequacy and ubiquitous preoccupation with being criticized by others, resulting in avoidance of most situations that require social interaction. Although differentiating between APD and non-generalized SP may be more clear, it becomes tricky when the adolescent fears so many social situations, as in the case of generalized SP, that it seems related to an underlying ubiquitous sense of inadequacy in succeeding in social situations commonly seen in APD. In the case of this severe form of generalized SP, it may be useful to provide both diagnoses in order to highlight the severity of social impairment. It is also important to note that the assignment of an Axis II diagnosis of personality disorder remains controversial, as it is often proposed that children and adolescents do not yet have the timeline and stability in presentation to warrant a characterological disorder [27].

In addition to disordered functional communication and restricted interests, children with *pervasive developmental disorder* (*PDD*) or *autism spectrum disorder* (ASD) often avoid social situations, instead preferring solitary activities. This avoidance of social interaction is not necessarily caused by fear but rather is a consequence of an inherent lack of interest in social interaction. Although some ASD children gain a desire for social interaction as they develop, their deficient social skills limit their chances of developing successful social relationships [28], and they may become the target of bullying [29]. As a result of their continued social rejection and peer victimization, children with ASD often develop significant anxiety in social situations [30]. Since this anxiety results from actual rejection and is not exaggerated, an SP diagnosis is unwarranted. Despite this nosological feature, it should be

noted that children with ASD are likely to require treatment specific to social anxiety, especially those who experience high physiological arousal to stressful situations along with poor social skills relative to other ASD children [31].

The differential between SP and a *depressive disorder* can be challenging in light of the high comorbidity between the two, as described above. When differentiating between these two disorders, it is important to understand the different patterns *in behavioral withdrawal* and *mood* symptoms. First, there is a difference between the avoidance of social situations that is a hallmark of SP and the *diminished interests* common to depressive disorder. Although children with SP may seemingly lose interest in activities, their avoidance is circumscribed to *social* activities only, while other interests (i.e., games, movies, playing with toys) remain unaffected. A loss of pleasure and diminished interest in all or most activities (which may include social interaction), on the other hand, are more consistent with symptoms of a depressive disorder. Second, although children with SP may show significant mood symptoms, such as withdrawal, agitation, irritability, crying, and tantrums, these behaviors occur almost exclusively when they are forced into social situations that increase their anxiety. When SP children are not immersed in social situations that cause emotional distress, they are able to function normally. Depressive children, on the other hand, are more likely to experience more persistent and chronic mood symptoms that are either dispositional or in response to many environmental antecedents, but not fear of social situations alone.

Etiology

The origins of social phobia have been studied from various perspectives. Although genetic and biological influences have been shown, social and environmental factors have also been linked to the manifestation and maintenance of SP.

Genetics

Although the research in this area has been sparse, kinship studies suggest that genetics have a mild to moderate effect on the development of SP. Research indicates that parents with SP are more likely to have children who develop SP than non-affected parents [32]. Twin studies have estimated that the heritability of social anxiety ranges from as low as 0.10 [33] to as high as 0.60 [34], suggesting that genetic influences account for 10–60 % of the variance in the development of social anxiety. Although these discrepant findings suggest an inconclusive genetic effect, a meta-analytic review of SP twin studies reveals that the genetic influence of social anxiety increases as the child gets older [35]. This suggests that the phenotypic expression of social anxiety increases as the child develops into an age where social relationships become more predominant. In other words, as a child who is genetically predisposed to develop social anxiety becomes an adolescent, and social relationships become more important, the greater the likelihood of phenotypically manifesting socially anxious traits.

Temperament

Longitudinal studies of biological disposition towards developing social anxiety have been conducted. Most of this research has investigated infant temperamental styles, tracking these children over time to determine if certain temperamental styles are associated with SP. In particular, investigators have

been interested in how the behavioral inhibition (BI) temperament style may lead to social anxiety. BI is characterized as a consistently anxious disposition, with an exaggerated physiological response to distress, constant hypervigilant attention, and behavioral avoidance in novel situations [36; see Chap. 3 for a more detailed description of BI]. In studying infants with and without BI temperament over time, those with BI are significantly more likely to develop SP in early adolescence [37], but not other childhood anxiety disorders [38], suggesting that BI has good discriminative ability in identifying children at risk for later SP.

Neurobiology

The amygdala plays a prominent role in detection of threat and processing fearful and salient stimuli in the environment [39]. Thus, this key region has been the focus of much neuroimaging research in anxiety disorders including social phobia. As most of this research has been conducted on adults, these are the studies that will be reviewed here. Studies of pediatric SP will be included wherever possible; see Chaps. 1 and 2 for more details of amygdala involvement in fear processing and in pathology across anxiety disorders, respectively.

Research with adults has consistently shown a link between social anxiety and amygdala functioning with greater amygdala responsivity associated with more generalized and severe social anxiety [39–42]. In these studies, researchers have focused primarily on amygdala responses to pictures of angry or harsh faces that may be particularly salient to adults with SP because they can elicit an interpretation of social rejection or disapproval. Results demonstrate a significant relationship between SP and heightened amygdala reaction in response to viewing these facial expressions [41]. This relationship is so robust that individuals with SP even show a heightened amygdala reaction to schematic line-drawn harsh faces [40]. However, increased amygdala responsivity is not limited to viewing harsh facial expressions; it has also been observed in response to other socially threatening stimuli, such as experiencing negative cognitions [43], receiving negative evaluation from others [44], and the anticipation of giving a public speech [45]. Diagnostically, SP is characterized by increased sensitivity to socially threatening cues, but not necessarily to cues unrelated to social situations. This has been supported by neuroimaging studies. For example, adults with SP show significant amygdala hyperactivity in response to harsh facial expressions, but not to other threatening cues, such as violent pictures [46]. Amygdala responses to fearful faces have even been able to discriminate between generalized SP and generalized anxiety disorder (GAD) [47], with adults with SP showing significantly greater amygdala activity than those with GAD.

Recent neurobiological models of anxiety, including social anxiety, posit alterations in the prefrontal cortex (PFC) as well as the amygdala. The PFC has been implicated in the regulation of emotion [48, 49], and the circuitry between the amygdala and the PFC has been associated with conditioning of fear responses [50]. BI models of anxiety suggest that individuals who are highly inhibited are hypersensitive to fear conditioning, or become conditioned to feared stimuli too easily [51]. This model suggests that circuits between the amygdala and PFC are hyperresponsive—such that when an anxious individual experiences an ambiguous or potentially threatening cue, it leads to overactivity in this circuit, which results in a fear response and behavioral inhibition. In support of this model, adults with SP demonstrate alterations in prefrontal function underlying emotion regulation. For example, when asked to engage in a cognitive emotion regulation strategy such as relabeling negative self-beliefs, SP adults show insufficient activation and delayed onset of amygdala activity [44]. Similarly, when shown harsh facial expressions and asked to conduct cognitive-linguistic strategies to cope with this threatening cue, adults with SP show reduced activity in the amygdala and dorsolateral and dorsomedial PFC, as compared to controls [46]. Both of these studies suggest that, when required to *regulate* their negative emotionality after exposure to social threat, SP adults have deficient neural functioning,

both in the amygdala as well as the circuitry between the amygdala and regions of the PFC implicated in the downregulation of emotion.

Critical developmental changes that occur in the PFC during puberty such as increased axonal myelination and synaptic pruning may play a specific role in the onset of social phobia during adolescence. These neurological changes may result in increased metacognition, causing the early adolescent to gain increased awareness and focused attention to how he/she is evaluated by others during a time when social demands increase, likely leading to the onset of social anxiety. Evidence supports the role of the PFC in response to social threats, particularly in socially anxious individuals. For example, adults with generalized SP show increased activity in the medial PFC compared to controls when presented with negative evaluative comments from others [43]. In a unique study, Guyer et al. [52] used a novel "chat room task" to investigate the amygdala-PFC circuitry of adolescents with social anxiety. Socially anxious adolescents and non-anxious comparisons were asked to rank 40 pictures of peers based on their desirability to chat with them. Subjects were informed that they would be able to chat with the peers whom they ranked the highest and that these peers would be aware of how they were ranked. Two weeks later, during an fMRI scan, subjects were asked to rate the likelihood of peers wanting to chat with them. This procedure was thought to elicit fear of social evaluation since other peers "knew" how they were ranked by each subject. Results from this study indicated that, compared to non-anxious comparisons, when looking at pictures of undesirable peers, adolescents with social anxiety exhibited increased coactivation in the amygdala and ventrolateral PFC (vlPFC).

Blair et al. [53] investigated the neural functioning of adolescents with SP and compared these neural patterns to those of SP adults, in a cross-sectional design. In this study, blood-oxygen-level-dependent (BOLD) contrast responses were compared for 39 SP subjects (25 adults; 14 adolescents) and 39 controls while viewing angry, fearful, and neutral facial expressions. Results indicated that both the adolescent and adult SP subjects showed higher activity than controls in both the amygdala and the rostral anterior cingulate cortex when viewing angry and fearful faces. Although longitudinal research is needed on the developmental trajectory of pathological neural regions, this suggests that neural deficits in SP are similar in adolescence and adulthood.

Clearly, additional research is needed to elucidate these neuroimaging findings in adults, as well as to replicate them with children and adolescents, since these brain circuits are just starting to mature and reorganize during this developmental period [49].

Environment/Parenting

Social phobia is characterized by cognitive biases about social situations; therefore, researchers have been interested in the environmental source of these cognitions, particularly in youth. Parenting style has been significantly linked with the development of anxiety and mood disorders in children [54], including SP. Research suggests that an overprotective parenting style is a risk factor for developing SP in children [55, 56]. Evidence also suggests that parenting style can discriminate between disorders. Specifically, parental rejection leads to child depression, and overprotection leads to onset and maintenance of generalized and social anxiety [57].

In a study of families of adolescents, Lieb et al. [32] found that adolescents with SP were significantly more likely to experience rejection and overprotection from parents, even after controlling for parental psychopathology. Laboratory tasks of fathers and their children working together to complete an origami task [58] showed that, after controlling for paternal depression and general anxiety, fathers of children with high social anxiety were significantly more controlling than fathers of non-anxious children, although these groups did not differ on other parenting behaviors, such as rejection. Studies investigating adult retrospective self-report of parental style during childhood and adolescence show that those with higher social anxiety rated their parents as much more overprotective,

controlling, and less warm than adults with lower social anxiety [55]. Retrospective accounts of parental overprotection are associated with lower social responsiveness in a concurrent social interaction laboratory task in adults with generalized SP, but not normally functioning adults [56].

Rather than children with SP being passive agents of their parents' overprotection, some models suggest a reciprocal relationship between the child's behavioral inhibition and the parent's assertion of control [59]. Since socially anxious children may demonstrate chronic apprehension and reticence in social situations, it may pull for protection and decision-making behaviors from the parent. This protective behavior can lead to a vicious cycle of child anxiety and self-perceived inadequacy, since parents are preventing the child from entering "risky" social situations, where they could otherwise practice skills and disconfirm cognitive biases.

Peer Victimization

Since bullying has become a prominent topic in child development and in the popular press, researchers have attempted to investigate negative developmental outcomes as a result of experiencing chronic peer victimization. In community-based studies, as well as in studies of SP adolescents, findings have consistently shown that children who are victims of bullying are at increased risk of developing social anxiety [60–62]. Children and adolescents who experience multiple types of peer victimization, including overt, relational, and reputational aggression, are at increased risk of developing fears of negative evaluation, physiological symptoms of anxiety, and social avoidance [63]. Erath et al. [64] indicate that not only do socially anxious children experience high peer victimization, they also experience chronically low peer acceptance in general.

Since studies have repeatedly shown that children with social anxiety are more vulnerable to being victimized, researchers have wondered about the reciprocal nature of social anxiety and chronic peer victimization [59]. In other words, does victimization cause SP, or do SP deficits cause peer victimization? Research suggests that SP children possess inherent deficits in social skills [64, 65]; thus, some investigators argue for the possibility these children's anxious behaviors during, and avoidance of, social situations increase their susceptibility to being victimized by peers. Whether the poor social skills demonstrated by SP children are an inherent deficit or failure to perform is debatable, however, and some researchers argue that children with SP do possess adequate social skills but inhibit their appropriate response when in anxiety-provoking social situations [66]. Despite this debate, research repeatedly demonstrates a strong relationship between SP and peer victimization; regardless of which variable is temporally primary, the continuous peer rejection seen in SP can easily create a vicious cycle and exacerbate social anxiety throughout the child's development.

Cognitive-Behavioral

Rapee and Heimburg [57] propose a cognitive-behavioral model of the etiology and maintaining factors of SP. Here, they assert that one of the first key cognitive elements inherent in SP is the distorted assumption that people are often critical and prone to evaluate others negatively. The individual also possesses the belief that it is highly important to please and be positively appraised by others. When the individual with SP evaluates the feared social situation, they form mental representations of themselves in the situation. These mental representations are theorized to involve two components: mentally encountering themselves as perceived by their "audience," or other individuals involved in the social situation, and mentally picturing their audience and especially their social cues that indicate negative evaluation. This model holds that the individual's level of social anxiety will depend on

the discrepancy between the expectation of others about social performance and the individual's evaluation of his/her actual performance. Given the notion that individuals with SP have irrational beliefs about others' perfectionistic expectations in social situations and that they are likely to be overly critical about their own social performance, it creates a high likelihood for experiencing significant anxiety in that social situation. Thus, when the individual enters that social situation, they will do so with heightened anxiety, including associated physiological and behavioral features, such as heavy breathing, increased heart rate, sweating, blushing, and freezing. These features lead to additional mental representations of what their audience must think of them and even more scrutiny in looking for indicators of negative evaluation, which at this point, may be evident since the individual may be showing overt signs of anxiety. This causes the individual to further criticize his/her performance, causing more distress and a vicious cycle of anxiety.

Biopsychosocial Model

A comprehensive biopsychosocial model of social phobia has been proposed that brings together many of these individual risk factors. Rapee and Spence [67] propose that the manifestation of SP results from an interaction of genetic and environmental influences, such that individuals may have a genetic predisposition to feel a certain level of anxiety in their social environment, a term they refer to as "set point" (Fig. 1). This set point may be altered, either up or down, depending on the environment. According to this theory, children with a high genetically predisposed set point will require only a low intensity of negative environmental influences necessary in order to manifest SP, whereas children with a low set point will require much greater negative influences to manifest the disorder. Negative environments that increase this set point include overcontrolling parenting and peer victimization, while other factors, such as pro-social peer relationships, may be protective and lower the child's set point [63].

Detweiler et al. [68] go further than Rapee and Spence and propose additional influences of neurobiological and developmental factors (i.e., temperament, attachment). They propose that the increase of social anxiety seen in early adolescence is a result of the tremendous increase in social demands typical of this age range that occur simultaneously with changes in PFC function that allow for increased self-reflection, as discussed earlier. As a result, the early adolescent places greater significance on evaluation from others than he/she did during childhood. Although most adolescents show a normative increase in social fears during this time, those with biological and developmental vulnerabilities for SP will enter this social-developmental period with significant difficulty. Moreover, Detweiler et al. [68] discuss that not only does the child's family and social environment influence his/her manifestation of social anxiety but his/her inherently inhibited style can influence the way that others respond socially, in a reciprocal interaction.

Assessment

The measurement of childhood social anxiety has shown great improvement over the past decade. Today, there are several assessment options when childhood SP is in question, including broad anxiety rating scales for screening, rating scales specific to childhood SP, structured diagnostic interviews for determining diagnosis, and behavioral assessments to observe symptoms during an anxiety-provoking situation. This section will describe several assessment tools used specifically to evaluate social phobia symptoms in children.

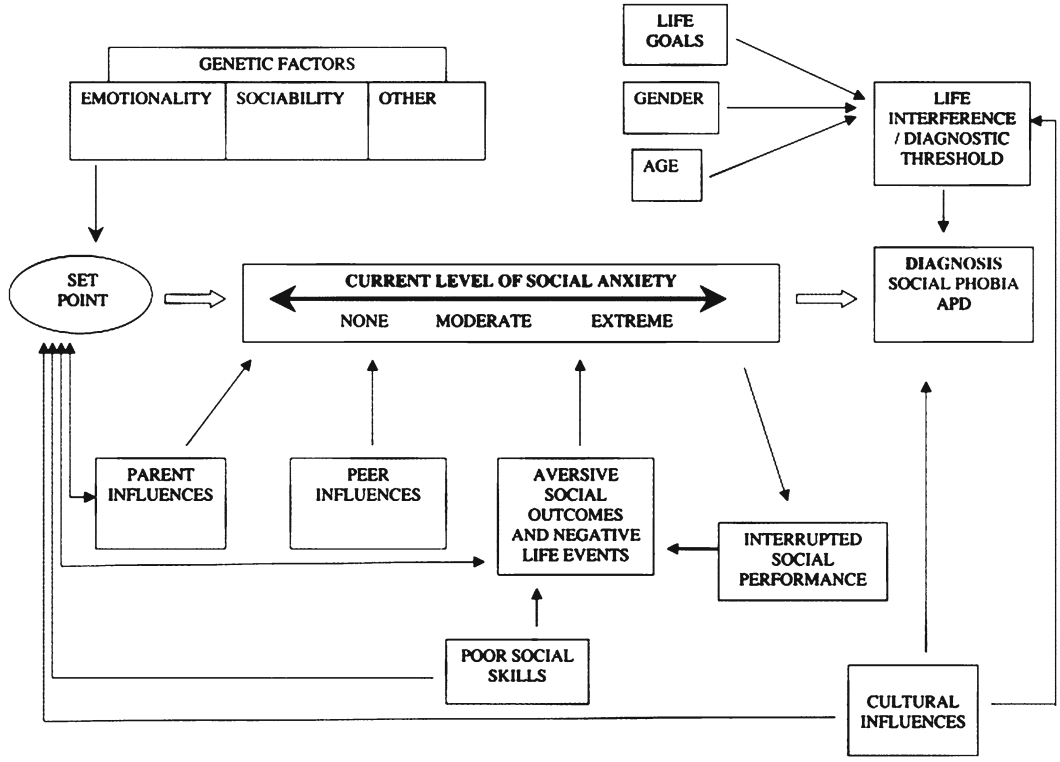

Fig. 1 A model of the development of social phobia (from Rapee [67]; used with permission)

Social Anxiety Rating Scales

Rating scales have been developed to specifically assess the severity of social anxiety symptoms across different social domains. These offer parent-report as well as self-report versions which is particularly important in light of the SP child's inherent tendency to respond in a way that pleases others [69]. Especially when using self-report rating scales to monitor treatment progress, one must be mindful that the SP child's rating may not be reliable, since they may respond favorably out of fear that the clinician will evaluate them negatively if they do not show progress.

The *Social Anxiety Scale for Children-Revised* (*SASC-R*) [70] was developed to measure SP in children ages 6–13; the SAS-Adolescent version can be used to assess older children, ages of 13–18. Parent-report versions are available in addition to self-reports. Both versions consist of 22 items, on a 5-point scale (not at all—all the time), and are composed of three subscales as well as a total score. The three subscales, derived from factor analysis, include fear of negative evaluation from peers, social avoidance and distress specific to new situations, and generalized social avoidance and distress. The SASC-R has shown adequate internal consistency, test-retest reliability, and construct and discriminative validity [71]. It also shows good sensitivity to clinical levels of social anxiety. A total score of 50 or higher suggests a possible diagnosis of SP.

The *Social Phobia and Anxiety Inventory for Children* (*SPAI-C*) [72] has also shown to be useful in measuring childhood SP. This scale assesses children ages 8–14 and includes a parent version [73]. The SPAI-C is composed of 26 items, on a 4-point scale (0–3; never or hardly ever-always), and contains five subscales: assertiveness, general conversation, physical and cognitive symptoms, avoidance,

and public performance. This scale shows adequate internal consistency, test-retest reliability, and construct validity [71]. It also shows good sensitivity to clinical levels of social anxiety. A total score of 18 or higher (out of a possible 52) suggests a diagnosis of SP.

The *Liebowitz Social Anxiety Scale for Children and Adolescents* (*LSAS-CA*) [74] is a clinician-based rating scale that measures SP in children ages 7–18. The LSAS-CA consists of 24 items with separate ratings of anxiety and avoidance on a 4-point scale for each item. In addition to a total score, two subscales are derived: social interaction situations and performance situations. Separate anxiety and avoidance levels for each subscale can also be obtained. Psychometric properties, including internal consistency, test-retest reliability, and construct validity, are all adequate [74]. A total score of 22.5 or higher suggests possible clinical levels of SP.

Behavioral Assessments

Behavioral assessments or behavioral approach tasks (BATs) are useful for clinicians to gather information about the child's functioning in a specifically feared situation (i.e., speaking with a strange peer). Although parent and child ratings provide information about social anxiety severity, children may not always have good insight about their socially anxious behaviors in specific situations, especially if they are chronically avoiding these situations, and parents may not have the opportunity to observe their child in certain social domains (i.e., socializing at school). Thus, BATs allow the clinician to observe and code for behaviors in a specific situation in a manner that allows for development of treatment goals and monitoring progress of social anxiety reduction and skill acquisition.

The *Social Performance Rating Scale* (*SPRS*) [75] is a tool used for observing and coding the target child's social behavior while holding a one-on-one conversation with another person. The clinician codes for specific behaviors on a 1- to 5-point scale, such as eye gaze, vocal quality, length of conversation, discomfort exhibited (i.e., fidgetiness, throat clearing, stuttering, or giggling), and conversation flow (i.e., initiating conversation, awkward pauses, maintaining conversation). The SPRS has shown high inter-rater reliability, acceptable internal consistency, and good discriminative validity.

The SPRS, as well as other BATs, has several limitations, however. First, they require a lot of training in order to reliably code for specific behaviors, making the real-world application of this assessment challenging. Second, assessment is restricted to one specific social domain and does not measure other social fears. Thus, although the clinician will have fruitful information about the intensity and quality of social anxiety in one specific domain, the BAT does not answer questions about the breadth of the child's other social fears, making it limited in its diagnostic utility. Also, there are very few BATs that have standardized coding and scoring of specific social behaviors, such as the SPRS. Most BATs are used to collect anecdotal or qualitative clinical information pertinent to treatment. Although this is clinically useful, it has low reliability as a standard diagnostic measure of social anxiety.

Assessment Summary

When childhood SP is in question, it is best practice to start with multiple informant ratings using either broad-based anxiety measures that contain social anxiety subscales, or SP-specific rating scales. If the child is rated in the clinically significant range on these screeners, then a diagnostic interview, such as the Anxiety Disorders Interview Schedule for Children (ADIS-C) [76], would help in establishing a formal SP diagnosis. Once in the treatment phase, the clinician could periodically administer child and parent rating scales, as well as coded BATs specific to the child's social fears, in order to monitor progress.

Treatment

The past decade has shown an increase in empirically supported treatments of childhood anxiety disorders, including SP [77]. Cognitive-behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRI's) have continuously garnered the most support [77–80].

Cognitive-Behavioral Treatments

The CBT literature has produced a solid evidence base for the treatment of childhood social anxiety. Most of these studies use manualized treatment packages, composed of a combination of cognitive and behavioral techniques [78, 81–83].

Many SP interventions, especially empirically supported manualized treatments, are provided in a group format. Although it may seem counterintuitive to place socially anxious children in a social treatment setting, this method has been shown to be highly effective. First, exposing an SP child to a social environment, in and of itself, may help that child gradually reduce their anxiety in social settings. Second, it allows the child to practice social skills in vivo, where he/she is likely to confront similar emotions and cognitions as in a natural setting.

Social skills training (SST) is a group cognitive-behavioral intervention shown to be effective in improving SP in children [81]. SST teaches children specific social skills (i.e., politeness, eye contact, taking turns in conversation, complimenting others) by learning the steps to each skill didactically, followed by role-playing these skills with the therapist and other members of the group and practicing them during weekly homework assignments. The role-playing and practice integrated into SST allow for continued skill refinement as well as constructive feedback on how to improve different aspects of these skills. The rationale for SST in SP stems from research demonstrating that children with SP often have inherent deficits in social skills that lead them to fear negative evaluation or rejection [65]. As a result, SP children consistently avoid social situations and miss out on opportunities to develop and hone social skills, causing any skill deficits to exacerbate. Thus, in SST, by focusing on development and practice of social skills, children are more likely to enter feared social situations with a more sophisticated ability to interact, thereby reducing the chances of being negatively evaluated by others.

Another effective cognitive-behavioral treatment for SP is Social Effectiveness Therapy for Children (SET-C; [84–86]). SET-C is a multifaceted behavioral treatment that includes peer generalization exercises, individual in vivo exposure exercises, parent and child psycho-education about anxiety, and components of SST. SET-C treatment lasts 12 weeks and consists of two sessions per week—one individual and one group. Treatment focuses on developing social skills in a group setting, such as greetings, starting and maintaining conversations, listening skills, joining groups, and speaking on the telephone. Techniques used include didactic instruction of skills, modeling, behavioral rehearsal, corrective feedback, and application of skills via homework assignments. SET-C also includes peer generalization activities, where the SP children participate in social outings and are encouraged to practice social skills learned in session with non-SP children. This component was added due to the finding that social skills learned in the group therapy setting do not always generalize to the natural environment. Lastly, individual sessions of in vivo exposure to feared social situations are included. Examples of typically feared social situations include reading in front of a group, writing on the blackboard, or acting out plays in front of an audience. The child completing the exposure exercise is required to remain in the situation until their anxiety abates. In a randomized trial of 8–12-year-old children with SP, SET-C was significantly more effective than a study skill comparison group. Results indicated that 67 % of children treated with SET-C no longer met SP criteria at posttreatment compared to only 5 % of the children in the study skills group [84].

Given that the efficacy of treating SP with SET-C had not yet been investigated in an applied clinical setting, Baer et al. [85] replicated Beidel et al.'s [84] study using a modified version of SET-C, consisting of 12 once-weekly, 1.5 h sessions with an experienced social worker and two supervised psychiatric residents. In this community-based study, the investigators compared SET-C to a wait-list control in a group of 12 adolescents ages 13–18 with SP. Results indicated that this community-based application of SET-C was more effective than no treatment. At posttreatment, children in the wait-list group received treatment. After analyzing their improvements, the investigators found that 91 % of SP adolescents who received outpatient SET-C treatment were considered responders, with 36 % going into full remission posttreatment.

Treatments such as SET-C, although conceptualized as CBT, use predominantly behavioral techniques and do not focus on cognitive skills. However, cognitive-behavioral models of SP suggest that a child's social fears are fed by cognitions that are often overgeneralized, have catastrophic social consequences, and magnify the potential for negative evaluation from others (i.e., "Others will think I am stupid if I get a question wrong in class." or "Kids are going to wind up laughing at me if I try to talk to them.").Thus, altering such cognitions can also be the vehicle used to treat social anxiety. A child with extreme fear of speaking in class, due to the unrealistic belief that others will make fun of him if he gets a question wrong, for example, can be coached to *identify* and *challenge* that belief, for example, by gathering evidence that counters his automatic thoughts (i.e., "Cindy got a question wrong in class yesterday, and nobody laughed at her.").

Cognitive-behavioral group therapy for adolescents (CBGT-A) [78] is a 16-session multifaceted intervention composed of behavioral and cognitive techniques. In this manualized treatment, sessions one and two offer psycho-education to adolescents and parents about social anxiety and rationale for treatment. Sessions 3–8 focus on skill building, including SST, social problem-solving, assertiveness training, and cognitive restructuring. Sessions 9–15 offer graded in vivo exposure exercises of feared social situations while applying skills learned in sessions 3–8. Children are also encouraged to complete homework assignments throughout sessions 9–15 in the form of between-session exposure exercises. Session 16 is composed of one final exposure, termination, and planning for posttreatment.

A pilot study of CBGT-A that treated five adolescents with SP [78] found significant treatment gains for all five adolescents, and four out of five adolescents were still in full remission at 12-month follow-up, with one in partial remission. Hayward et al. [87] conducted a larger investigation of CBGT-A, by randomly assigning 35 adolescent females to receive either CBGT-A ($n=12$) or a wait-list control ($n=23$). Although CBGT-A was significantly more effective than no treatment in improving SP, improvements were not as robust as the previous pilot study [78]. At posttreatment, the CBGT-A group showed significantly greater SP remission than the control group (45 % versus 4 %, respectively); however, this significant difference did not hold up at 12-month follow-up. Although the CBGT-A group maintained their remission 1 year after treatment, a large percentage of subjects in the control group also showed remission, resulting in a nonsignificant difference between the two groups in SP diagnosis 1 year after treatment. The authors also analyzed risk for major depression. Amongst subjects with a history of major depression, those in the no-treatment group (64 % of subjects) were more likely to relapse than the CBGT-A group (17 %), although this difference was nonsignificant due to a small sample size. Thus, this study shows that CBGT-A is a moderately effective short-term treatment for SP and may reduce the risk of relapse for comorbid major depression.

Standard CBT designed for child and adolescent SP typically involves only the child (either individually or in a group), with minimal or no parental involvement; however, studies have shown that providing adjunctive family therapy to CBT improves SP outcomes [81]. The rationale for providing such treatment stems from findings that parental behaviors may exacerbate the child's symptoms [55]. Parents' enabling of social avoidance, by minimizing it as *shyness* or "*just a phase*," can often strengthen the child's socially avoidant behaviors. Also, parents who express catastrophic fears toward their child about the risks of social interactions, what others will think of him, or failure on a performance

can inadvertently increase their child's anxiety. Thus, treatments have been developed to involve parents so that these issues can be directly addressed.

Spence et al. [81] tested whether adding parental involvement to CBT would improve outcomes for children with SP. Fifty children, ages 7–14, were randomly assigned into one of three groups to receive 12 weeks of CBT alone, CBT plus parental involvement, or a no-treatment wait-list control. The CBT alone treatment consisted of 12 group sessions of SST, relaxation training, social problem-solving, cognitive challenging, positive self-talk, and gradual exposure to feared social stimuli. Parent involvement group training sessions consisted of modeling, teaching, prompting of skills, ignoring (not reinforcing) social avoidance, and encouraging participation of social activities and homework assignments outside of sessions. At posttreatment, both CBT treatment groups showed significantly higher remission rates than the control group (87 % of CBT + parent training, 58 % of CBT alone, and 7 % of control group). Moreover, at 12-month follow-up, both treatment groups maintained their treatment gains, with 81 % of the parental involvement and 53 % of the CBT alone groups still not meeting diagnostic criteria. Although the parental involvement group had a higher percentage of children in remission both at posttreatment and 12-month follow-up, their improvement was not statistically different from that of the CBT alone group.

Recent adaptations of cognitive-behavioral therapies for children and adolescents with social phobia also show promise. These include brief intensive interventions and shifting the therapy setting to the community or school. An intensive, brief group CBT intervention has been shown to be effective [88]. Twenty-three 8–11-year-old children were randomly assigned into either brief CBT or no treatment. Three sessions, each consisting of 3 h, focusing on psycho-education, behavioral exposure, and cognitive strategies, were shown to be more effective than no treatment at posttreatment. The brief CBT group showed significant improvement in social phobia at posttreatment, when compared to the nontreatment group. Results showed that 41.7 % of parents and 58.3 % of children no longer reported social phobia at posttreatment. Moreover, children receiving this brief therapy maintained their gains or showed even greater improvement at a three-week follow-up assessment, with 50 % of parents and 83.3 % of children no longer reporting significant social phobia on the ADIS-C.

Recently, SP-specific treatment programs have been tested or extended for application in the school setting [83, 89–92]. Children with SP are rarely referred for treatment in the community [82]. This is in part due to parents and teachers often thinking of SP as typical childhood shyness and something the child will grow out of. Additionally, children with SP, who are typically withdrawn, tend to "fly under the radar" in the classroom since they are more manageable than externalizing, disruptive children. Thus, the need for proper assessment and treatment of childhood SP within the school setting is essential [83]. Skills for Academic and Social Success (SASS) [91, 93] is a group treatment program adapted from the SET-C and CBGT-A manuals to fit a school environment. SASS has consistently shown to improve adolescent SP in the school setting, compared to no treatment [91, 94] as well as to an attention control group [93]. In addition to 12 treatment sessions, SASS includes three posttreatment booster sessions, weekend social events, two parent meetings, and teacher consultation. The treatment is composed of five core components: (1) psycho-education about anxiety; (2) development of "realistic thinking," by relabeling overestimated negative outcomes and exaggerated consequences; (3) SST focusing on initiating and maintaining conversations, establishing friendships, listening skills, and assertiveness training; (4) graded in vivo exposures; and (5) relapse prevention, to prepare the adolescent for posttreatment challenges as well as red flags for emerging symptoms.

Pharmacotherapy

Selective serotonin reuptake inhibitors (SSRIs) have demonstrated the most consistent pharmacological efficacy across childhood anxiety disorders [80, 95] and for SP specifically [79, 86, 96]. For example,

after an eight-week open label trial [96] of sertraline, 36 % of children with social phobia were considered responders, and 29% were considered partial responders. Significant response to treatment was observed by week 6. Sertraline was generally well tolerated, showing only minimal adverse effects. Research has also investigated SSRI treatment of child SP using double-blind placebo control procedures [79]. A sixteen-week treatment with paroxetine resulted in a 77.6 % response rate, with 75 % of children deemed as "much improved" or "very much improved" in their global functioning, compared to only 38 % of the placebo group.

In addition to open label and randomized placebo-controlled trials, researchers have also investigated the efficacy of SSRI's in treating SP when compared to CBT (SET-C) [86]. Results demonstrated that both SET-C and fluoxetine were more effective than a placebo in improving SP, yielding 79 % and 36 % treatment response rates, respectively. However, SET-C was superior to fluoxetine in reducing SP symptoms at posttreatment—53 % of SET-C children no longer met SP criteria, compared to only 21 % of the fluoxetine group. SET-C was also associated with improved social skills and self-ratings of social competence. Moreover, whereas fluoxetine's effect showed a plateau at week 8, SET-C continued to yield improvements after 12 weeks of treatment. At 12-month follow-up, 61 % of the fluoxetine group qualified as treatment responders, compared to 100 % of the SET-C group.

Treatment Summary

Although there are many unanswered questions about treatment efficacy, the past decade has shown an increased in evidence-based treatments for childhood SP. Amongst psychotherapies, behavioral and cognitive-behavioral therapies have garnered the most support. Several manualized treatments specific to childhood SP have demonstrated effectiveness, including SET-C [84] and CBGT-A [78, 87]. CBT treatments have also shown successful application in treating SP in the school setting [82, 91, 93], with gains lasting upwards of 5 years [90]. Pharmacologically, SSRIs have repeatedly shown to be effective in treating childhood SP [86, 97]. Yet, treatment with CBT improves social skills and rating of social competence more so than SSRIs and shows continued improvements beyond treatment termination [87]. Although studies have not examined the combination of SSRI and CBT treatment in childhood SP specifically, this combination treatment has shown to be the most effective intervention across childhood anxiety disorders and may likely be the best option for treating childhood SP [80, 98].

Case Follow-Up

Upon presenting for treatment, Mike was diagnosed with social phobia and dysthymia, but he also had the complication of school refusal behavior. Targets and goals were collaboratively developed by the therapist, Mike, and his parents, with an emphasis on returning to school comfortably. A "fear and avoidance" hierarchy was established that identified specific social situations that provoked increasing levels of anxiety. Mike agreed to confront each of his fears over the course of treatment through exposure exercises.

Mike initially began individual CBT as he refused to enter a group treatment. Mike was taught to monitor his thoughts during anxiety-provoking social situations, particularly at school. He was able to identify negative self-talk and participate in behavioral exposures which were primarily focused on school reentry. The therapist introduced these exposure exercises by role-playing them with Mike during therapy sessions and then having him complete them in vivo either in session or between sessions for homework. Exposure tasks included calling classmates or meeting them socially after school hours or on weekends, going to the school and sitting in the parking lot, and talking to his favorite

guidance counselor about school, first on the telephone and then in person. After only three individual sessions, Mike was able to begin attending school for at least part of the day and was attending consistently after his sixth session. While combination treatment of CBT and medication is often warranted in severe cases of school refusal, it was not needed in this situation because Mike's parents acted quickly to seek CBT once the school refusal occurred. After his return to school, Mike continued in treatment and agreed to join a group with other teenagers who presented with social phobia. The group role-played realistic social challenges that are common for teenagers, such as being turned down for a date or having people laugh during an oral report. After 12 sessions of group therapy, Mike was reporting a significant decrease in social phobia symptoms.

Overall, given his positive response to treatment and his strong social support system, Mike's prognosis is favorable. However, given that he would soon be graduating from high school and entering college, it is possible that his symptoms may relapse. Thus, Mike was given relapse prevention guidelines that outlined how to manage his anxiety if he felt problematic anxiety returning.

Summary

Social phobia is one of the most common adolescent psychiatric disorders, with a typical onset in late childhood. If left untreated, SP children may likely experience unremitting symptoms and impairment throughout their adolescent development and have a high likelihood of developing comorbid disorders, making it important to accurately assess and treat SP when symptoms emerge. Common treatments for SP include CBT and SSRI antidepressant medications. Treatment studies consistently show that these therapies provide significant reduction of social anxiety and improvement in functioning.

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Specific Phobias

Thomas H. Ollendick, Maria J.W. Cowart, and Ella L. Milliner

Abstract Specific phobias are highly prevalent, affecting 5–10 % of children and adolescents in community samples and 15 % in mental health settings. Phobic youth experience significant interference and distress in their day-to-day lives and are at an increased risk of academic and social difficulties as well as adult psychopathology. Phobias have a complex etiology, developing from a multiplicity of factors including genetics, learning history, parenting, and evolutionary preparedness. This chapter reviews empirically supported assessment and treatment interventions for phobic youth. Strong empirical support currently exists for cognitive and behavioral treatments. In particular, the chapter focuses on the one-session treatment (OST) approach, which incorporates cognitive behavioral techniques into an intensive (3-h) treatment package. OST is a cost-effective and rapid treatment for phobic youth, with four randomized trials in four different countries now supporting its use. A case report illustrating the implementation of this treatment is presented.

Keywords Specific phobia • Clinical phenomenology • Etiology • Assessment • Behavioral approach task • Treatment • One-session treatment

Case Scenario

Andrew, an 8-year-old Caucasian boy, lived with his mother and 5-year-old sister. Andrew's parents had separated when he was 4 years of age. He and his sister had minimal contact with their father who had moved to another state. Andrew was referred to our clinic for a phobia of being in the dark alone that interfered with his own and their family's lives.

Andrew's mother stated that he slept in her room every night. She permitted co-sleeping to ensure that Andrew got a good night's sleep before attending school. On weekends, he slept in a room that he shared with his sister. However, he would insist on having the television on and a night and hall light illuminated. If disturbed during the night, Andrew called out to his mother until she awoke and

T.H. Ollendick (✉) • M.J.W. Cowart
Virginia Tech, Child Study Center, Blacksburg, VA 24060, USA
e-mail: tho@vt.edu

E.L. Milliner
Griffith University, Room 3.15, Business 1 Building (G01), Parklands Drive, Southport, Gold Coast, QLD 4222, Australia

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responded. Andrew also avoided entering dark rooms in the family house. He refused to go into the basement and, if asked to bring his mother something from upstairs at night, he would become highly distressed and ask his sister to go for him. When arriving home in the car at night when it was dark, Andrew waited for his mother to enter the house and turn on the lights and then he would sprint inside. During a recent power outage, Andrew was crying, shaking, and clinging to his mother. Andrew has never been able to sleep over at friends' houses because of his fear. He was able to go trick-or-treating and to the movie theater in the dark; however, during these times he stayed close to his mother. Andrew's mother stated that she had not previously sought assistance for Andrew's fear because she initially believed Andrew would "grow out of it" and that his fear was "just a phase." However, as time progressed and Andrew's fear worsened, she decided they needed assistance.

Description of the Disorder

Fear is a normal part of child development [1, 2]. The content of childhood fears follows a predictable course that is associated with increasing cognitive development, progressing from concrete fears (e.g., fears of strangers and animals) in infancy and toddlerhood to increasingly abstract fears in childhood (e.g., ghosts and the supernatural) and into adolescence (e.g., social fears, agoraphobia; see [3–5]). Specific fears become less common over the course of childhood, peaking in early childhood between the ages of 7–9 years and declining in children 10 years and older [4]. As a result of this trend, parents and health professionals often attribute children's fears to being "just a phase" and expect them to diminish over time [5]. However, in a subset of children, these transient or "normal fears" become more frequent, intense, and durable and eventually evolve into a phobia [2].

The Diagnostic and Statistical Manual of Mental disorders [6] delineates the following criteria for a child's fear to be classified as a specific phobia: the fear must be intense, enduring, and cued by the presence or anticipation of a specific object or situation (Criterion A); exposure to the phobic stimulus must trigger an immediate anxiety response or panic attack (Criterion B); the person must realize their fear is excessive and unreasonable (however this criteria is not necessary in children) (Criterion C); the child must attempt to avoid the phobic stimulus or, if such is not possible, to endure it with distress (Criterion D); avoidance of the phobic stimulus must interfere significantly with the child's academic, social, and family functioning (Criterion E); in youth the fear must be present for at least 6 months (Criterion F); and the fear cannot be better accounted for by another mental disorder (Criterion G) [6]. The DSM-IV-TR criteria take into consideration the tenets of developmental psychopathology [5, 7]. A child must experience their fear for a long enough time period (6 months) to suggest that it is not developmentally appropriate or "just a phase." Moreover, unlike adults, children are not required to recognize that their fear is excessive or unreasonable.

According to Lang's tripartite model [8–10], fear and the phobic response are comprised of a neural network of three components: cognition, physiology, and behavior. When exposed to a fearful object or situation, a child may think catastrophic thoughts (cognitive component) and experience an activation of their autonomic nervous system, including an increased heart and/or breathing rate, sweating and shaking (physiological component), and engagement in avoidance behavior such as running away, having a tantrum, crying, freezing up, or clinging to their caregiver (behavioral component) [11]. These components are considered concordant if they covary together and discordant if they vary independently of one another. Concordance is thought to be associated with greater levels of fear [12]. In a recent study, Ollendick, Allen, Benoit, and Cowart [13] investigated concordance and discordance in a group of 73 phobic youth who completed phobia-specific behavioral tasks. The results showed that overall when confronted with their feared object/situation, most phobic youth tended to

show concordant responding; however, significant intersubject variability was observed. Specifically, a minority of youth were characterized as responding predominantly along one dimension and not the others. For example, primarily physiological responders exhibited increased physiological arousal (e.g., increased heart and/or breathing rate, sweating and shaking) in the absence of negative cognitions or behavioral avoidance. The significance of concordance versus discordance is not fully understood at this time.

Prevalence and Course

Specific phobia is one of the most common psychological disorders, affecting approximately 5–10 % of children and adolescents in community samples and 15 % in mental health settings [14–16]. Specific phobias are classified into five major types: animal (e.g., dogs, insects, snakes), natural environment (e.g., thunderstorms, heights, darkness), situational (e.g., elevators, flying), blood-injection-injury (e.g., seeing blood, injections), and others (e.g., loud noises, costume characters) [6]. Among the phobia subtypes, animal and natural environment are the most frequently observed in children [17–19]. The average age of onset for specific phobias is 9–10 years of age [3, 20]. However, similar to the pattern observed with normative fears, the onset of specific phobia subtypes follows a developmental progression with animal phobias emerging at about 7 years of age, followed by blood-injection-injury phobias at 9 years, situational fears at approximately 13 years of age, and claustrophobia at 20 years of age [21]. Phobic youth frequently experience increased risk of academic difficulty [22–24] as well as social and personal distress [25–27]. Furthermore, if left untreated, phobias can persist into adolescence and adulthood [2] and contribute to the development of other psychiatric disorders including adult anxiety, depression, and substance use [28].

Comorbidity

Comorbidity (i.e., co-occurrence of other disorders) is the rule rather than the exception in children and adolescents with specific phobia. Community and clinical studies suggest that 25–72 % of phobic youth meet criteria for at least one comorbid psychiatric diagnosis [17, 19, 25, 29, 30]. Specific phobias are most commonly comorbid with other anxiety disorders including generalized anxiety disorder (GAD), social anxiety disorder, separation anxiety disorder, and obsessive-compulsive disorder. Prevalence rates suggest that 50 % of phobic youth also meet criteria for more than one phobia [29]. Comorbidity between specific phobia and mood or externalizing disorders is also observed [17]. Current research suggests that the presence of comorbidity does not negatively affect phobic treatment outcome. Moreover, Ollendick and colleagues [30] found that successful treatment of specific phobias resulted in reductions in the clinical severity of other comorbid anxiety disorders.

Etiology

Childhood phobias have a complex and multifactorial etiology [7] Several pathways, including genetic influences, learning experiences, as well as parenting and evolutionary preparedness are thought to be involved in the development of a specific phobia [11].

Genetics

Family and twin studies indicate that specific phobia is a familial disorder [31]. Research suggests that phobias "breed true" in that the offspring of phobic individuals are more likely to develop the same type of phobia as their parent. In a recent literature review, LeBeau and colleagues [32] found evidence of familial aggregation, with children of phobic individuals at increased risk only for the phobia exhibited by their parent. Conversely, some studies suggest a common genetic vulnerability for animal, natural environment, and situational types of phobia and a separate and distinct genetic risk for blood-injection-injury phobia [33]. Additional research indicates that there is a general genetic vulnerability that makes individuals susceptible to a range of anxiety disorders and that other factors determine the specific anxiety presentation [34]. Hence, genetics appear to play an important role in the etiology of phobias. However, at this time, there is insufficient information to determine its exact role.

Learning

Rachman [35, 36] proposed that phobias are acquired through three learning pathways: direct/classical conditioning, vicarious conditioning (modeling), and the transmission of negative information. Phobia acquisition, as a result of direct conditioning, must involve a direct negative experience with the phobic object/situation. For example, a child that is bitten by a dog and then develops a dog phobia is said to have acquired their phobia through direct conditioning. Second, children may acquire their phobia vicariously through modeling and the observation of others' anxious behavior towards the phobic object/situation. An example of this type of learning would include a child who develops a phobia of spiders after observing his/her mother or father behave in a fearful manner around spiders. The third pathway proposed by Rachman is that a child may acquire a phobia through hearing negative information about the phobic object. For example, a child may develop a phobia of storms after watching a news story about someone being struck by lightning or a town affected by a tornado or hurricane. Multiple learning pathways may be simultaneously involved in the acquisition of a child's phobia [37, 38].

Parenting

Parenting factors are also thought to play a role in the development of child phobias. Research suggests that the parents of anxious children have a more "intrusive" and "overprotective" parenting style [39–43]. Such parents are more likely to intervene and attempt to protect their child from negative emotional experiences [44]. In interaction studies where parent and child dyads are observed in ambiguous or stressful situations, parents of anxious children are more likely to intrude on their children in an attempt to protect them from potential upset or harm [39, 41]. In relation to phobias, parents may accommodate and reinforce their child's avoidance of the phobic object/situation in order to prevent them from having a negative experience [11]. For example, a parent may allow (or even invite) their child to sleep in their bed if the child fears the dark or may avoid going to football games because their child is afraid of costumed characters and becomes upset when they see team mascots. These patterns prevent children from gaining positive information about their phobic object, which could challenge their fear-related beliefs [11]. Hence, in these instances, the child does not have the opportunity to learn that the fearful events they anticipate in fact do not occur.

Nonassociative

The aforementioned etiological pathways may not account for all causes of specific phobia. According to the nonassociative model of fear acquisition, some fears (e.g., waters, heights, snakes) may be biologically prepared through evolution [45–47]. That is, at some point in time, these fears were evolutionarily adaptive and necessary for survival and then were passed on to us from our ancestors and therefore may not require critical learning experiences. This may account for fears and phobias that parents report have "always" been present in their child. In particular, studies of water-phobic children have predominantly found a nonassociative onset, with few children experiencing a direct or indirect conditioning event [45, 48]. In comparison to other studies investigating fear acquisition in animal-phobic children [37, 49, 50], it appears that water-phobic children do not require a negative learning experience. However, further research is still necessary to determine whether water phobias are a "special case" in terms of their etiological pathway [37].

Assessment

Given the complex clinical presentation (e.g., etiology, phenomenology, and comorbidity) of specific phobia, a thorough, evidence-based assessment is critical to the effective provision of treatment. A comprehensive assessment should ideally be multi-method (e.g., clinical interview, questionnaires, observation) and multi-informant (e.g., child, parent, teacher) to gain an accurate diagnostic picture of the child across contexts and settings [51–53]. To develop a complete understanding of the child's phobia, it is also necessary to investigate all aspects of the phobic response (cognition, psychophysiology, and behavior). As discussed previously, specific phobias are frequently comorbid. Accordingly, a broad assessment of psychopathology is required to identify comorbid conditions and assist in differential diagnosis (e.g., separation anxiety versus phobia of the dark). It is also important for clinicians to consider the developmental trajectory of fears and consider what is normative for the child's developmental level [11]. A variety of tools are recommended for the assessment of phobias, including diagnostic interviews, questionnaires, and observational methods. A more thorough description of broad based measures of anxiety is presented in Chap. 12. This chapter will focus on phobic specific measures for children.

The Fear Survey Schedule for Children-Revised (FSSC-R; [54]) is considered the gold standard specific phobia questionnaire. It assesses overall fearfulness and yields information about a range of specific phobias and social phobia. The measure requires youth to rate their level of fear of 80 specific objects and situations. Higher scores indicate greater overall fearfulness and suggest the presence of a specific phobia. The FSSC-R consists of five factors including fear of danger and death, fear of failure and criticism, fear of the unknown, fear of small animals, and medical fears. Examination of specific phobia items can be helpful in identifying the presence and severity of a phobia. The FSSC-R has well-established reliability and validity and provides norms for boys and girls of various ages and nationalities. Additionally, it has been translated into several languages [55].

Questionnaires designed for the assessment of individual types of phobia are also available, such as the Spider Phobia Questionnaire for Children. This questionnaire consists of 29 items and provides the clinician with an overall spider fear score (SPQ-C; [56]).

Behavioral approach tests (BATs) are an integral part of any phobia assessment as they allow the clinician to observe the child's phobic behaviors directly. The BAT is a controlled and standardized test in which individuals are asked to approach a phobic object or stimuli so that their avoidance behavior can be objectively observed [2]. For example, a child who is afraid of costumed characters

may be brought to a door and informed that inside is a costumed character (e.g., a clown) sitting on a chair. The child is then instructed to enter the room, shake hands with the costumed character, and interact with it for a few minutes. Additionally, the child is told that he/she only needs to complete as much of the task as he/she feels comfortable with and can stop at any time. The degree to which the child complies or avoids the therapist's instructions provides an objective measurement of phobic avoidance [2]. Periodically throughout the BAT, the clinician may ask the child to rate his/her level of fear on a 0 (not at all) to 8 (very high) scale. Physiological data, such as heart rate and heart rate variability, may also be collected. This enables the clinician to assess all three components of the child's phobic response (cognition, physiology, and behavior) [11]. The BAT allows the clinician to observe the child's avoidance behavior directly in the presence of the phobic object or situation and confirms information obtained from diagnostic interviews and questionnaires.

While behavioral approach tasks are sometimes challenging to arrange (e.g., retrieving, storing, and caring for stimuli or scheduling offsite visits), especially for private practitioners with limited resources, assistance, and space, the incorporation of BATs into the assessment process is strongly recommended [51]. The BAT is an essential tool in treatment planning. It provides a foundation on which to build a graduated exposure hierarchy for use in treatment [11]. The child's behavior during the BAT gives an indication of a possible starting point for treatment and the child's ability to interact with the phobic object or stimuli. Additionally, the BAT may provide insight into the child's motivation to face their fear and their willingness to engage in therapy [11]. A standardized BAT format can be developed and adjusted for a range of possible phobia types. BAT performance is measured by the percentage of steps completed by the child [e.g., open the door (step 1), stays arm's length from costumed character for 10 s with no attempt to shake hands (step 4)], and his/her fear ratings [2].

To investigate the cognitive component of the child's phobic response further, the clinician may choose to interview the child to elicit their catastrophic beliefs about the phobic object or situation (e.g., "The needle will touch my bone," or "the dog will bite me," or "a bat will fly out of the dark and attack me"). To gain a more objective measure of the child's phobic beliefs, the child can be asked to rate on a 9-point scale (0–8) how likely the belief is to occur (probability), how bad it would be if it actually occurred (danger), and how sure the they are that they could cope with the event were it to occur (self-efficacy). This can be carried out for the child's most severe phobic beliefs and be reevaluated during and following the completion of treatment.

Andrew and his mother were interviewed using the Anxiety Disorders Interview Schedule for DSM-IV Child/Parent version (ADIS-IV-C/P; [57]*) during their initial appointment at our clinic. Based on Andrew's report and that of his mother during the interview, Andrew was diagnosed with a specific phobia of the dark (Clinician Severity Rating = 7) and GAD (Clinician Severity Rating = 4). Following the interviews, a BAT was administered during which Andrew was asked to enter a dark room by himself and sit in a chair with the door closed for 5 min. Andrew refused to enter the room and reported his subjective anxiety to be at a 7 (on a scale ranging from 0 to 8).*

Treatment

Behavioral therapy and cognitive behavioral therapy (CBT) have received strong empirical support in the treatment of childhood phobias [5, 52]. CBT uses a combination of behavioral techniques to address behavioral avoidance and physiology associated with anxious behaviors and cognitive techniques to address catastrophic cognitions, attentional biases, and cognitive distortions [58–61]. For specific phobias, CBT involves graduated exposure, reinforcement, participant modeling, psychoeducation about the feared object or situation, behavioral skills to assist with interacting with the feared object, and cognitive techniques such as skills to identify and challenge cognitive biases and distortions. Exposure-based therapies have been found to be particularly efficacious [62]. Specifically, techniques

such as systematic desensitization, reinforced practice or contingency management, and modeling and participant modeling have all been shown to be effective with these youth [52]. There is limited evidence to support the use of psychopharmacological intervention in phobic youth [63]. Behavioral techniques will be discussed below followed by a description of a one-session CBT session that utilizes these methods. Additionally, psychopharmacological interventions will be explored.

Behavioral Techniques

Systematic Desensitization

One of the earliest and most influential treatments for specific phobia in children is systematic desensitization [51, 64, 65], a form of "counterconditioning," which is the opposite of classical conditioning. This approach, developed by Wolpe [66], is purported to work through the process of reciprocal inhibition, which is based on the notion that an individual cannot experience two incompatible emotions (e.g., fear and relaxation) simultaneously. Systematic desensitization involves exposing the patient to a feared object or situation, while an emotion other than fear (e.g., relaxation) is experienced [51]. Treatment typically consists of training in progressive muscle relaxation and the development of a graduated fear hierarchy. The latter involves creating a list of different situations that trigger fear, followed by rating each fear on a scale of 0–8. Systematic desensitization involves having the child utilize progressive muscle relaxation before they are exposed to low-level exposure tasks. Hence, the child experiences minimal levels of anxiety in the presence of the phobic object or situation. Stronger versions of the phobic stimulus are gradually introduced with dissipation of anxiety at each stage through relaxation techniques. In theory, the association between the phobic object and the child's fear response should be weakened when the child does not feel excessively afraid during exposure tasks [60, 64]. Due to the physical and cognitive demands of systematic desensitization, it has been used less frequently with young children [11, 52]. Systematic desensitization (imaginal and in vivo) has been found to be superior to no treatment [67–72] for childhood fears and phobia. Additionally, imaginal systematic desensitization has been found to be superior to relaxation training [68], however inferior to modeling [70].

The theory and procedures underlying systematic desensitization have been increasingly scrutinized in recent years [5]. Research into extinction of fear associations has resulted in an understanding of exposure as creating a new positive learning experience as opposed to Wolpe's [66] hypothesis of "counterconditioning" or unlearning of the fear response [51, 73]. Additionally, systematic desensitization has not been shown to consistently affect a child's physiological responses to fear. This finding opposes the notion that the clinician is conditioning a different, competing physiological response (e.g., relaxation) [60]. Enthusiasm for systematic desensitization research has therefore waned over the past several decades, and the field has moved towards in vivo exposure with fewer distractions (e.g., relaxation and diaphragmatic breathing) [60]. Based on early investigations, systematic desensitization has enough research support to warrant *probably efficacious* empirical status for alleviating fears; however, large-scale randomized controlled trials with carefully diagnosed youth have not been carried out. Hence, this approach is still considered experimental for the treatment of childhood phobias [11, 51].

Reinforced Practice

Reinforced practice (also referred to as contingency management) is another behavioral approach used to treat childhood-specific phobia. Reinforced practice has received considerable research support

and as such is considered an evidence-based treatment for childhood fears [60]. Based on operant conditioning principles, reinforced practice involves reinforcing successive steps towards the feared object or situation, thus stopping avoidance behavior [60, 65]. Similar to systematic desensitization, reinforced practice requires the development of a fear hierarchy with the child. However, reinforced practice does not include the use of a competing response, e.g., relaxation [11]. The goal of reinforced practice is to alter avoidance behavior through the manipulation of the consequences of the behavior. The clinician works with the child to develop a list of desirable reinforcers (e.g., social praise, stickers, and food items). Following this, the clinician gives the child the discussed reinforcers contingent upon the completion of increasingly difficult steps on the fear hierarchy. Using this technique, behavior can be shaped and changed over time, with reinforcers decreased and eventually faded out [60]. Reinforced practice has been found to be more effective than no treatment [74, 75], verbal coping [76], and modeling [77] and equivalent to CBT [18] for the treatment of childhood fears and phobia.

Reinforced practice and systematic desensitization have often been confused in the literature, and their distinction is of theoretical and practical importance. The critical issue is when a competing response (as in systematic desensitization) or reinforcer (as in reinforced practice) is delivered. In systematic desensitization, a competing response is initiated *before* the fear occurs in an attempt to prevent the fear response from occurring [5]. Conversely, in reinforced practice, the reinforcer is given as soon as possible *after* the approach behavior and coincident fear response occurs. Thus, the goal of reinforced practice is for the child to experience a manageable amount of fear and for extinction of the avoidance behavior to occur by strengthening positive associations with the phobic stimulus through reinforcement of approach behaviors [51].

Modeling and Participant Modeling

Modeling is based on social learning theory [78] and involves the therapist (e.g., model) demonstrating how to approach and appropriately interact with the phobic object or situation [60]. Observing another person interact successfully with the feared stimulus is thought to weaken the association between the object and experience of fear in the observer, as new learning competes with his/her fear [5]. Participant modeling expands upon modeling by encouraging the observer to interact with the model and the feared object or situation [5]. Phobic children are encouraged to interact with the therapist and phobic stimuli using a number of techniques, ranging from simple verbal instructions to physical contact such as hand-over-hand assistance [51, 64]. For example, when treating a dog-phobic child, participant modeling may progress as follows: (1) the therapist models patting the dog, (2) the child is instructed to place their hand on the therapist's shoulder, and (3) the child is gradually encouraged to move their hand down the therapist's arm and finally, (4) the therapist uses hand-over-hand assistance to assist the child to pat the dog. The goal of participant modeling is to gradually phase out the therapist's instruction and physical contact and for the child to be able to engage independently in steps from his/her fear hierarchy.

Participant modeling is a well-established treatment for childhood fears [60]. It has been found to be superior to no treatment [79, 80], live [81], and filmed modeling [82, 83] and also to systematic desensitization [82]. The benefits of participant modeling include skill building (e.g., learning how to safely approach and pet a dog) and breaking down exposure tasks into smaller, more manageable, steps (e.g., patting a dog versus watching someone pat a dog followed by moving their hand slowly down the therapist's arm while they pat the dog). Often participant modeling has been misconstrued as only usable with animal phobias [84, 85]. However, in actuality, participant modeling can be used with multiple phobia types, such as natural environment, blood-injury-injection, and costumed characters. For example, the therapist may model having their blood pressure taken (e.g., blood-injury-injection phobia), followed by the child having their blood pressure taken with the therapist placing their hand under the blood pressure cuff.

One-Session Treatment

More recently, cognitive behavioral procedures have been incorporated into an intensive one-session treatment (OST) package in the treatment of specific phobia in children and adults [86]. OST involves a single, 3-h session of massed exposure that includes aspects of psychoeducation, skills training, cognitive restructuring, graduated in vivo exposure, reinforced practice, and participant modeling.

The single session is preceded by a 45-min functional assessment session, during which the therapist meets with the child and his/her parent(s) to elicit the child's phobic cognitions (e.g., phobic beliefs assessment, refer above), develop a graduated exposure hierarchy, and give information about the OST session [11, 84]. The therapist explains to the family the rationale for treatment. The child is encouraged to think of himself or herself as a "scientist" or "detective" who will be testing out their cognitions through a series of behavioral "experiments" (e.g., exposure tasks; [11, 51, 84]). Children are advised that treatment will proceed at their pace and that nothing will be done without their permission. They are also informed that the goal of the session is not to shock or surprise them, rather for the clinician and child to work as a team to face the child's fear gradually. The clinician explains that the child will need to experience some fear during the session to overcome his/her fear, however this will be a manageable amount of fear and that if he/she remains in the situation, without avoiding, his/her fear will subside or considerably reduce [84]. In addition to providing important details about the child's fear, the functional assessment session gives the therapist an opportunity to build rapport with the child and increase his/her motivation for treatment. It is ideally carried out 1 week prior to the OST to allow time to use the information gathered to prepare for the exposure session.

OST sessions may vary considerably from child to child, even when the same type of phobia is treated [51]. This is because the therapist works at the child's pace and adjusts his/her approach based on the child's response (e.g., fear levels and behavior) to various exposure activities. Consequently, there is no standard format for structuring an OST session [64]. Ideally, at least three phobic objects/situations (approximately one per hour) are introduced during the session. In order to engage the child and increase his/her motivation, exposure activities should be as fun and engaging as possible. For example, when treating a child with a blood-injury-injection phobia, the therapist and child could pretend to be doctors, dressing up in scrubs and treating fake wounds on each other. Throughout the session, the therapist should frequently praise the child for engaging in exposure tasks and reinforce approach behaviors to make the experience more positive for the child [11].

Throughout treatment, behavioral experiments are completed. While there is some variation, behavioral experiments typically proceed as follows: (1) the therapist and/or child suggests and discusses a possible exposure task, (2) the therapist models the proposed experiment, (3) the child attempts the modeled task (with the assistance of the therapist if necessary), and (4) success or failure is discussed [51, 84]. After agreeing about a behavioral experiment, the cognitions identified during the functional assessment are used to prompt the child as to what they believe will happen during the experiment (e.g., "Do you think the dog will bite you if you pat him on the head?"). Following the experiment, the child and the clinician review what actually happened and discuss whether the child's cognition came true [51]. While carrying out the behavioral experiments, the therapist provides the child with psychoeducation about the phobic object, highlighting positive information (e.g., snakes help control mice and rat populations) and training in how to successfully interact with the phobic object (e.g., how to read a dog's body language to determine if it is friendly; [11]). To assist in generalization, exposure tasks should be repeated and, if possible, across multiple contexts (e.g., interact with a dog in a therapy room, a backyard, and an open unfenced park). At the conclusion of the session, the child and his/her family should be reminded to schedule regular practice exposure tasks to further progress and prevent relapse.

OST is considered an evidence-based treatment for childhood-specific phobia [51]. The efficacy of OST has been supported by two large randomized controlled trials (RCTs, [87, 88]) and two smaller clinical trials [89, 90]. In the first of the large randomized controlled trials, Öst and colleagues [88]

in Sweden compared OST alone, with OST with a parent present and a waitlist-control condition. In the parent's present condition, the parent acted as source of support for the child and if necessary was called upon by the therapist during the session to be either a model for the child or to comfort them in times of high anxiety. Sixty children and adolescents (7–17 years) with a diagnosis of a specific phobia participated in the study. Both OST conditions were found to be superior to the waitlist-control condition on the primary outcome measures of subjective distress, behavioral avoidance, and independent assessor ratings of the severity of phobias at posttreatment. Treatment gains in both OST groups were maintained at 1-year follow-up. In a subsequent large-scale randomized control trial, Ollendick et al. [87] evaluated the efficacy of OST (alone without parent present) to an education support treatment and a waitlist-control condition. One hundred and ninety-six children and adolescents (7–16 years) with various specific phobias participated in the study. Participants were recruited from Sweden and the USA. OST and the education support treatment were found to be superior to the waitlist-control condition. Moreover, OST was found to be superior to the education support treatment on clinician ratings of phobic severity, percentage of participants diagnosis-free (55 % OST versus 23 % EST) at posttreatment, child ratings of anxiety during the behavioral avoidance test, and treatment satisfaction as reported by youth and their parents. Treatment gains were maintained at 6 months follow-up.

OST has been shown to be effective for approximately 50–60 % of children [87]; hence a number of children continue to experience clinically significant levels of fear following treatment. Given that research suggests that parents may inadvertently reinforce and maintain their children's fears [39], treatment that includes a parent component may lead to enhanced outcomes [91, 92]. Ollendick and colleagues are currently evaluating a parent-augmented OST, in which standard OST is supplemented with parent training [11]. Parents are given the opportunity to observe their child's treatment to learn strategies to engage their child in exposure activities at home. Moreover, parents are invited to join the last half hour of the OST session and are assisted in leading an exposure activity with their child. Hence, control over exposure activities is gradually transferred from therapist to parent. Additionally, parents receive psychoeducation regarding fear and anxiety and are trained in the use of a contingency management program. Parents are then encouraged to implement a program at home that rewards their child for engaging in exposure tasks. The approach appears promising.

Pharmacological Treatments

There is limited support for the use of psychopharmalogical approaches as stand-alone treatments for specific phobia. Currently, in the child and adult literature, only a few case reports and small controlled trials exist [93–95]. A 9-week open label trial of fluoxetine (mean dose: 24 mg children and 80 mg adolescents) showed that four of the six participants with specific phobia responded to treatment [95]. Many phobic children and adolescents have comorbid anxiety disorders. Pharmacological and cognitive behavioral treatments are therefore frequently used to treat these comorbid anxiety disorders [63, 96]. Selective serotonin reuptake inhibitors (SSRIs) have previously been proven to be effective in pediatric generalized anxiety disorder, social phobia, separation anxiety disorder, and obsessive-compulsive disorder [63, 96–98]. Based on this literature, SSRIs may be beneficial in the treatment refractory phobic youth [5].

There is a growing body of research examining the augmentation of exposure therapy for specific phobia with the cognitive enhancing drug D-cycloserine (DCS). DCS is hypothesized to have an effect on the formation and consolidation of fear and learning extinction. DCS may strengthen extinction memories, thus making them easier to recall when exposed to the phobic object or situation in future (see [99] for review; [11]). DCS has been proven to be effective with adults with specific phobia of

heights [100], but not effective in the treatment of subclinical spider phobia in adults [101]. Studies evaluating the effectiveness of OST treatment augmented with DCS in pediatric samples are currently underway. DCS augmentation of exposure therapy is a promising development in the treatment of child- and adolescent-specific phobia. However, at this time it is considered experimental and future research is needed to determine whether these approaches are as efficacious with children as they have been with adults.

Case Follow-Up

Functional assessments were conducted with Andrew and his mother (separately) to establish (1) the antecedents and consequences of Andrew's avoidant behavior, (2) his faulty cognitions about being in the dark alone, and (3) an avoidance hierarchy of his fears. Andrew reported that he was scared of the dark because of a "scary movie" he had seen. He was afraid the characters from the movie would appear when he was in the dark. He reported that the sounds he heard at night and the shadows he saw frightened him because he believed it could be one of the movie characters walking around or hiding in the house. He stated that the worst thing that could happen to him when he was in the dark would be someone breaking into the house. While Andrew met with the child therapist, his mother simultaneously met with the parent therapist. In addition to completing a functional assessment of Andrew's phobia, the parent therapist provided Andrew's mother with psychoeducation about the cycle of fear/anxiety and about the factors that maintain these symptoms in children. At the conclusion of the functional assessments, Andrew and his mother were brought together and the treatment rationale for OST was explained. The treatment was scheduled for 1 week later.

The first hour of treatment was carried out at our clinic. The family's appointment was scheduled at nighttime to allow for maximum opportunity for exposure to the dark and elicitation of Andrew's fear. Initially, the child therapist provided Andrew with psychoeducation about the dark (e.g., why it becomes dark at night, why we hear strange noises at night, how our vision changes in the dark, and education about nocturnal animals). Following this, the lights in the room were turned off and Andrew and the therapist played games with glow-in-the-dark toys, such as glow sticks. For example, Andrew and the therapist took turns hiding glow sticks for the other to find. The therapist gradually increased the number of rooms they could hide glow sticks in as well as reducing the number of glow sticks used in the game so that there was less light. At the end of the first hour, Andrew was able to wait alone in the "base room" by himself in the dark with the door closed for up to 5 min. Throughout the first and subsequent 2 h of treatment, the child therapist provided Andrew with profuse praise for facing and coping with his fears. A playful, supportive, and trusting relationship was developed.

The second and third hours of treatment were conducted outside of the clinic in an old two-story house that had been converted into offices in order to expose Andrew to a more realistic "in vivo" home situation in the hope that this would result in greater generalization of his treatment gains. Andrew and the therapist first sat quietly in one of the dark rooms focusing on the sights and sounds they could see and hear. Following this, Andrew stayed in the room alone for 2 min. When the therapist returned, Andrew appeared upset and reported that he had seen a shadow that looked like someone walking by. The therapist helped Andrew challenge and disconfirm his catastrophic cognition by investigating and discovering that the trees moving outside had made the shadow. This exposure task was then repeated three more times to ensure that Andrew sufficiently habituated to his anxiety. Following this, Andrew and the therapist played hide-and-seek across both levels of the two-story house. Andrew's mother and the parent therapist observed the session from an observation room. Throughout the course of the 3 h, the parent therapist pointed out the child therapist's use of instruction, modeling, reinforcement, and cognitive challenges to help Andrew to face his fear. Andrew's mother

was educated regarding contingency management strategies and generating an exposure hierarchy to practice with Andrew following the completion of the treatment.

At the commencement of the third hour, the therapist had Andrew lie down on a couch, pretend he was in bed, and focus on his scary thoughts while she left the room. Afterwards he reported that he had thought about the "scary" movie characters. The therapist pointed out that, although he had scary thoughts, nothing bad had happened and that he was able to cope. This task was then repeated three times. During the last half hour of the session, Andrew's mother joined them, and she and Andrew hid glow sticks in the woods outside their house and took turns finding them. This provided the mother an opportunity to practice exposure activities with Andrew and to foster a transfer of control from the child therapist to her. Andrew and his mother were reminded that this was only the beginning of Andrew's treatment, and for the treatment to work fully it would be important for them to continue exposure activities outside of therapy for at least the next month to solidify the gains that had been made.

Upon post-testing 1 week later, Andrew's fear had reduced considerably from his pretreatment levels. However, his phobia of the dark was still clinically significant, as evidenced by his Clinician Severity Rating of 5 on the ADIS-IV C/P and his inability to sit in a dark room at the clinic for a full 5 min alone (a BAT identical to that used at pretreatment). Andrew and his mother were encouraged to continue practicing exposure tasks outside of treatment for the next month. One month later, Andrew was reevaluated. His mother reported that they had been practicing on a regular basis. She stated that Andrew could now go outside at nighttime to say goodnight to his rabbits (who were kept outside), bring things in from the car at night, and go into the basement and play with glow sticks and shadow puppets in the dark. Additionally, Andrew had transitioned from sleeping in his mother's bed to lying in his own bed for 15 min before going to his mother's room, and then sleeping in his own room with his sister present and the nightlights on, and finally to sleeping in his room alone with minimal nightlights on. Andrew's ADIS-IV C/P rating for a specific phobia of the dark was a 3 (subclinical level) and for GAD, a 2. During the BAT at follow-up, Andrew was able to stay alone in the dark room for a full 5 min. At the 6 months follow-up, Andrew continued to have little or no fear about being in the dark alone. He was able to sleep alone in his room in the dark without any nightlights. He was also able to attend sleepovers with friends. Furthermore, his mother reported that she felt more confident in managing Andrew's anxious behavior.

Summary

Transient fears are a normative part of childhood development. However, for some children fears persist and increase in frequency, intensity, and duration, eventually becoming a phobia [2]. Specific phobia is one of the most common psychological disorders in children and adolescents. Phobias often cause significant interference and distress and place youth at risk of academic and social difficulties, as well as adult psychopathology. Specific phobias have multi-determined etiologies. Genetics, learning history, modeling, parenting, and evolutionary preparedness have all been implicated in their development. Assessments should ideally be multi-method (e.g., diagnostic interviews, questionnaires, behavioral approach tasks) and multi-informant (e.g., child, parent, and teachers). The information gathered during the assessment is then used to determine the most appropriate treatment approach. Cognitive behavioral treatments, particularly exposure-based treatments including systematic desensitization, reinforcement practice, and modeling and participant modeling are considered efficacious for the treatment of childhood-specific phobias. A one-session treatment (OST) package incorporating all of these cognitive behavioral procedures is currently an evidence-based treatment for treating this condition. It is expected that a parent augmented OST will further enhance treatment outcomes for phobic youth.

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Separation Anxiety Disorder

Aleta G. Angelosante, Magdalena A. Ostrowski, and Rachel R. Chizkov

Abstract Separation anxiety disorder (SAD) is one of the most commonly diagnosed anxiety disorders among children presenting for treatment. A child with SAD experiences excessive anxiety concerning separation from home or from caregivers as well as persistent, unrealistic worry about harm to self or loved ones. Fears may manifest as an unwillingness to leave home, reluctance to be alone, physical complaints around separation, and frequent reassurance seeking regarding safety. This chapter provides a review of the current literature regarding the course and etiology of SAD, with a focus on genetic studies, environmental factors, and parenting. The link between childhood SAD, panic disorder, and other forms of psychopathology in adulthood is also considered. Assessment and treatment of SAD are discussed, with a review of the empirical evidence for the use of traditional cognitive-behavioral therapy (CBT), camp-based CBT, modified parent–child interaction therapy, and psychopharmacological treatments. Research on assessments and treatments specifically for SAD has been scarce. Given the relatively high prevalence of this disorder, and its role as a predictor of later psychopathology, further study is warranted. Future research might examine treatments designed specifically for SAD or recruit a subject pool that would allow for independent investigation of results for those with SAD within a larger heterogeneous anxiety sample. Furthermore, additional attempts to understand SAD as a risk factor may lead to prevention of adult psychopathology in these children.

Keywords Separation anxiety disorder • Children • Etiology • Course • Cognitive-behavioral therapy • Parent–child interaction therapy

Case Scenario

Melissa is a 9-year-old girl in the 4th grade whose parents brought her in for an evaluation because of her fears of being away from them. Before going to school each morning, she checks in with her mother about who is picking her up and where she should wait. Her mother reminds her that the plan

A.G. Angelosante (✉)
NYU Child Study Center, NYU Langone Medical Center, New York, NY 10016, USA
e-mail: aleta.angelosante@nyumc.org

M.A. Ostrowski
Kean University, North Avenue, Hillside, NJ 07205, USA

R.R. Chizkov
Department of Child and Adolescent Psychiatry, NYU Langone Medical Center, One Park Avenue, 7th Floor, New York, NY 10016, USA

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is always the same and that the schedule is on the refrigerator, but Melissa says she "just wants to be sure." Last week, when Melissa's mother got stuck in bad traffic on the way to pick her up and arrived 20 minutes late, she found Melissa in tears in the principal's office. When she saw her mother, Melissa hugged her tightly and said, "I thought you were dead!" Melissa has many friends, and although she will go to their homes, she much prefers to have play dates at her house. Her friends have recently begun having sleepovers for their birthday parties; Melissa will go to the party but will leave before everyone goes to bed. She tells her friends that her mom will not let her stay, but in truth, she is too nervous to sleep anywhere other than her own house. Each night, Melissa's mom reads to her and then must stay in her room until Melissa falls asleep. If Melissa wakes in the middle of the night, she will immediately go into her parents' room and either crawl into their bed or make a bed of blankets and sleep on their floor. Melissa was invited to go with her best friend to Disney World for a long weekend; although she was worried about it, she desperately wanted to go and said yes. The night before she was going to leave, she told her mother that she did not think she could go. She continued to cry all night and could not fall asleep. When her friend's family arrived to pick her up, she clung to her mother and refused to let go. The family left without Melissa, worried they would miss their flight. Melissa felt awful for having disappointed her friend and was extremely embarrassed about "acting like a baby."

Description of the Disorder

Separation anxiety is typical in infants between the ages of 8 and 14 months. Infants in this age range will often cry or become agitated when their parent or caregiver leaves. This behavior may wax and wane up until age 3 or 4 years when children are typically able to calm down shortly after the act of separation [1]. Separation anxiety becomes a disorder when the fear is excessive for the child's developmental age and begins to interfere with his/her daily functioning. The hallmark fear for children with separation anxiety disorder (SAD) is a developmentally inappropriate fear that something bad will happen to them (e.g., they will get kidnapped) or to their parents (e.g., they will get in a car accident or murdered) while they are apart. Children with SAD are often described as "clingy" and may stay extremely close to their parents even when they are nearby. For example, the child may not want to be on a separate floor of the house or even in a different room.

SAD is most often diagnosed in young children and therefore is classified within the "Disorders first recognized in infancy or childhood" section of the DSM-IV TR [2]. Diagnostic criteria for SAD state that symptoms must be present for at least 4 weeks and include the following: the child must experience excessive anxiety concerning separation from home or from caregivers; persistent, unrealistic worry about harm to self or loved ones; unwillingness to leave home, attend school, or go on outings; reluctance to be alone, especially at night; physical complaints when separation occurs or is anticipated; and frequent seeking of reassurance regarding safety of self and loved ones. Some researchers have found differences in symptom presentation across development. For example, Francis and colleagues [3] found that young children were more likely to have nightmares and bedtime separation fears, children in middle childhood were more likely to display distress when having to physically part from their parents (e.g., to attend school), and preteens and adolescents were most likely to experience significant somatic symptoms.

At the time of this writing, DSM-5 is undergoing field trials to test updates to various disorders. For SAD, the restriction of this disorder exclusively to childhood and adolescence is being lifted, and the presence of adult SAD is being recognized. Towards this end, SAD is being moved from the "Disorders first recognized in infancy or childhood" section to the "Anxiety Disorders" section. As a result, the language of the criteria is being changed throughout to more accurately describe the presentation of the disorder in both children and adults. For example, the word "child" is replaced with

"individual," reluctance to go to work is added to the criterion regarding unwillingness to leave home or attend school, and the phrase "major attachment figures" replaces "parents or caregivers" throughout, since for those with adult SAD, the anxiety is often regarding separation from spouses, partners, or children (www.dsm5.org).

Prevalence

SAD has a lifetime prevalence of 5.2 % [4] with the disorder being more common at younger ages. Peak age of onset for SAD appears to be between ages 7 and 9 [5]. Of youth who will develop SAD, 75 % will do so by age 10 and 90 % will do so by age 13 (Kessler et al., 2005) [4]. SAD prevalence appears to decline with age as findings show rates of 4.1 % in 9–10-year-old children, 1.2 % in 11-year olds, 0.6 % in 12-year olds, and progressively lower rates throughout adolescence. A study by Costello and colleagues [6] found a 3-month prevalence rate of 1 % in youth ages 9–16. SAD is also one of the most common anxiety disorders in children presenting for treatment. Last and colleagues [7] examined 73 consecutive admissions to their outpatient child anxiety-treatment clinic and found that SAD was the most common disorder, with approximately 1/3 of all children seeking treatment meeting criteria for the disorder. Reports of gender differences in SAD are mixed; several studies [7–10] found SAD to be more prevalent in girls, while others [3, 5] found no gender differences.

Course

There is significant evidence that SAD often remits in childhood or adolescence with persistent SAD being related to higher levels of comorbid externalizing behaviors. In a community sample of youth ages 8–16 followed over an average of 18 months, only 20 % of SAD cases persisted over the course of the follow-up period; at follow-up, 63 % of children diagnosed with SAD were new cases [10]. Last and colleagues [5] reevaluated a sample of anxious youth annually for 3 years and found that those diagnosed with SAD had the highest recovery rate (80 %).

Despite this high remission rate, SAD appears to be a risk factor for the development of other anxiety disorders in adolescence [11] and adulthood [12]. One study interviewed adults currently diagnosed with anxiety disorders about their history of symptoms and diagnoses; those who reported a history of SAD were more likely to have lifetime diagnoses of two or more additional disorders, including other anxiety disorders, depressive disorders, or substance use disorders. This suggests that SAD in childhood may be a vulnerability factor for the development of later psychopathology [12]. Another study examined the retrospective report of adults with panic disorder, from both referred and non-referred samples [13]. Both overanxious disorder and SAD during childhood independently predicted panic disorder in adulthood. In a follow-up study of the non-referred adults, Biederman and colleagues [14] found that SAD, along with specific phobia and social phobia, each independently predicted panic disorder.

Link Between Sad and Panic Disorder

In 1964, Donald Klein first postulated that separation anxiety in childhood was specifically linked to the development of panic disorder (with or without agoraphobia) in adulthood [15]. Since that time, many studies have examined the possibility of this link, which has resulted in mixed findings. Some studies examined retrospective reports of adults with panic disorder, while others examined

the offspring of adults with panic disorder to see if there is a high rate of SAD. Lewinsohn et al. [16] provided evidence for a specific link, using retrospective reports. It was found that children with SAD were more likely than children without SAD to develop panic disorder and depressive disorders in adulthood but were not more likely to develop other anxiety disorders. Another retrospective study found that retrospective reports of childhood SAD were associated with greater rates of adult panic disorder; however, it was also associated with nearly equal rates of adult social phobia [17]. Thus, retrospective studies have not provided unequivocal evidence as to whether the link between SAD and panic disorder is unique.

Others have looked at correlates of both SAD and panic disorder, such as ventilatory physiology. Hypersensitivity to CO_2 inhalation is a frequently observed biological correlate of panic disorder in adults [18–20]. Similarly, Pine and colleagues [21] found that children with SAD and to a lesser degree those with generalized anxiety also showed CO_2 hypersensitivity; no association was seen for social phobia. Another study examined this phenomenon by conducting a CO_2 challenge in the offspring of matched samples of parents with and without panic disorder [22]. This study found that offspring of parents with panic disorder who met criteria for SAD had a threefold increase in the rate of panic attacks in response to CO_2 challenge as compared to offspring without SAD and to children with SAD whose parents did not have panic disorder. This group of children also showed increased rates of panting during the challenge, similar to panting behaviors displayed by adults with panic disorder in other studies, suggesting that youth with SAD who display hypersensitivity to CO_2 may be at increased risk for developing panic disorder in adulthood.

Several longitudinal studies have examined the course of SAD over time, specifically investigating this hypothesized link between childhood SAD and adult panic disorder. Pine and colleagues [23] examined a large sample of youth who had undergone psychiatric interviews between the ages of 9 and 18 (Time 1). This sample was reassessed 2 years later (Time 2) and again 10 years later (Time 3). SAD at Time 1 was significantly related to "fearful spells" (which closely resemble panic attacks) at Time 3. Although Time 1 SAD was positively related to a diagnosis of panic disorder at Time 3, the relationship did not reach statistical significance. Aschenbrand and Kendall [11] conducted a follow-up study of individuals who had participated in an anxiety-treatment program as children and adolescents, on average 7.4 years previously. Given the hypothesized link between SAD and panic disorder, they examined whether those youth who presented with SAD would be more likely to meet criteria for panic disorder than those who had presented with other anxiety disorders (e.g., social phobia or overanxious disorder). Both treatment successes and treatment failures were included. While a history of SAD was predictive of later anxiety disorders, it was not specifically predictive of panic disorder.

Comorbidity

Anxiety disorders are highly comorbid with one another, and it is in fact more likely for a child to meet criteria for more than one disorder than for just a single disorder. Last and colleagues [24] found that 79 % of youth with SAD met criteria for an additional disorder; in this study, those with SAD were most likely to have a concurrent diagnosis of overanxious disorder or major depression. More recent studies of SAD have found concurrent comorbidity of 20 % with generalized anxiety disorder and depressive disorders [25]. In addition to being comorbid with other anxiety disorders, SAD is most often associated with school refusal behavior; this is understandable given that school is the one place where children are required to be that separates them from their parents. One study of children who engaged in school refusal behavior found that SAD was the most common diagnosis, occurring in 22 % of the sample [26]. As discussed previously, there is a hypothesis that SAD leads to future panic disorder; one recent study examined youth who met criteria for both SAD and panic disorder concurrently [27]. Youth with comorbid SAD and panic disorder had a later onset of SAD and a greater number of additional comorbid diagnoses than those with only SAD.

Etiology

There are many pathways towards the development of SAD. In this section, we will review the genetics and biological vulnerabilities, parenting styles, and early developmental factors that appear to be influential in the onset of SAD.

Genetic and Biological Vulnerabilities

Family studies have revealed a genetic link for SAD. Weissman and colleagues [28] found significantly higher rates of anxiety disorders, particularly SAD, in the offspring of parents with anxiety and depressive disorders. Similarly, Biederman and colleagues [29] found increased rates of SAD in the offspring of parents with major depression, panic disorder with agoraphobia, or both, when compared to normal controls. Feigon and colleagues [30] examined separation anxiety symptoms, zygosity (i.e., physical similarity standing in for DNA markers), and shared environmental factors in a sample of twin pairs and their siblings. In the complete sample, genetics accounted for nearly 50 % of the variance, while shared environment factors accounted for about 20 %. However, this relationship was moderated by sex (with genetic influences greater in girls than boys, environmental factors greater in boys than girls) and by age (with genetic influences increasing with age). While this may suggest that shared genetics is more important than shared environmental factors, they also found that twins had a greater degree of shared environment variables than non-twin siblings, complicating interpretation of these data. Cronk and colleagues [31] also examined heritability and environmental influences in SAD by assessing the zygosity and shared environmental variables in female twin pairs. Unlike Feigon [30], they used categorical diagnostic criteria, rather than dimensional separation symptoms, as their measure of SAD. They found that genetics accounted for 62 % of the variance and shared environment accounted for 20 % of the variance, when examining participants who met full diagnostic criteria for SAD. Topolski and colleagues [32] investigated both genetic and environmental influences finding that genetics only accounted for 4 % while shared environment accounted for 40 % of the variance associated with an SAD diagnosis.

As our understanding of neurobiology grows, researchers have been examining the neurobiological bases of psychopathology. One recent study examined hypothalamic–pituitary–adrenocortical (HPA) system function in youth with SAD by measuring cortisol levels over the course of an experimental manipulation; all samples were collected in the afternoon [33]. Consistent with the study hypothesis, it was found that children diagnosed with SAD had higher cortisol secretion across all study timepoints (and therefore increased HPA activity) than controls. However, an additional hypothesis that children with SAD would also show additional cortisol increase following a separation paradigm (in which the child's mother left him/her alone with an unfamiliar examiner for a few minutes) was not confirmed; a ceiling effect could account for this lack of finding.

Parenting

Multiple studies have found that parents of anxious children tend to be overprotective [34], overly intrusive [35], and less likely to grant psychological autonomy [36] when compared with parents of non-anxious children. One study, directly examining adolescents' perceptions of psychological and behavioral control found that teens who endorsed high levels of separation anxiety symptoms reported that their parents were increasingly controlling and demanding and less sensitive to their needs [37]. Of note, however, is that the reports of adolescent anxiety symptoms and of parental behaviors were

based on adolescent report and therefore subject to reporting bias. Additional studies are needed to examine whether this relationship would hold in a sample of youth *diagnosed* with SAD and with observational evidence of parental control.

As noted previously, anxious youth often have parents who are anxious themselves, and these parents appear to both model and reinforce anxious behaviors, such as avoiding stressful or potentially dangerous situations [38]. One longitudinal study examined the role of parental anxiety on the development of SAD [39]. In a study of over 900 9-year-old children in New Zealand, mothers' reports of their own fear of being alone positively predicted children's separation anxiety symptoms 2 years later.

Early Developmental Factors

Several studies have examined the putative role of early experiences and behavioral tendencies in the development of SAD. One study examined whether early stranger anxiety could differentiate youth with SAD from those without [40]. This study found that parents of children with SAD (ages 4–14) described their children as having greater stranger anxiety as toddlers than parents of youth without SAD. While these data are compelling, it should be noted that this was a retrospective report of stranger anxiety; such parental report could be biased by the child's current separation anxiety. In addition, the retrospective report was simply one dichotomous variable, asking mothers to indicate whether or not the child had experienced stranger anxiety as a toddler. Additional prospective data would be useful here, as would dimensional measures that provide greater variability. Some researchers have wondered about the role that early separation experiences may have on the development of later separation anxiety. Poulton and colleagues [39] found that, in fact, early planned separations from parents (e.g., dropping child off at day care) were actually related to fewer separation anxiety symptoms in later childhood and adolescence. While this study offered prospective data, separation anxiety was examined only at a symptom level; it is not yet clear if these planned separations could actually act as a preventative measure against the development of SAD.

Assessment

General assessment of anxiety disorders is covered elsewhere in this volume. Here we will focus only on evaluations that specifically assess for symptoms of SAD. Questionnaire measures are not sufficient for diagnosing disorders, but they can provide valuable information about specific symptoms and/or their severity. While there are currently no questionnaires that assess solely for symptoms of SAD, several child anxiety questionnaires have subscales that are designed to reveal SAD symptoms.

Multidimensional Anxiety Scale for Children

The Multidimensional Anxiety Scale for Children (MASC) is a 39-item questionnaire normed for use with children ages 7–19 [41]. Both child-report and parent-report versions are available. The MASC assesses overall anxiety as well as four empirically derived domains of common childhood anxiety, one of which is called "separation anxiety/panic." This 9-item scale measures specific fears and worries that a child with SAD or panic might have using items such as "the idea of going away to camp scares me." The MASC has demonstrated adequate test-retest reliability and differentiates children with anxiety disorders from both those without any psychiatric disorders and those with psychiatric disorders other than anxiety [42].

Screen for Child Anxiety Related Emotional Disorders

The Screen for Child Anxiety Related Emotional Disorders (SCARED) was developed by Birmaher and colleagues [43] based on DSM-IV definitions of four of the most common anxiety disorders in children and adolescents: social phobia, SAD, panic disorder, and generalized anxiety disorder. It also contains a scale that assesses for school phobia, which, while not an official DSM-IV diagnosis, is a fear that is commonly seen in children with a wide array of diagnoses. The SCARED is comprised of 41 items on a 3-point Likert scale and has identical but separate versions for child-report and parent-report (only substituting you/your child). The SCARED has good internal consistency and reliability [43] and has also been found to have good reliability and validity when used in a clinical sample [44]. Unlike the MASC which combines symptoms of SAD and panic disorder into one scale, the SCARED has a separate 8-item scale specifically assessing symptoms of SAD, including items "I follow my mother or father wherever they go," and "I don't like to be away from my family."

Spence Children's Anxiety Scale

Like the SCARED, the Spence Children's Anxiety Scale (SCAS) was developed to assess specific DSM-IV factors of anxiety [45]. The SCAS is designed for use with children ages 8–12 and uses a 4-point Likert scale. It consists of 44 items, 6 of which are filler items asking about positive attributes of the child that are not factored into the total score or subscales; these items are meant to reduce the possibility of a negative response bias. In addition to a total anxiety score, the SCAS provides several subscale scores including a 6-item separation anxiety subscale that asks questions such as "I worry about being away from my parents," or "I feel scared if I have to sleep on my own." The SCAS has demonstrated good internal consistency, retest reliability, and convergent and discriminant validity [45]. As part of the move towards dimensional rather than categorical definitions of disorder in the new DSM-5, a 10-item scale from the SCAS has been developed that focuses specifically on SAD and is applicable across the life span. This measure is being assessed as part of the field trials and may be included in the DSM as a way of noting SAD severity.

Separation Anxiety Inventory

The Separation Anxiety Inventory (SAI) is a 12-item, 5-point Likert scale measure of separation anxiety symptoms in children that can be completed by the parent or the child (cf. [46]). Currently, it is not routinely available as it was developed as part of an unpublished thesis and appears to only be used by the research group that developed it. It demonstrated good reliability in one study [46], but more research is needed to determine if this will begin to fill the void of SAD measures.

Treatment

Many types of interventions are available for the treatment of SAD. Here, we will describe empirically supported treatments for SAD including traditional cognitive-behavioral approaches, novel behavioral approaches, and psychopharmacology.

Cognitive-Behavioral Approaches

In reviewing the literature, empirical evidence for treatment approaches for children with SAD is largely taken from trials conducted with groups of children with heterogeneous anxiety diagnoses. Randomized controlled studies of anxiety treatment in youth have primarily focused on a cognitive-behavioral therapy (CBT) approach. Psychoeducation, cognitive restructuring, exposure, modeling, relaxation strategies, and homework assignments are components of the CBT protocols for anxious youth. Recently, Silverman et al. [47] used the criteria of Chambless et al. [48] and Chambless and Hollon [49] to evaluate the evidence for various treatment approaches. According to these criteria, individual cognitive-behavior therapy (ICBT) and group cognitive-behavior therapy (GCBT) were classified as *probably efficacious* treatment approaches for children with anxiety disorders, including but not specific to SAD. Additional studies of CBT with various family components (FCBT) were assessed for which the evidence was found to be mixed. As children diagnosed with SAD were included in a majority of CBT trials [50–63], results provide evidence for the efficacy of these approaches for children with this disorder; however, none of those studies focused exclusively on outcomes for children diagnosed with SAD, nor did they examine the specific outcomes of those diagnosed with SAD. These treatments and their supporting evidence will be discussed in greater detail in Chap. 13.

The trials described above all include participants with diagnoses of SAD; however, results for children with that particular diagnosis were not reported in isolation from the rest of the group. Recently, a randomized controlled trial was conducted to evaluate a protocol specific to SAD, which includes CBT and parent-training components [46]. Within this trial, 43 children ages 5–7 were randomly assigned to either a wait-list or treatment condition. The treatment protocol included a combination of individual and family sessions, with SAD-specific psychoeducation, in addition to cognitive restructuring, exposure, and behavior management training. It was reported that 76 % of children receiving treatment were free of an SAD diagnosis 4 weeks after treatment completion, compared to 13.6 % of children assigned to the wait-list condition. It was noted that the disorder-specific nature of the protocol allowed for the inclusion of more severe SAD cases and that the effects of treatment were larger than those reported in meta-analyses of treatments for groups with various anxiety disorders. These results are promising, and further evaluations of SAD-specific protocols are warranted in order to determine whether such an approach leads to greater treatment gains than nonspecific CBT interventions for pediatric anxiety.

Preliminary evidence suggests that treatment protocols aimed at training parents to manage their child's anxiety may be beneficial for children diagnosed with anxiety disorders [64]. In a multiple baseline design, six families of children with SAD participated in a parent-training intervention with the goal of training parents to implement CBT methods with their children. Five of the six children no longer met SAD criteria following the intervention [65]. These results suggest that parent-training-based interventions may be particularly useful in the treatment of children diagnosed with SAD.

Novel Behavioral Treatments

While standard CBT for SAD has some empirical support, the unique features of SAD (e.g., oppositionality) have led clinical researchers to investigate innovative behavioral interventions to treat this disorder.

Parent–Child Interaction Therapy

Parent–Child Interaction Therapy (PCIT) is an approach that has been effective in treating childhood disruptive disorders and has provided a solid foundation for a novel approach to the treatment of

separation anxiety. The overarching goal of PCIT is to improve child and family functioning through effective behavior management while fostering a warm and responsive parent–child relationship [66]. Standard PCIT includes two phases conducted during an average of 13, 1-hour sessions. The Child-Directed Interaction (CDI) phase focuses on behavioral management skills whereas the Parent-Directed Interaction (PDI) phase promotes clear and effective communication methods. Parents are coached during these phases by a therapist using a one-way mirror and a "bug-in-the-ear" [67]. A pilot study of three children (6–8 years old) was conducted to test the application of standard PCIT methodology to the treatment of children with SAD [68]. All three cases were considered "recovered" meaning that none of these cases met criteria for SAD following six to seven treatment sessions [68]. However, a slightly larger pilot study (10 participants, ages 4–8) found that while some improvement in SAD severity was reported, nonclinical levels were not achieved [69].

As a result of the potential utility of standard PCIT in the treatment of SAD, the Center for Anxiety and Related Disorders at Boston University developed an adaptation of PCIT to address SAD concerns more specifically [70]. The Bravery-Directed Integration (BDI) phase was developed and added to the existing CDI and PDI phases. The BDI phase provides psychoeducation to parents as well as instruction on effective separation exposure practice in order to decrease avoidance. In an RCT of the modified PCIT for SAD, 34 children were randomized to either modified PCIT or wait-list control. Significant improvements from pre- to post-intervention in SAD severity were reported, along with improvements in academics, sibling behavior, and parenting stress [70]. Upon further investigation, the modified PCIT protocol may prove to be an effective treatment approach to address the specific needs of families of children with SAD.

Summer Camp

In emphasizing the importance of disseminating and implementing cognitive-behavioral interventions for youth with anxiety disorders, camp-based CBT has been highlighted for its accessibility and efficiency in treating this population [71]. Summer treatment programs for externalizing disorders have been supported by empirical studies [72, 73], and presently similar intensive protocols are being evaluated for internalizing disorders. Among these protocols is Camp CARD (Center for Anxiety and Related Disorders), a 1-week intensive group cognitive-behavioral intervention for children with SAD [74]. The treatment's authors propose that the camp utilize creative and novel techniques in a social context in order to implement traditional, research-supported CBT components within a developmental model. Psychoeducation, somatic anxiety management, cognitive restructuring, problem solving, exposure, relapse prevention, and a parent component serve as the foundation of the treatment approach. Differential reinforcement and shaping of behavior during in vivo separation exposures occurs throughout the 7-day intervention, as parental involvement is faded. A pilot study of the Camp CARD program was recently conducted with five girls with a principal diagnosis of SAD. Clinically meaningful reductions in SAD severity were noted for all participants; three participants no longer met criteria for a diagnosis of SAD immediately after the intervention, and no child met SAD criteria at the 2-month follow-up [74]. Improvements in parent- and child-reported separation anxiety as well as fear and avoidance were also reported. This preliminary evidence suggests that this intensive camp-based protocol has promise in the treatment of SAD; further research is needed to examine its efficacy and effectiveness with larger samples and community-based programs.

Psychopharmacological Treatment

Several pharmacological agents are also empirically supported for the treatment of anxiety disorders in youth, including SAD. One study by Walkup and colleagues [75] examined youth ages 6–17 with

SAD, generalized anxiety disorder, or social phobia. Children treated with fluvoxamine [a selective serotonin reuptake inhibitor (SSRI)] had fewer anxiety symptoms and better overall functioning at the end of 8 weeks than the placebo group. Overall, 76 % of those treated were much improved or very much improved by the end of the 8 weeks. However, results were not broken down by disorder, such that the specific effects on SAD in particular are not known. Other SSRI studies [76–78] had similar positive results for treatment of anxiety in youth, though SAD was not examined separately.

While SSRIs are most often studied and prescribed currently, earlier studies investigated tricyclic antidepressants (TCAs). Gittelman-Klein and Klein [79] conducted a small RCT for children who were exhibiting school refusal behavior, which the authors attributed primarily to separation anxiety concerns. Children who were prescribed imipramine were significantly more likely to return to school and had better overall functioning after 6 weeks than those who had been prescribed the placebo. However, later studies [80–82] failed to find TCAs superior to placebo when treating school refusal/SAD. It should be noted that in these early studies, as with the more recent SSRI studies, SAD was not evaluated independently. In these studies, school phobia or school refusal was seen as a proxy for SAD, and in the SSRI studies, the samples are comprised of youth with a variety of anxiety disorders including, but not limited to, SAD. Future research should examine the specificity of psychopharmacological treatment for SAD.

Melissa's Story: Treatment and Outcome

After the Disney World incident, Melissa's parents decided to bring her to a psychologist for help. Melissa met with a psychologist who specialized in CBT. Melissa first learned about recognizing her emotions and distinguishing physiological, emotional, and cognitive responses to anxiety. She was taught skills to manage her anxiety, such as relaxation and arguing back with her anxious thoughts (e.g., when thinking, "Mom is late—she must have gotten into an accident," she can remind herself that her mother has never been in a serious accident and people run late for many, non-tragic, reasons). Finally, she engaged in a set of gradual in vivo exposure exercises both with her therapist and on her own for homework. In session, Melissa started with easy exposures, such as having her mother leave the clinic to get a cup of coffee, and worked up to more challenging ones, like walking alone to a bookstore two blocks away and meeting her mother there. Her homework took a similar path, from easy exercises like having her mother leave her bedroom while she was still awake and resisting the urge to go to her parents' room in the middle of the night, to having her mother purposefully pick her up late from school, and finally to sleeping over at her best friend's house. The course of treatment took about 14 weeks, and Melissa and her parents reported that she was no longer fearful of bad things happening to her parents and was able to successfully calm herself down on the few occasions that she did become nervous.

Summary

SAD is a common disorder of childhood characterized by the fear that bad things will happen to the child and/or his/her parents, which often manifests itself in difficulty being away from parents or from home. While it seems clear that SAD in childhood is a risk factor for psychopathology later in life, little is known about what other specific variables may contribute to what that later psychopathology may be. Additional prospective studies of youth with SAD are needed in order to understand why SAD is a risk factor and how to use this information to prevent adult psychopathology in these children. Overall, very little research has been conducted on the assessment and treatment of SAD

specifically, nor have specific SAD results been examined within the context of larger anxiety studies. Future intervention studies would do well to examine treatments designed specifically for SAD or, in larger heterogeneous anxiety samples, to recruit a subject pool large enough to look at results for those with SAD independently. The development of additional SAD-specific assessment tools would also be valuable; there is only one, relatively new, questionnaire measure currently available that is specifically aimed at measuring symptoms of SAD. This is unusual, in that other anxiety disorders (e.g., social phobia, generalized anxiety disorder, and obsessive-compulsive disorder) have multiple questionnaire measures available both for the pediatric and adult populations. Such measures would assist in screening youth for SAD but could also be useful for measuring treatment effects. Given the relatively high prevalence of this disorder, and its role as a predictor of later psychopathology, improved understanding of SAD is needed.

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Panic Disorder

Aleta G. Angelosante and Magdalena A. Ostrowski

Abstract Panic disorder with or without agoraphobia is characterized by recurrent panic attacks, some of which occur without apparent warning or trigger, and ongoing worry about future attacks. While panic disorder is very rare in school-age children, incidence rates increase dramatically among adolescents. When panic disorder includes related symptoms, such as agoraphobia, diagnostic decision-making can be complicated; however, a differential diagnosis may be determined by considering the nature of the feared consequence. In the chapter that follows, the current literature regarding the course and etiology of child and adolescent panic disorder will be reviewed, with a focus on genetic studies, anxiety sensitivity, carbon dioxide sensitivity, and the link between panic disorder and childhood separation anxiety disorder (SAD). Assessment and treatment of panic disorder in youth will be discussed with a review of the empirical evidence for the use of traditional cognitive-behavioral therapy, an intensive treatment protocol, and pharmacological treatments. Research on panic disorder in children and adolescents is still in its infancy; suggestions for future research include additional prospective studies of the purported link between early SAD and panic and investigation into other risk factors for the development of panic disorder. As described in the chapter, there is also a relative lack of research on the treatment of pediatric panic disorder; additional studies are necessary to establish a gold standard of treatment in this age group and to elucidate factors which may influence treatment response.

Keywords Panic disorder • Children • Adolescents • Etiology • Course • Cognitive-behavioral therapy • Intensive treatment

Case Scenario

Joey is a 12-year-old boy in the 7th grade who was brought for an evaluation by his parents. They reported that his symptoms began during the summer when Joey became overheated and felt dizzy while playing soccer with his friends. The previous night, the news had been full of safety information about heat stroke and dehydration. As a result, Joey became incredibly worried that these feelings meant he was dehydrated and might suffer heat stroke. He began to hyperventilate and shake and

A.G. Angelosante (✉)
NYU Langone Medical Center, One Park Avenue, 7th Floor, New York, NY 10016, USA
e-mail: aleta.angelosante@nyumc.org

M.A. Ostrowski
Kean University, North Avenue, Hillside, NJ 07205, USA

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complained that his chest hurt. His friends called 911, and an EMS team arrived and took Joey to the hospital. Shortly after arriving, all of his symptoms had subsided, though he was still anxious and concerned about the incident. The doctors ruled out any medical conditions and suggested that he had a panic attack. Joey refused to play soccer with his friends for the rest of the summer. When he went outside, he made sure that he always had his cell phone and a bottle of water with him. A few weeks later, while sitting on his couch playing videogames, Joey felt the same sensations—his heart was racing, he could not catch his breath, and he felt overheated and dizzy. Joey was sure something was horribly wrong and thought he might even be dying. He called his mother, but she was in a meeting and did not answer the phone. By the time she called him back, 20 minutes later, the symptoms were almost completely gone. He worried that if it could happen while he was on his couch, it could happen anywhere. He started insisting on sitting on the aisle at the movies, in case he needed to get out; one time, when the theater was crowded and he was forced to sit in the middle, he worried so much about whether or not he would be able to get out that he started to feel panicky and left the theater. When he returned to school in the fall, he continued to keep a bottle of water and his cell phone with him at all times. His parents expressed concern that he is limiting his activity for fear that these symptoms will return. For example, his gym teacher noticed that he has forgotten his gym clothes or sneakers several times, requiring him to sit out of gym.

Description of the Disorder

A panic attack is a feeling of intense fear and physiological arousal; the peak intensity is reached in approximately 10 minutes, and the sensations tend to subside within 20–30 minutes. Symptoms of a panic attack include increased heart rate, increased breathing rate, hyperventilation, shaking, sweating, dizziness, muscle tension, headache, blurred vision, dissociation, and feeling of unreality. In addition to these physiological symptoms, panic attacks include cognitive symptoms such as the belief that one is dying, going "crazy," or about to lose control. Panic attacks are relatively common and approximately 23 % of people will experience an isolated panic attack at some point in their lives [1]. Usually, these are cued panic attacks, meaning that the person becomes scared in the face of a frightening situation (e.g., when faced with a phobic stimuli or after enduring a traumatic event).

Uncued panic attacks, the hallmark of panic disorder, are those which seemingly come "out of the blue." Panic disorder can occur either with or without agoraphobia. Those with agoraphobia will frequently avoid situations that they fear may cause a panic attack or would be difficult or embarrassing to escape if a panic attack did occur. For example, they may need to sit on the aisle in a theater or avoid subways, planes, shopping malls, crowded places, or places where they feel "trapped." Those without agoraphobia experience significant anxiety about the possibility of additional panic attacks and may engage in safety behaviors in the hopes of either preventing future attacks (e.g., carrying water or an anxiolytic medication) or preventing harm should an attack occur (e.g., insisting on having a cell phone with them at all times) but do not engage in any avoidance of places or situations. In clinical samples, there is a very high co-occurrence of agoraphobia with panic disorder [2]. In non-referred samples, however, panic symptoms more frequently occur without agoraphobia [3]. This disparity suggests that panic disorder with agoraphobia is more impairing than panic disorder alone, leading these individuals to seek treatment. Most of the research in panic disorder combines those with and without agoraphobia, so the abbreviation PD will be used throughout this chapter to refer to both of these types, except when referring to studies which purposefully differentiate between or compare panic disorder with, and panic disorder without, agoraphobia.

The DSM-IV TR [4] criteria for panic disorder states that recurring, unexpected panic attacks must be present and be followed by at least 1 month of persistent concern about (1) having additional attacks, (2) worry about the implications of the attack or its consequences (e.g., losing control, having

a heart attack, "going crazy"), or (3) a significant change in behavior related to the attacks. Panic disorder with agoraphobia includes the above but also significant anxiety about being in places or situations from which escape might be difficult (or embarrassing) or in which help may not be available in the event of having a panic attack or panic symptoms. Such situations are avoided (e.g., travel is restricted) or else are endured with marked distress about having a panic attack or panic symptoms or require the presence of a companion (aka a safe person). The panic attacks cannot be caused by medical issues (e.g., a thyroid disorder) or substance abuse. They also cannot solely occur in the presence of a feared object (e.g., specific phobia) or situation (e.g., while separating from a parent).

Differential Diagnosis

Accurate diagnosis of panic disorder can often be a challenge since the symptoms show significant overlap with those of other pediatric anxiety disorders. First, the panic attacks observed in individuals with panic disorder must be differentiated from those experienced in the context of other anxiety disorders. Panic attacks can occur in the face of any feared situation and, therefore, may be present in any anxiety disorder. However, as mentioned earlier, to be considered symptoms of panic disorder, at least some panic attacks have to be uncued. Second, agoraphobic avoidance must be distinguished from the situational avoidance observed in other disorders. For example, a child with a specific phobia of vomiting may not like to be away from his parents for fear that he will vomit and they would not be nearby to take care of him. He may avoid going to school or attending extracurricular activities for fear that he will vomit in front of his friends. He will likely be overly sensitive to physical sensations, becoming extremely concerned if his stomach "feels weird" or even if he just feels the sensation of a full stomach. The main differential to be noted is the nature of the feared consequence. A child with panic disorder with agoraphobia will fear these same situations, but the feared consequence of, for example, attending school, is that she will have a panic attack, not that she will vomit. Similarly, symptoms of separation anxiety disorder (SAD) can resemble those of panic disorder and require differentiation based on understanding the feared outcome. A child with SAD will want to have her parent nearby, may have trouble attending drop-off playdates or birthday parties, may have difficulty attending school, and might complain of somatic symptoms (e.g., stomachache, nausea) when anticipating separations or at the time of required separations from parents. Such a child may even have panic attacks (or limited symptom attacks) when it is time to separate from her parents (e.g., if they go out and leave her with a babysitter). For the child with SAD, however, the feared outcome is not a panic attack but rather that while they are apart, something catastrophic will occur to either herself (e.g., getting kidnapped) or her parents (e.g., getting in a car accident) that will keep them from ever seeing each other again. Finally, it is important to be able to differentiate panic disorder from anxiety disorder due to a general medical condition or substance-induced anxiety disorder. The physical symptoms of these disorders, such as accelerated heart rate and hyperventiliation, can mimic panic symptoms. Therefore, a physical exam is needed to rule out any medical (e.g., cardiac) syndromes or medications that could cause such symptoms.

Prevalence

Panic disorder has a lifetime prevalence of 4.7 % [5]. Among people who develop PD, 25 % will do so by age 16 and 50 % by age 24. It is very rare in school-age children, but incidence rates increase dramatically in adolescence and into young adulthood. For example, in a sample of youth ages 9–16, Costello and colleagues [6] found an overall 3-month lifetime prevalence of 0.2 % (very low in childhood, but increases to 0.5 % in mid-adolescence). Hayward and colleagues [7] found that onset of

panic was related to physiological development rather than chronological age. In a sample of middle school girls, they found that the onset of panic disorder symptoms significantly increased after the onset of puberty, regardless of chronological age. Regarding gender differences, while cued panic attacks occur equally frequently in males and females [8], panic disorder with or without agoraphobia is more common in females [9].

The lower prevalence rate in childhood is theorized to be related to children's emerging cognitive development. While children can certainly experience uncued panic attacks, they appear to attribute these symptoms to external factors and therefore do not have the cognitive appraisals such as "I am dying" or "I am going crazy" [10]. This externalizing of symptoms has been tied to Piagetian theory of cognitive development; children in the preoperational stage of development cannot differentiate between the self and the world, making them concrete and egocentric, and children in the concrete operational stage cannot conceptualize hypothetical events. As such, it is not until children reach formal operational thinking that they can recognize the way thoughts can impact physiological responses and hypothesize about the future [10]. As a result of the low incident rates of PD in children as well as a theoretical understanding for why this disorder does not emerge until early adolescence, most of the research in this area has been in adult samples. Only more recently have researchers begun to examine the disorder, and its assessment and treatment, in youth.

Course

There is limited information about the course of PD in youth, but there is some information regarding the course of this disorder in adults. One recent study of adults investigated the course of panic disorder with and without agoraphobia separately [11]. They followed a sample of 235 adult patients (Mean age = 38 years) with either disorder over 3 years, finding that those with panic disorder had a recurrent, relapsing course while those with panic disorder with agoraphobia had a more chronic course. This finding is similar to other studies, which found that only 39 % of patients with panic disorder and 17 % of those with panic disorder with agoraphobia remitted after 1 year. Among those who did remit, nearly 1/3 relapsed within 1 year [12]. A naturalistic study of adults with panic disorder with or without agoraphobia found that nearly half of those who remitted relapsed within 2 years [13].

Comorbidity

Comorbidity is very high with 50–90 % of youth with PD meeting criteria for at least one additional psychiatric disorder [2, 14]. Youth with PD have high rates of comorbidity with other anxiety disorders but also with disruptive behavior disorders and mood disorders. In one study of youth with PD, 75 % also met criteria for major depressive disorder, 65 % met criteria for oppositional defiant disorder, and 58 % met criteria for attention-deficit hyperactivity disorder [2]. In an epidemiological study of 13 and 14 year olds, those who had experienced a panic attack were three times more likely to have contemplated suicide and twice as likely to have attempted suicide than those who had never experienced a panic attack [15].

Etiology

Here, we review several factors that are important in the development of panic disorder including genetic hereditability, anxiety sensitivity, suffocation hypothesis, and childhood separation anxiety.

Genetics

Panic disorder has long been found to run in families. In a study of nearly 278 relatives of 41 patients with PD and 262 relatives of 41 matched controls, 17 % of probands' relatives met criteria for lifetime PD as opposed to only 2 % of those in the control group [16]. Another study found that relatives of both early- (prior to age 20) and later-onset PD had a significantly higher rate of the disorder than normal controls. Further, relatives of early-onset patients had a 17-fold increased risk, while the risk in relatives of those with later onset had a sixfold increase, indicating that adolescent onset of PD may have a stronger familial basis than adult onset [17]. In differentiating familial aggregation of internalizing disorders, Goldstein and colleagues [18] found that relatives of patients with PD had a significantly higher risk for panic attacks than those relatives of either patients with major depression or controls. Finally, when the relatives of a sample of adults with PD were compared with relatives of patients with other anxiety disorders (e.g., simple phobias, social phobia), they specifically exhibited higher rates of PD and not of other anxiety disorders [19].

In addition to these family studies, several twin studies have examined the role of genetics in adults with PD. One study of a large sample of adult female twins found that genetics accounted for 44 % of the variance regarding risk factors for a panic disorder diagnosis, while individual factors and shared familial factors accounted for 55 % and 1 % of the variance, respectively [20]. A more recent study by Hettema and colleagues [21] used a mixed sample of male and female twins to examine panic disorder and agoraphobia separately and found that genetics accounted for 28 % of the variance for panic disorder and 36 % of the variance for agoraphobia. Finally, some preliminary evidence from genome-wide association studies have begun to identify specific genetic markers that may be implicated in the development of panic disorder, though larger studies are required to clarify these findings [22].

Anxiety Sensitivity

Anxiety sensitivity is a construct which describes increased awareness of physiological symptoms of anxiety (e.g., increased heart rate, increased respiration, nausea) as well as anxiety regarding the meaning of those symptoms. In Barlow's model of panic [23], catastrophic interpretations of these sensations lead to panic attacks. Not surprisingly, then, several studies have examined the relationship between anxiety sensitivity and panic disorder with or without agoraphobia, though only a few of these studies have been conducted in the pediatric population (for a review of the link between anxiety sensitivity and panic disorder in adults, see [24]). Kearney and colleagues [25] found that youth with PD reported significantly higher anxiety sensitivity than youth with other disorders. Hayward and colleagues [8] also found that anxiety sensitivity predicted panic attacks in a high school sample. In another sample of non-referred youth, anxiety sensitivity predicted panic attacks even after controlling for trait anxiety, general anxiety, and depression [26]. Finally, in a community sample of African-American youth, anxiety sensitivity, panic symptoms, and panic attacks were assessed initially (time 1) and then again 6 months later (time 2) [27]. The study team found that anxiety sensitivity was related to concurrent panic symptoms (i.e., anxiety sensitivity at time 1 was correlated with panic symptoms at time 1 and anxiety sensitivity at time 2 was correlated with panic symptoms at time 2). In addition, anxiety sensitivity measured at time 1 differentiated between those who had ever experienced a panic attack and those who had not, both at time 1 and time 2 [27].

Childhood Separation Anxiety Disorder

There are mixed findings regarding the potential link between SAD in childhood and panic disorder in adulthood. Retrospective accounts by adults with panic disorder often include reports of SAD in their childhood. One study asked women in a community sample to report on their memories of separation anxiety symptoms in childhood and found that women with panic disorder recounted significantly more separation symptoms than those with other anxiety disorders (e.g., generalized anxiety disorder, phobias; [28]). Another study examined the retrospective report of adults with panic disorder, from both referred and non-referred samples [29]. Overanxious disorder of childhood and SAD each individually predicted lifetime panic disorder with or without agoraphobia, while a history of SAD uniquely predicted adolescent-onset PD. In a follow-up study of only the non-referred adults in the previous study, SAD, along with specific phobia and social phobia, each predicted later panic disorder [30]. Some studies have examined panic disorder with, and without, agoraphobia separately. In a study of retrospective reports of school refusal and separation anxiety, Delito and colleagues [31] found that while none of the patients with pure panic disorder reported a history of school refusal or separation anxiety, 60 % of those with panic disorder with agoraphobia reported those symptoms. Another larger study found a significant difference in history of separation anxiety symptoms between those with panic disorder with or without agoraphobia and normal controls; moreover, they also noted a trend towards differentiation between panic disorder with, and without, agoraphobia, with 17 % in the latter group reporting a history of SAD symptoms and 21 % in the former group [32]. Despite this evidence, however, it should be noted that other retrospective reports have not found a significant difference in separation anxiety symptoms between individuals with panic disorder and those with other anxiety disorders [33, 34] or with other psychiatric disorders [35]. As such, there is no unequivocal link between childhood SAD and later panic disorder.

Retrospective reports are obviously flawed in that they rely on patients' memories of symptoms which may be influenced by their current symptoms. Prospective studies, which follow subjects forward in time, are more reliable because their symptoms can be verified and documented at each time point. One longitudinal study supports the link between early SAD and later panic disorder. Pine and colleagues [36] examined a large sample of youth who had undergone psychiatric interviews at time 1 and were reassessed 2 years later (time 2) and again 10 years later (time 3). SAD at time 1 was positively related to panic disorder at time 3, though the relationship did not reach statistical significance. SAD at time 1 was significantly related to "fearful spells" (which closely resemble panic attacks) at time 3. However, two additional longitudinal studies [14, 37] did not find a relationship childhood SAD and later PD.

Further evidence for the link between SAD and panic disorder comes from common physiological markers such as hypersensitivity to carbon dioxide (CO_2) inhalation, which has been identified as a biomarker of panic disorder in adults (described in more detail below). Pine and colleagues [38] assessed hypersensitivity to CO_2 in children with SAD, generalized anxiety disorder, and social phobia. The strongest relationship was found between hypersensitivity to CO_2 and SAD, while generalized anxiety disorder was also associated with hypersensitivity, and social phobia was not linked at all.

Carbon Dioxide Sensitivity

The role of carbon dioxide has proven to be very important in the understanding of panic disorder. The suffocation hypothesis states that it is evolutionarily important to respond to the sensation of smothering with panic attack symptoms such as hyperventilation and an attempt to escape. A highly sensitive suffocation alarm, which detects and reacts to increases of CO_2, can lead to uncued panic

attacks, putting one at higher risk for panic disorder [39]; for a recent in-depth review of the suffocation false alarm hypothesis, see [40]. Empirical support for this theory comes from studies using a CO_2 challenge (i.e., breathing in a high level of CO_2 which creates the sensation of being smothered). These studies have found that participants with panic disorder report a significant increase in overall anxiety as well as specific panic symptoms; healthy controls do not report such responses [41]. This sensitivity appears to be genetic; for example, healthy relatives of adults with PD report higher rates of anxiety than controls after engaging in the same CO_2 challenge [42]., CO_2 sensitivity also appears to be specific to panic disorder, rather than a trait common to those with other related disorders. For example, one study compared CO_2 responses across three groups: those with at least one panic-disordered relative, those with at least two manic and/or depressed relatives (putting them at high risk for depression or anxiety), and those with no family history of anxiety, mood, or substance disorders [43]. Nearly 50 % of those in the panic group had a panic attack following the challenge, while no panic attacks occurred in the other groups. As carbon dioxide sensitivity is under opioid control, it has been suggested that panic disorder may be caused by an endogenous opioid deficit [40]. This theory may have implications for treating panic disorder through the use of opioid agonists, though this has not yet been tested in youth.

Assessment

Currently, there are no measures specifically designed to assess panic disorder symptoms in children and adolescents. Rather, there are measures of general pediatric anxiety that include subscales specific to panic symptoms as well as adult measures that have been adapted for use with younger populations. These measures will be discussed here. See Chap. 12 for a discussion of measures used in the broader assessment of pediatric anxiety disorders.

Panic Disorder Severity Scale

The Panic Disorder Severity Scale (PDSS) is a brief interview measure designed to assess the severity of panic symptoms and level of impairment of those symptoms [44]. This seven-item assessment provides a 5-point Likert scale that assesses the following domains: frequency of panic attacks, distress caused by panic attacks, amount of fear/avoidance related to the attacks, anticipatory anxiety about the attacks, avoidance of symptoms that mimic attacks, and work and social impairment. The PDSS has good inter-rater reliability and both convergent and discriminant validity [45]. The interview has been adapted as a self-report questionnaire [46] with good psychometric properties. One caveat is that all of the psychometric data available to date, both for the self-report and for the interview, are based on adult samples. However, the benefit of the interview format is that it can easily be used with children and adolescents, with only mild word changes to adapt to the child's developmental level and with school impairment replacing work impairment. At least one clinical study of panic disorder treatment in a pediatric population [47] has used the PDSS in this way to good effect.

Multidimensional Anxiety Scale for Children

The Multidimensional Anxiety Scale for Children (MASC) is a 39-item questionnaire normed for use with children ages 7–19 [48]. Both child-report and parent-report versions are available. The MASC

assesses overall anxiety, as well as four empirically derived domains of common childhood anxiety, one of which is called "Separation Anxiety/Panic." This 9-item scale assesses specific fears and worries that a child with SAD or panic disorder might have, such as "The idea of going away to camp scares me." The MASC has demonstrated adequate test-retest reliability and differentiates children with an anxiety disorder from both those without any psychiatric disorders and those with psychiatric disorders other than anxiety [49].

Screen for Child Anxiety Related Emotional Disorders

The Screen for Child Anxiety Related Emotional Disorders (SCARED) was developed by Birmaher and colleagues [50] based on DSM-IV definitions of the most common anxiety disorders in children and adolescents, including panic disorder. The 13-item panic disorder scale focuses primarily on physiological arousal (i.e., "When my child gets frightened, his/her heart beats fast.") The SCARED is comprised of 41 items on a 3-point Likert scale and has identical but separate versions for child report and parent report (only substituting you/your child). The SCARED has good internal consistency and reliability [50] and has also been found to have good reliability and validity when used in a clinical sample [51].

Spence Children's Anxiety Scale

Like the SCARED, the Spence Children's Anxiety Scale (SCAS) was developed to assess DSM-IV specific factors of anxiety [52]. The SCAS is designed for use with children ages 8–12 and uses a 4-point Likert scale. It consists of 44 items, 6 of which are filler items asking about positive attributes of the child, which do not get factored into the total score or subscales; these items are meant to reduce the possibility of a negative response bias [52]. In addition to a total anxiety score, the SCAS provides several subscale scores including a 9-item panic/agoraphobia subscale, which asks questions such as "All of a sudden I feel really scared for no reason at all" or "I suddenly feel as if I can't breathe when there is no reason for this." The SCAS has demonstrated good internal consistency, retest reliability, and convergent and discriminant validity [52].

Medical Assessment

The somatic symptoms of panic attacks can be very similar to symptoms with a physiological or medical basis. Thus, it is essential that children experiencing such attacks be assessed by a physician to rule out any cardiac, respiratory, and/or neurological conditions that may be causing these symptoms. It is also important to rule out adverse effects of medications or illicit drugs, particularly in adolescents [53, 54]. Alternatively, children and adolescents who present with chest pain and/or other cardiac symptoms should be evaluated for panic disorder once all medical causes have been ruled out. A study of noncardiac chest pain in youth found that over half of those youth met criteria for an anxiety disorder, primarily panic disorder [55]. Thus, a thorough medical evaluation should be conducted before concluding that symptoms result from panic disorder, and a thorough psychiatric assessment is needed once all medical causes have been eliminated.

Treatment

As the research into panic disorder in children and adolescence remains in its infancy, there are very few intervention studies for this population. There are a handful of behavioral intervention trials and only a few noncontrolled psychopharmacological trials.

Cognitive-Behavioral Treatments

Cognitive-behavioral treatments for panic disorder are similar to those used for other anxiety disorders with one unique component, interoceptive exposure. During these exposures, the patient engages in exercises to bring on the sensations of panic (e.g., racing heart, dizziness, hyperventilation) in controlled way. This serves to desensitize patients to these sensations and change their cognitions regarding their dangerousness. Other elements of CBT for panic disorder include emotion identification, cognitive restructuring, and in vivo exposure (to situations that may be avoided due to panic symptoms). Psychoeducation about the nature and utility of anxiety as well as the safety of panic attacks is also a feature of most CBT approaches to panic in order to change common cognitive appraisals of panic symptoms (e.g., "I am dying" or "panic attacks will damage my heart") [56]. Earlier treatments for panic disorder included relaxation training; however, more recent treatments have eschewed the practice feeling that it can increase rather than decrease panic symptoms. When implemented in the midst of a panic attack, relaxation exercises often fail, leading the individual to believe that the symptoms are not panic after all but something more dangerous and uncontrollable (e.g., a heart attack) [57].

Panic Control Treatment (PCT), a cognitive-behavioral intervention developed to treat panic disorder in adults [58] has been adapted by several researchers for use with adolescents. One controlled, multiple baseline study of PCT was conducted by Ollendick [59] as an initial investigation of cognitive-behavioral treatment of panic disorder with adolescents. Four adolescents were treated with six to nine sessions of a modified PCT protocol which included psychoeducation, relaxation, cognitive coping procedures, and in vivo exposure components. Participants were considered to be "recovered" once they were free of panic attacks for 2 consecutive weeks. It was reported that each of the four participants achieved recovery by the end of treatment along with reductions in agoraphobic avoidance and increases in self-efficacy. Treatment gains were maintained at 6-month follow-up. Researchers at the Center for Anxiety and Related Disorder at Boston University also adapted the PCT protocol for adolescents (PCT-A). The 11-session treatment addresses the cognitive/misinterpretational aspects of panic as well as hyperventilatory response and conditioned reactions to physical sensations [57]. Two preliminary case studies supported the potential efficacy of this treatment approach as adolescents evidenced both substantial reductions in panic attacks and avoidance of agoraphobic situations [57]. This initial support led to a randomized control trial to evaluate the treatment compared to a self-monitoring control group in a sample of 26 adolescents diagnosed with panic disorder. Adolescents in the active treatment condition had significantly greater improvements in clinician-rated panic disorder and self-reports of anxiety and depression, with gains maintained at 3- and 6-month follow-up assessments [60]. These findings lend support to the potential efficacy of PCT-A for adolescent panic disorder.

Novel Behavioral Treatments: Intensive Treatment Protocol

In an effort to increase the dissemination of PCT-A, a brief, intensive protocol has been developed to address family requests for more rapid alleviation of the adolescent's panic symptoms. Adolescent Panic Control Treatment with In Vivo Exposures (APE) which is described in more detail

in [61] is administered over an 8-day period. Across the first three 2-h sessions, adolescents receive psychoeducation, create a fear and avoidance hierarchy, and engage in cognitive restructuring, interoceptive exposure, and homework exercises. In vivo exposures are conducted during two 6-h sessions, and adolescents are encouraged to practice exposure over the weekend on their own. A final 2-h session serves as a review of treatment progress and planning session for the maintenance of skills learned during in session and out of session exposures. Additionally, four 30-minutes weekly telephone check-ins are conducted to review the adolescent's progress and plan for skills practice. Two case studies in which APE resulted in significant improvement in panic symptoms were reported by Angelosante et al. [61]. Preliminary data from 12 patients has provided promising findings, with adolescents experiencing significantly fewer panic attacks, as well as decreased avoidance and improvements in academic, social, and family functioning [62].

Pharmacological Treatments

As stated earlier, while many medication trials exist for the treatment of panic in adults, no such randomized trials exist for pediatric populations. However, there is some evidence that psychopharmacologic treatments for children with panic disorder can be effective. Lepola and colleagues [63] provided anecdotal evidence from 3 children (ages 9–16) with panic disorder and school refusal behavior treated with citalopram. They found that the treatment was both safe and effective for these youth; at the end of treatment, they no longer exhibited panic attacks. Other anecdotal evidence was provided by Fairbanks and colleagues [64] who as part of an open trial of fluoxetine (40–60 mg) for youth with anxiety disorders, reported on five youth (ages 10–16) with panic disorder as part of their diagnostic profile. All five were rated much improved or improved by the end of the trial (6–8 weeks in length), though four of the five still met diagnostic criteria for panic disorder at that time. A pilot study by Renaud and colleagues [47] of 12 youths with a primary diagnosis of panic disorder also assessed the use of selective serotonin reuptake inhibitors (SSRIs) in this population. This sample consisted predominantly of adolescents, with 11 participants ranging in age from 14 to 17 years of age and one 7-year-old participant. After a 6–8 week trial, participants were followed for 6 months; at that time, 75 % of the sample was rated as much improved or very much improved, and 8 of the 12 no longer met criteria for a diagnosis. Fluoxetine was primarily used, though if participants had a previous negative experience with that medication, another one was tried such that one participant was given sertraline and two were given paroxetine, instead. Finally, Masi and colleagues [65] conducted a chart review of 18 youths (ages 7–16) diagnosed with panic disorder who were treated with paroxetine. At the end of treatment (which lasted 2–24 months), 15 of the 18 were rated as much or very much improved.

Joey's Story: Treatment and Outcome

Joey's parents brought him to a psychiatrist after he quit the soccer team mid-season and his first-quarter report card indicated that he failed gym due to lack of preparedness and participation. The psychiatrist recommended cognitive-behavioral therapy. The therapist started by explaining the CBT model of anxiety and providing extensive psychoeducation about the nature of panic attacks. Treatment then focused on somatic responses to anxiety in order to demystify those symptoms, thereby making them less anxiety producing. Joey responded very positively to these early interventions. He then began interoceptive exposures. Joey found the exercises that caused his heart to race or him to feel overheated to be the most useful. Finally, with his therapist's guidance, Joey began gradually engaging

in behaviors he had been avoiding, such as working out, sitting in the middle of the row at the movies, or going out with friends while leaving his water bottle and his cell phone at home. Treatment took approximately 12 weeks, and both Joey and his parents were very pleased with his progress.

Summary

Panic disorder with or without agoraphobia is a disorder characterized by recurrent panic attacks, some of which occur without apparent warning or trigger, and ongoing worry about future attacks. Research in panic disorder in children and adolescence is still in its infancy and, as such, a great deal of research is needed in almost all areas. Much of the research around risk factors for panic disorder have focused on the purported link with early SAD; as the evidence regarding this link is far from definitive, additional prospective research within the SAD population is needed. Furthermore, greater research into other risk factors for the development of panic disorder is needed. There is also a relative lack of research in the treatment of pediatric panic disorder; additional studies are necessary to establish a gold standard of treatment in this age group and to elucidate what factors may influence treatment response. Larger studies of either traditional or intensive cognitive-behavioral interventions are needed to establish CBT as an efficacious treatment as per the standards set by the American Psychological Association [66]. Moreover, there have been no controlled trials of psychopharmacological treatments in this age group, so such investigations are sorely needed.

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Obsessive-Compulsive Disorder in Children and Adolescents

Adam B. Lewin, Jennifer M. Park, and Eric A. Storch

Abstract Pediatric obsessive-compulsive disorder (OCD) is a chronic and debilitating neuropsychiatric disorder that is associated with significant psychosocial and functional impairment. This chapter reviews the literature on pediatric OCD, including clinical characteristics and etiological theories. Assessment methods, available treatment modalities (psychopharmacological and behavioral approaches), methods of treatment augmentation, and directions for future research regarding treatment dissemination are discussed.

Keywords Obsessive-compulsive disorder • OCD • Children • Adolescents • Treatment • Assessment • Phenomenology

Case Scenario

Zoe, an 11-year-old girl, was evaluated at an outpatient child psychiatric clinic specializing in obsessive-compulsive disorder (OCD) on her parents' referral. She said that following a salmonella outbreak at her aunt's farm, everything associated with the farm was now "contaminated." Because her father was at the farm at the time of the outbreak, her father and all of her father's possessions were contaminated (including pictures of her aunt's family/farm). Later, she had to wash her hands repeatedly throughout the day after touching any person or object that she believed was "contaminated." She also took 60–90-min showers each day. Zoe stated that the level of contamination could increase if two already contaminated objects (or people) were to touch. If she imagined the farm, she would say a "cleansing" prayer ten times in her head. By the time that she was seen in the clinic, she had not touched her father in 3 months and refused to enter any room in the house that he may enter, eat from dishes, or sit in furniture he may have used. Her hands and arms were raw and chapped

A.B. Lewin (✉)
Neuropsychiatry – University of South Florida, 880 6th Street South, Suite 460, Rothman Center - Box 7523, Child Rehabilitation and Development Building, St. Petersburg, FL 33701, USA
e-mail: alewinhealth@usf.edu

J.M. Park
Department of Psychology, University of South Florida, 4202 E. Fowler Avenue, PCD4118G, Tampa, FL 33620, USA

E.A. Storch
University of South Florida, 880 6th Street South, Suite 460, Rothman Center - Box 7523, Child Rehabilitation and Development Building, St. Petersburg, FL 33701, USA

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from the repeated washing. Her parents related that she was unable to maintain her friendships because of these behaviors and that her grades in school suffered due to her symptoms as well. She acknowledged that she was probably "not really going to get sick" but was too afraid to "risk it" by not ritualizing.

Description of the Disorder

OCD is a chronic and disabling neuropsychiatric disorder that is characterized by the presence of intrusive and distress-provoking thoughts or images (obsessions) and/or repetitive or ritualistic behaviors or mental acts (compulsions) [1]. Pediatric OCD is often associated with significant psychosocial and functional impairment [2–4]. Youth with OCD endorse high rates of academic difficulties, such as concentrating on and completing homework, as well as increased rates of family dysfunction [2, 3, 5]. Relative to their unaffected peers, youth with OCD are prone to increased victimization and are less likely to participate in social activities [4, 5]. These impairments, coupled with symptom severity and the presence of comorbid disorders, contribute to an all-encompassing diminished quality of life [6]. When left inadequately treated, OCD often follows a debilitating trajectory, where early OCD-related impairments contribute to later psychological difficulties, such as an increased presence of comorbid psychiatric disorders [7, 8]. Given these concerns, it is not surprising that OCD is one of the top ten leading causes of adult disability in the developed world [9].

According to the DSM-IV, an OCD diagnosis requires the presence of obsessions or compulsions that are distressing, impairing, and/or time-consuming [1]. The symptom profile of OCD is heterogeneous; symptoms appear in various themes (e.g., contamination, aggressive, sexual, religious), which can fluctuate and change over time [7, 10]. It is not uncommon for symptoms to exacerbate during times of significant stress or change, such as moving to a new location, changing schools, or having a sickness or death in the family [11, 12]. Children and adults with OCD exhibit similar symptom presentations where the most common obsessions include fear of contamination, fear of harm to self and/or others, concerns regarding symmetry, fear of offending God, preoccupation with right and wrong, need for exactness and order, and saving obsessions [13, 14]. Common compulsions include excessive or ritualized cleaning; checking, arranging, repeating, or counting rituals; hoarding or collecting behaviors; and praying, confessing, or reassurance-seeking [15]. Factor analyses of various obsessive-compulsive symptoms in both children and adults have produced four- and five-factor models comprising distinct symptom dimensions: contamination/cleaning, aggressive/checking, sexual/religious, symmetry/ordering, and hoarding [16]. Symptom dimensions can be suggestive of illness course and prognosis [17, 18]. For example, a longitudinal study examined 45 individuals with OCD and found that at the 9-year follow-up, children who initially presented with hoarding symptoms as their primary OCD symptom had remission rates of only 10 % compared to a 54 % remission rate for children with other primary OCD symptoms [10].

Although symptom manifestation in children and adults is similar, some developmental differences exist. Compared to adults, youth with OCD may present with a general discomfort, or unpleasant feeling, rather than fear/anxiety when rituals cannot be completed. For example, vague or diffuse symptoms such as the "not just right" phenomenon are common in youth. The "not just right" phenomenon as defined by the need to engage in specific behaviors/rituals until the child feels better is often described as preceded by an urge rather than a specific fear/thought/worry. That is, youth who experience the "not just right" phenomenon often report that their behavior relieves a sense of "incompleteness" and/or sensory discomfort rather than harm/fear avoidance [19, 20]. Rituals involving family members, especially parents, are highly prevalent symptoms in youth with OCD. For example, reassurance-seeking, confessing/apologizing rituals, and family accommodation, which refers to family involvement in rituals and modifications in routine and functioning due to obsessive-compulsive symptoms, are

commonplace [21, 22]. Another distinguishing feature of pediatric OCD is limited insight. Whereas an OCD diagnosis for adults requires some recognition of the excessive and unreasonable nature of the thoughts and behaviors [1], children are exempt from this requirement and commonly present with diminished insight [23, 24] and may not consider their symptoms to be distressing.

OCD is currently classified as an anxiety disorder in the *DSM-IV-TR*. However, several substantial changes have been proposed regarding the classification of OCD in the upcoming *DSM-5,* with some suggesting that OCD should be removed from the anxiety disorders category and subsumed under a new classification of obsessive-compulsive-related disorders (OCRDs), which include body-dysmorphic disorder (BDD), hypochondriasis, Tourette's syndrome (TS), trichotillomania (TTM), eating disorders, addictions, and autism [25]. Others maintain that there are marked differences between OCD and the majority of these disorders and therefore, OCD should remain categorized as an anxiety disorder [26].

Proponents of the OCRD classification base their arguments on an etiological model that cite similarities in symptom presentation, familial rates, comorbidity, brain circuitry, and pharmacotherapy treatment response as evidence for the combined classification [25]. However, these assertions may be premature. The John Hopkins OCD Family Study found amongst 80 individuals with OCD to have the following rates of anxiety disorders in their first-degree relatives: 16.3 % OCD, 25 % specific phobia, 22.6 % social phobia, 15.6 % GAD, and 12.6 % separation anxiety [27], while the rates of OCRDs were the following: 1 % TTM, 4 % "any" eating disorders, and 17 % grooming disorder [28]. In regards to comorbidity, OCD and OCRDs have comorbidity rates that occur higher than by chance, with individual studies reporting rates up to 16 % for hypochondriasis, 15 % for BDD, 13 % for tic disorders, 9 % for anorexia nervosa, 4 % for bulimia, and 5 % for TTM [28, 29]. However, considerably higher comorbidity rates for anxiety disorders, such as generalized anxiety disorder (GAD) and social phobia, are consistently found in those with OCD [27]. Due to the increased rates of familial anxiety disorders and comorbid anxiety disorder in individuals with OCD, the argument that OCD and OCRDs are related due to family history and comorbidity is difficult to uphold.

Recommendations have also been made to remove hoarding as a subtype of OCD and classify compulsive hoarding as a separate disorder in the DSM-5 [30]. Phenomenologically, hoarding appears similar to OCD, as it is characterized by persistent concern of losing items that are sentimental or may be needed in the future; the acquisition of items and avoidance of discarding items can be characterized as compulsions. However, hoarding appears to be distinct from OCD in a number of ways. Hoarding frequently occurs in the absence of other OCD symptoms and has weaker associations with OCD-related comorbid disorders, such as anxiety and depression, relative to other OCD subtypes [31–33]. Most striking, compulsive hoarders often do not respond to standard pharmacological and/or behavioral treatments that are efficacious for OCD [34–36]. Additionally, the literature has consistently found distinct differences in genetics and the neurobiology of individuals with compulsive hoarding compared to those with other OCD subtypes [37–39].

Prevalence and Course

OCD has a prevalence of approximately 1–2 % among youth [40, 41]. Initial symptom presentation is bimodal, typically occurring during prepuberty (early-onset OCD) and in late adolescence/early adulthood, with a mean age onset between 6 and 11 years old for early-onset OCD [42]. Age of onset varies by gender with a male preponderance among those with prepubertal onset; by adolescence, the gender distribution becomes roughly equivalent [43, 44]. Early-onset OCD is associated with high rates of familial risk for the disorder, while adult onset OCD has shown low rates of familial risk, suggesting that genetic factors may play an important role in the manifestation and development of symptoms in early-onset OCD [45, 46].

As previously noted, OCD is a chronic disorder; 80 % of adults with OCD report a childhood onset of the disorder [43]. Moreover, in a meta-analysis of studies examining the long-term course of 521 individuals with childhood-onset OCD, 60 % remained symptomatic at follow-up points ranging between 1 and 15 years [47].

Comorbidity

Comorbid disorders are the norm rather than the exception in pediatric OCD with up to 75 % of children diagnosed with a comorbid psychiatric condition [48–50]. Across several studies, high rates of anxiety disorders (26–70 %), tic disorders, (17–59 %), depressive disorders (10–73 %), disruptive behavior disorders (10–53 %), and attention deficit hyperactivity disorder (ADHD; 10–50 %) are reported [48, 51–53]. Indeed, in a large randomized clinical trial, 80 % of those with pediatric OCD had at least one other psychiatric disorder, with 63 % endorsing at least one internalizing disorder and 27 % endorsing at least one externalizing disorder [54]. The presence of even one comorbid condition can have a significant negative impact on presentation and outcome; comorbidity is associated with increased functional and psychosocial impairment, attenuated treatment response (both behavioral and medication therapy), and increased risk of relapse posttreatment [55–57].

Differential Diagnosis

A diagnosis of pediatric OCD requires the presence of time-consuming, interfering, and/or distressing obsessions and/or compulsions. Although seemingly straightforward, OCD can be difficult to differentiate from other disorders that may present with similar symptom presentations.

GAD is highly comorbid with OCD [58]. A common symptom of GAD is excessive worry that is often described as intrusive, difficult to control, hard to resist, and extremely distressing. Additionally, individuals with GAD may compulsively engage in reassurance-seeking or checking behaviors to alleviate the anxiety caused by the intrusive thoughts. Although symptoms seem to overlap considerably, the main differentiation between GAD and OCD is the content of the worries. Worries associated with GAD are generally related to normal everyday situations (e.g., finances, making good impressions, safety of family), while thoughts associated with OCD are often senseless or irrational (e.g., if I don't do everything three times, my parents will die) [59, 60].

Tic disorders also commonly co-occur with OCD [15]. Simple tics, such as sniffing and throat clearing, can be easily distinguished from OCD due to their brief duration and involuntary nature [61]. Complex motor and phonic tics, however, can be difficult to separate from OCD-related compulsions [61, 62]. Individuals with complex tics often report experiencing premonitory urges prior to the tics [63] and as such are usually aware of when the tics are about to begin. However, tics and compulsions may be differentiated based on the function of the behaviors (tics to reduce unpleasant sensations and compulsions to reduce anxiety). In other words, tic behaviors are often provoked by physical urges or sensations while OCD-related behaviors occur in response to anxiety, distress, or fear. As a result, children with tics will often report that resisting these sensations will cause physical discomfort, whereas those with OCD may indicate that refraining from compulsions will result in increased anxiety and/or a feared consequence.

Obsessions and compulsive behaviors are also hallmark traits of individuals with anorexia nervosa. However, in anorexia nervosa, these thoughts and behaviors are constrained to content regarding food, diet, exercise, weight, and appearance [64, 65]. Individuals with anorexia have markedly poor insight, and their behaviors are driven primarily by appearance and weight-oriented goals.

On the other hand, individuals with OCD may suffer from severe weight loss due to their OCD-related symptoms, but these cases are generally due to fears of eating certain types of food (i.e., "contaminated" foods) rather than fears of weight gain or concern regarding personal appearances [66].

Perseverative thoughts, fixated interests, and repetitive behaviors are commonly seen in children diagnosed with an autism spectrum disorder (ASD) [67, 68]. To determine whether these symptoms could be attributed to ASD or OCD, gathering information regarding the function of the behaviors is essential. Obsessive-compulsive behaviors are anxiety driven; the thoughts often cause distress, and the ritualistic behaviors are performed to avoid or decrease anxiety. In contrast, in ASD, behaviors, such as preoccupations with specific objects or interests, are considered rewarding. While parents may describe these interests as "obsessive," the function of these behaviors is unlikely related to the relief of anxiety. Similarly, ASD children engage in repetitive behaviors because they find it soothing or pleasurable [69].

Etiology

Biological

Neurobiological models have primarily implicated abnormalities in the corticothalamic striatal circuitry (CTSC) in OCD [70–72]. These circuits between the frontal lobe and basal ganglia are involved in both initiation and engagement of routine behavior, as well as emotional and motivational processes. These models cite deficits in the basal ganglia's ability to filter and inhibit cortical inputs [73, 74]. As abnormalities in the PFC can cause disruption in the ability to inhibit behaviors and thoughts, deficits within the CTSC may explain the presence of obsessions and ritualized behaviors in OCD [75–77]. Neurobiological models of OCD have been studied via neuropsychological assessment, structural imaging techniques such as computerized tomography (CT) and structural magnetic resonance imaging (MRI), and functional techniques such as positron emission tomography (PET), single positron emission computerized tomography (SPECT), and functional magnetic resonance imaging (fMRI) [72, 78–81]. Additionally, translational ablation studies suggest that lesions in the prefrontal cortex (PFC) of primates, which includes regions such as the anterior cingulate, have been shown to cause perseverative interference in behavioral performance [82].

Although the CTSC model of neuropathogenesis of OCD is better researched in adults, preliminary evidence derived from volumetric studies provides support for the involvement of CSTC in pediatric OCD. Pediatric OCD patients have shown neuroanatomical differences from healthy controls, such as decreased globus pallidus volumes and increased gray matter in the anterior cingulate gyrus [72, 83]. Rosenberg and Keshavan [72] also reported elevated volume in the anterior cingulate gyrus amongst youth with OCD. Gilbert et al. [84] found that drug-naïve pediatric OCD patients have increased thalamic volume relative to healthy controls. To lend further support for this model, there is evidence that thalamic volumes decrease after treatment in those with pediatric OCD [84]. Woolley et al. [81] found that while engaging in an inhibitory control task, youth with OCD showed decreased activations in the right orbitofrontal cortex, thalamus, and basal ganglia relative to healthy controls.

It is notable that while data across these methodologies is starting to converge, the exact pathogenesis of OCD in youth is not completely understood. This is in part due to small sample sizes, lack of replication across studies, and wide variability of neuropsychological tests administered in the context of functional assessments. Further, specifics of treatment studies that examine cortical and subcortical changes vary considerably with mixed results [74, 84, 85].

The neuroanatomical literature is also supported by complementary findings regarding neurochemical function in individuals with OCD. Neurochemical abnormalities in the serotonergic system

have been cited as possible mediators of obsessive-compulsive symptom expression [74, 84, 86]. The strongest support for this theory is based on the efficacy of selective serotonin reuptake inhibitors (SSRIs) and clomipramine in OCD treatment. Amongst those with OCD, SSRIs and clomipramine have been found to modulate serotonin neurotransmission within the frontal cortex and thalamocortical circuits as well as decrease orbitofrontal glucose metabolism and thalamic volumes [84, 86]. Abnormalities within the glutamate and dopaminergic systems have also been associated with the pathophysiology of OCD [87]. Specifically, children and adolescents with OCD have shown not only reduced glutamate levels in the anterior cingulate [88], but also, glutamate antagonists, such as riluzole, have been shown to be efficacious in reducing OCD symptoms [89]. In regard to dopaminergic systems, abnormal dopamine-binding patterns in the caudate and putamen have been identified in adults with OCD [88, 90, 91]. Additionally, atypical antipsychotics have been successful in reducing OCD symptoms in treatment-resistant adults [92].

Cognitive Behavioral

Behavioral perspectives regarding the etiology and maintenance of OCD are based on a two-factor model where the fears are first acquired through classical conditioning (an aversive association is made with an otherwise neutral stimulus) [93, 94] and maintained through operant conditioning (negative reinforcement) [95]. Exposure to the feared stimuli (physical objects and/or distressful thoughts) causes an increase in anxiety or distress, and the rituals/behaviors serve to prevent or neutralize the negative emotions thus maintaining the ritual via negative reinforcement. Likewise, because the association between the neutral stimulus and the perceived feared consequence is preserved, extinction of the classically conditioned fear is not achieved. Faulty cognitions, such as intrusive thoughts, inflated sense of responsibility, distorted interpretations, and pathological doubt, are highlighted in cognitive models of OCD [96]. These faulty cognitions exacerbate the initial distressing worries and propel the compulsive and/or avoidance behaviors [96, 97]. Cognitive models may have reduced relevance in the treatment of pediatric OCD given poor insight [23, 24]; thus, behavioral (exposure-based) models are emphasized [98].

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus

Coined by Swedo et al. [99], PANDAS refers to the acute onset and progression of neuropsychiatric symptoms, including obsessions/compulsions and tics putatively resulting from an autoimmune response following exposure to the Group A β (beta)-hemolytic streptococcus (GAS). Inflammation of the basal ganglia, caused by the GAS autoimmune response, is hypothesized to mediate PANDAS-related OCD symptoms and associated neurological abnormalities [100–102] in a mechanism similar to the pathophysiology of rheumatic fever and Sydenham's chorea. Putative diagnosis of PANDAS-onset OCD requires prepubertal, abrupt onset of OCD (and/or tic) symptoms, episodic or sawtooth progression and severity of symptoms, temporal association with GAS, and neurological abnormalities (e.g., choreiform movements, hyperactivity, abnormal movements). Not uncommon are reports of emotional lability, sudden deterioration of motor functioning, neurocognitive abnormalities, stuttering, and enuresis. Like other psychiatric diagnoses, there are no laboratory tests for PANDAS, and the diagnosis is made by expert clinician review.

Notably, there has been some debate regarding the impact of infection-mediated immunoresponse on the pathogenesis of neuropsychiatric symptoms such as OCD and tics. Although more empirical studies are needed, Murphy et al. provide a comprehensive review, including debate within this emerging area [100].

Assessment

Various factors may complicate the presentation of OCD in children and adolescents. It is not uncommon for children to be secretive and unwilling to report embarrassing thoughts or compulsions [103]. Some children (particularly younger children) may be unable to verbalize their obsessions or be aware of the link between their cognitions and behaviors. Additionally, parents may be unable to properly identify OCD symptoms. For example, family members may mistake OCD-related tantrums to be acts of oppositional behavior, while clinicians can generally differentiate between the two. Given these factors, as well as the presence of reduced insight, symptom heterogeneity, and comorbidity, a multimethod and multi-informant assessment approach is necessary for an accurate diagnosis [104]. The following measures are focused on OCD-specific assessments. Broad-based assessment instruments are covered in Chap. 12.

Clinician-Rated Measures

Assessment and evaluation of obsessive-compulsive symptom severity is essential to monitor and track treatment progress. The Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) [105] is a 10-item, semi-structured, clinician-administered interview. Considered the gold-standard measure for OCD severity, the interview provides a comprehensive checklist of commonly endorsed obsessions and compulsions, which are rated individually based on frequency, distress, efforts to resist, perceived control, and interference. Ratings are then combined to provide a composite severity score.

As family accommodation occurs frequently in pediatric OCD, it is important to measure the presence, frequency, and severity of the accommodating behaviors. The Family Accommodation Scale (FAS) [106] is a brief clinician-rated measure that provides a composite score that is reflective of the degree to which family members have accommodated their child's behavior over the past month.

Parent- and Self-report Measures

Parent- and self-report measures are time- and cost-efficient methods that can supplement clinician assessment. They are easy to score and interpret and can be used to obtain specific, detailed information regarding the nature of the child's obsessive-compulsive symptoms and associated impairment. For identifying *specific OCD symptom types* that the individual may display (i.e., ascertaining specific OCD obsessions and compulsions the child may have), the Obsessive Compulsive Inventory-Child Version (OCI-CV) [107] and the Children's Florida Obsessive Compulsive Inventory (CFOCI) [13] may be appropriate tools. The CFOCI also assesses OCD symptom severity. The OCI-CV total score and subscale scores have demonstrated strong internal consistency, test-retest reliability, and treatment sensitivity [107]. The CFOCI has shown good construct and discriminant validity, as well as acceptable internal consistency [13]. To measure *OCD functional impairment* (e.g., impairment in school, home, family), the Child OCD Impact Scale-Revised, Parent and Child Reports, (COIS-RP, COIS-RC) [3] can be utilized. The COIS-RP and COIS-RC have demonstrated good internal consistency, test-retest reliability, and concurrent validity. For a self-report assay of *OCD symptom severity*, the Children's Obsessional Compulsive Inventory (ChOCI) can be administered [108]. The ChOCI has shown good internal consistency and criterion and convergent validity [108]. Notably, to obtain a comprehensive OCD assessment, it is recommended to include an assessment of symptom types, severity, and impairment, which requires the administration of multiple measures.

Treatment

Currently there are two well-established treatment modalities for pediatric OCD: pharmacotherapy using SSRIs and cognitive behavioral therapy (CBT) with exposure and response prevention (E/RP). Both treatment methods, as well as their combination, have demonstrated efficacy in a number of methodically sound research trials [54, 109–119]. Studies looking at direct comparisons between SSRIs and CBT have found that CBT monotherapy and combination CBT + SSRI are superior to SSRI monotherapy [54, 116]. Indeed, practice parameters suggest that CBT alone should be used as a first-line treatment for mild to moderate cases and combination CBT + SSRI for severe cases [98].

Pharmacotherapy

There are four medications that carry Federal Drug Administration (FDA) indications for use in pediatric OCD (see Table 1). Clomipramine, a tricyclic antidepressant, is approved for those 10 years old and older (dosages from 50–200 mg). Table 1 provides the ages and dose ranges for the three SSRIs approved for use for pediatric OCD (sertraline, fluoxetine, fluvoxamine). To date, citalopram and escitalopram are not FDA approved for pediatric OCD.

All four medications have produced modest but positive results for the treatment of pediatric OCD. Clomipramine, once considered the frontline pharmacological approach for OCD, has demonstrated treatment efficacy in a number of randomized-controlled trials in adults and youth. A recent meta-analysis summarizing these studies indicated that clomipramine was superior to SSRIs in the reduction of obsessive-compulsive symptoms in children [120]; nevertheless, clomipramine is not considered a first choice pharmacotherapy due to the side effect profile and risks associated with clomipramine, such as anticholinergic, anti-adrenergic, and anti-histaminergic responses (e.g., dry mouth, constipation, dizziness, sweating) [98, 117], as well as medical monitoring of heart rate and blood pressure irregularities [109]. Recent practice parameters for the treatment of childhood OCD published by the American Academy of Child and Adolescent Psychiatry (AACAP) outline baseline evaluation (including general pediatric examination and system review and assessment of personal and family history), precautions, and contraindications associated with the use of clomipramine in children [98]. Please refer to the practice parameters for specific recommendations concerning clomipramine and other SRIs. Due to these concerns, clomipramine should be prescribed with caution. See Table 1 for randomized-controlled trials of clomipramine.

More recently, the utilization of SSRIs for pediatric OCD has received significant attention. Fluoxetine is the most studied SSRI for pediatric OCD and has been tested in three positive randomized-controlled

Table 1 Controlled pharmacotherapy trials for FDA-approved medications for pediatric obsessive-compulsive disorder

Medication	FDA-approved ages	Studies	Dose ranges	Treatment response rates[a]
Fluoxetine	7 years and up	Liebowitz et al. [114] Geller et al. [111]	20–80 mg/day	55–57 %
Fluvoxamine	8 years and up	Riddle et al. [115]	50–200 mg	42 %
Sertraline	6 years and up	POTS [54] March et al. [121]	25–200 mg	42–53 %
Clomipramine	10 years and up	DeVeaugh-Geiss et al. [118] Flament et al. [117]	50–200 mg	60–75 %

[a]Response rates based off of multiple outcomes (e.g., CY-BOCS, Clinical Global Impressions-Severity)

trials. In a 13-week, double-blind, placebo-controlled trial ($n=103$; ages 7–17 years), Geller et al. [111] found that fluoxetine demonstrated superior efficacy in reducing obsessive-compulsive symptoms relative to placebo with 49 % of the fluoxetine group and 25 % of the placebo group deemed treatment responders. Similarly, Liebowitz et al. [114] conducted a 16-week, placebo-controlled trial ($n=43$; ages 6–18 years) and found significantly reduced obsessive-compulsive symptoms for those who received fluoxetine as opposed to placebo; 57 % of the fluoxetine group was considered treatment responders relative to 27 % of the placebo group. Fluvoxamine was demonstrated superior to placebo in a 10-week randomized, placebo-controlled trial ($n=120$, ages 8–17 years), with treatment response rates of 42 % for fluvoxamine and 26 % for placebo [115].

Finally, research also supports the use of sertraline in the treatment of pediatric OCD. March et al. [121], in a 12-week, double-blind, placebo-controlled trial ($n=187$, ages 6–17 years), found that sertraline was significantly more efficacious in reducing obsessive-compulsive symptoms relative to placebo with treatment response rates of 42 % for sertraline and 26 % for placebo. Similarly, a multicenter, double-blind, placebo-controlled trial ($n=112$, ages 7–17 years) found that sertraline combined with CBT-enhanced treatment outcome was superior in reducing OCD symptoms relative to sertraline alone [54].

Several SSRIs that have not been FDA approved have also been shown to be efficacious treatments for pediatric OCD. Geller et al. [122] reported that paroxetine, in a 10-week, double-blind, placebo-controlled trial ($n=203$, ages 7–17 years), significantly reduced obsessive-compulsive symptoms, relative to the placebo group. Obsessive-compulsive symptoms were also significantly decreased in an 8-week open-label trial of citalopram ($n=15$, ages 6–17 years) [123]. Although paroxetine and citalopram have shown evidence for reducing symptoms in pediatric OCD, due to the stronger efficacy and safety data available for sertraline and fluoxetine, some caution use of these non-FDA-approved drugs.

Across trials, SSRIs were well-tolerated with low rates of discontinuation due to adverse events. Although generally considered safe, SSRIs have been the focus of attention regarding "behavioral activation syndrome," which is the stimulation or increase in suicidal thoughts or behaviors as a side effect of SSRI initiation or dosage increase [124]. Behavioral activation symptoms can include a worsening of symptoms, increased hyperactivity, impulsivity, talkativeness, or irritability [125–127]. These symptoms have been shown to occur in approximately 3 % of children and adolescents following initiation or change in SSRI treatment [128]. These concerns have lead to the FDA-mandated "black box" warning labels to remind physicians and patients to carefully monitor SSRI-related side effects.

Although SSRIs have been shown to be efficacious in the treatment of pediatric OCD, complete symptom remission occurs infrequently, and up to 42 % of individuals fail to respond to treatment [129]. For these children, additional pharmacotherapy interventions may be utilized such as atypical antipsychotic augmentation of SSRIs. These atypical antipsychotics are prescribed off-label and largely rely on the modest results shown in adult OCD populations. To date, no controlled pharmacological studies utilizing atypical antipsychotics in pediatric OCD have been reported; rather, the literature consists of several case studies and open-label trials. For example, Thomsen [130] conducted an open-label trial of 1–2 mg of risperidone-augmented SSRIs with medication-resistant adolescents and young adults ($n=17$, ages 15–19 years) and found significant reductions in obsessive-compulsive symptoms posttreatment. Similarly, Masi et al. [131] found in an open-label study ($n=39$, ages 12–18 years) that 5–20 mg of aripiprazole augmentation of SSRIs was successful in reducing obsessive-compulsive symptoms in medication-resistant cases, producing a treatment response rate of 59 %. Although the use of atypical antipsychotics in refractory cases seem promising, the lack of supporting efficacy data and the high frequency of associated side effects (e.g., significant weight gain) [132] suggest that further research in this area is warranted.

Cognitive Behavioral Therapy

CBT for pediatric OCD consists of three main components: psychoeducation, E/RP, and cognitive training. The first session(s) is focused on psychoeducation and rapport building. Next, a fear hierarchy is created where the child and parents list anxiety-provoking stimuli and rank them from lowest to highest degree of fear. Third is the core element of CBT for pediatric OCD, namely, E/RP. During exposure sessions, children are systematically exposed to the feared stimuli outlined in the fear hierarchy. Children gradually move from low-anxiety exposures to high-anxiety exposures, all the while refraining from engagement in compulsions or rituals. Exposure and response prevention is based on the notion that fear extinction can be facilitated through extended and repeated exposures to feared stimuli. Once a child consistently habituates (i.e., experiences elevated distress at the beginning of the exposure and eventually experiences substantial decreases in distress at the end of the exposure), the therapist moves on to the next feared stimuli on the hierarchy. Generalization is common; even stimuli initially perceived to be extremely anxiety-provoking are often manageable following mastery of E/RP with lower-level stimuli during the course of treatment.

During treatment, cognitive strategies may be employed when developmentally appropriate (usually in older children, adolescents, and sometimes bright younger children). Youth are taught to counter maladaptive cognitive thoughts via cognitive restructuring and constructive self-talk. Cognitive restructuring teaches children to challenge the validity of their obsessions by developing alternative explanations for the thoughts. By doing this, the value/importance placed on the obsessions should putatively decrease, thereby reducing the distress associated with the thoughts (i.e., shrinking the meaning associated with a given intrusive thought). For younger children, coping phrases ("I can say 'NO' to OCD!") can be helpful in competing against problematic intrusive thoughts that may emerge ("My OCD controls me and I can't do anything about it"). However, therapists should use caution when employing self-talk and other cognitive techniques, making sure the child is not substituting self-talk and phrases provided in therapy in the place of their rituals (i.e., ritual replacement).

Treatment for pediatric OCD often occurs within the context of the family, even when a specific family-based intervention is not implemented. As previously noted, children and adolescents with OCD frequently involve family members in their obsessive-compulsive symptoms; family members often aid by enabling avoidance of feared stimuli or facilitating the actual compulsions (e.g., washing contaminated clothes, providing reassurance). Additionally, children and adolescents are substantially embedded within the family unit and are therefore subjected to a number of variables outside of their control (e.g., marital dysfunction, family dynamics) and are dependent on their families for support. Because of this, individual therapy for pediatric OCD is not indicated without substantial parental support, and structured family-based interventions have been implemented in a number of CBT efficacy studies.

Although CBT with E/RP has been identified as an efficacious and advantageous method of treatment, there are a number of factors that may impede treatment response (for review, see Storch et al. [133]). Variables that are associated with poor treatment outcome include lack of insight and motivation, expectancy factors, increased family accommodation, and the presence of comorbid disorders. Clinically, limited insight poses to be problematic, as oftentimes individuals who are less aware of their symptoms do not attempt to resist or control their obsessions or behaviors. Indeed, children with poor insight have been found to have greater impairment, increased OCD symptom severity, family accommodation, and depressive symptoms [23, 57]. Similarly, treatment expectancy and motivation have been shown to be strong predictors of treatment outcome. Parent and child's expectations regarding treatment are associated with OCD symptom reduction as well as treatment adherence [134].

As previously noted, family accommodation occurs frequently in pediatric OCD [22]. Although family members participate in rituals (e.g., providing reassurance, opening doors, washing clothes) to reduce the child's anxiety or anger, family accommodation is related to increased familial stress and functional impairment [21]. The presence of comorbid disorders, particularly disruptive disorders,

Table 2 Controlled psychotherapy trials for pediatric obsessive-compulsive disorder

Randomized-controlled trials	Intervention	Duration	Treatment response rates[a]
Barrett et al. [112]	CBT with E/RP-based individual family therapy vs. group family therapy	14 weeks	Individual family = group family
Storch et al. [113]	Family-based CBT with E/RP intensive (daily) vs. weekly sessions	Intensive: daily for 3 weeks Weekly: 14 weeks	Intensive = weekly
Piacentini et al. [110]	Family-based CBT (FCBT) with E/RP vs. psychoeducation plus relaxation (PRT)	14 weeks—12 sessions	FCBT > PRT
POTS [54]	CBT with E/RP vs. SSRI vs. combination CBT + SSRI	12 weeks	Combination CBT + SSRI > CBT = SSRI > placebo
Asbahr et al. [119]	Group CBT vs. sertraline	12 weeks	Group CBT = sertraline
de Haan et al. [116]	CBT vs. clomipramine	12 weeks	CBT > clomipramine

[a]Response based upon multiple outcomes (e.g., CY-BOCS, CGI-Severity, CGI-Improvement)

can lead to attenuated treatment response [56]. Indeed, Storch et al. [57] found that the presence of comorbid externalizing disorders (ADHD, oppositional defiant disorder, etc.) was related to lower remission rates.

CBT for pediatric OCD has demonstrated robust treatment response rates with studies showing that up to 90 % of children and adolescents respond to treatment (See Table 2 for an overview of CBT efficacy trials). These studies have shown efficacy of CBT in comparison to wait lists as well as other types of psychotherapy. For example, Piacentini et al. [110] reported in a 14-week, randomized-controlled study ($n = 71$, 8–17 years) that family-based CBT was superior in decreasing obsessive-compulsive symptoms compared to individual psychoeducation/relaxation training [110]. The manual detailing this treatment is commercially available [135]. Similarly, Barrett et al. [112] compared the efficacy of individual family-based CBT and group family-based CBT in a 14-week randomized, wait-list controlled trial ($n = 77$, ages 7–17 years) and found that both groups produced significant decreases in obsessive-compulsive symptoms relative to wait-list controls with treatment response rates of 61 % (individual CBT) and 65 % (group CBT). In a 12-session pilot study of 5- to-8-year-olds with OCD ($n = 42$), family CBT was superior to family-based relaxation therapy (for the completer sample but not the intent-to-treat sample) [136]. Among completers, remission was achieved in 69 % of youth receiving CBT but only 20 % receiving relaxation therapy.

Few studies have compared efficacy rates between CBT and pharmacotherapy treatment. A recent meta-analysis of randomized-controlled trials for pediatric OCD identified an effect size of 1.45 for CBT and 0.48 for pharmacotherapy [137]. The POTS trial (Pediatric OCD Treatment Study) [54], the largest study of its kind, compared sertraline alone, CBT alone, and combination sertraline and CBT. Although all three groups showed significant decreases in obsessive-compulsive symptoms relative to the placebo group, those who received CBT alone and combination CBT and sertraline showed the greatest reductions in symptoms with effect sizes of 0.96 and 1.4, respectively (note: reductions in CY-BOCS symptoms did not differ statistically between the CBT alone and sertraline alone groups). Remission rates were fair with 39 % for CBT alone, 21 % for sertraline alone, and 56.3 % for combination CBT and sertraline. Notably, there was a group by site interaction, with youth receiving CBT at the site directing CBT for the trial doing better than youth receiving CBT at the site directing pharmacotherapy. The POTS II trial followed up the initial study in a sample of SSRI treatment-refractory patients by comparing SSRI management alone, SSRI management with CBT instructions provided by a physician, and SSRI management with CBT [138]. When compared to SSRI management alone, SSRI management with CBT had greater decreases in symptoms than SSRI management with CBT instructions (effect size of 0.85 and 0.16, respectively). It is important to note, however, that the CBT instructions condition did not include contact with a therapist trained in CBT for OCD. A limitation of the POTS II trial is that youth who did not respond to community SSRI treatment were recruited as

opposed to prospectively examining SSRI partial-responders/nonresponders following a study-initiated course of medication. Consequently, there is likely marked heterogeneity in subjects prior to randomization, obfuscating interpretation of the results. In an older study, DeHaan et al. [116] reported a statistically significant advantage for CBT with an effect size of 1.58 (66 % response rate) for intensive CBT and 1.45 (50 % response rate) for clomipramine in a 12-week trial with 22 youth ages 8–18. Based on these few comparative efficacy trials, CBT has emerged as the most-often recommended initial first-line treatment for youth with mild to moderate OCD [139, 140].

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus

Prophylactics, such as penicillin and azithromycin, have been examined as novel treatment methods for PANDAS subtype of OCD and/or tic disorder [102, 141, 142]. Garvey et al. [142] found in an 8-month, double-blind, placebo-controlled, crossover study of penicillin that penicillin was not significantly better at decreasing neuropsychiatric symptom exacerbation relative to the placebo group. In contrast, Snider et al. [141] reported that in a double-blind, randomized, controlled study of penicillin and azithromycin ($n=23$, ages 5–9), neuropsychiatric symptom exacerbations decreased significantly for both prophylactics. It is important to note that the use of antibiotic prophylactics for the treatment of PANDAS-subtype OCD and/or immunoglobulin therapy (IVIG) is an experimental treatment that should be discussed in consultation with an expert in pediatric psychoneuroimmunology. No data suggest the benefit of surgical approaches to abate or prevent symptoms (e.g., tonsillectomy/adenoidectomy). Behavioral treatment for PANDAS-subtype OCD is the same for non-PANDAS OCD and is the only recommended intervention without specialty consultation [143].

Novel Treatments

To target the sizable minority that remain either unresponsive or relapse following treatment, research has begun to focus on novel treatment methods. D-Cycloserine (DCS) is an *N*-methyl-D-aspartate (NMDA) partial agonist that has been shown to enhance learning and facilitate fear extinction [144–146] and has been examined as an adjunctive agent to CBT. Storch et al. [147] conducted a double-blind, placebo-controlled treatment trial ($n=30$; ages 8–17 years) in youth with a primary diagnosis with OCD. Results showed that those who received DCS + CBT had greater improvements at posttreatment relative to those who received placebo + CBT, suggesting that DCS + CBT may enhance fear extinction in children with OCD. Riluzole, a glutamate antagonist, has been examined as a possible treatment method for treatment-resistant youth [89]. In a 12-week open-label trial ($n=6$; ages 8–16 years), Grant et al. [89] found that 4 out of 6 youth experienced substantial reductions in OCD symptoms. Notably, no practice decisions should be based on a six-subject open trial.

Storch et al. [113] examined the efficacy of intensive (daily sessions for 3 weeks) vs. weekly (once per week for 14 weeks) family sessions for the treatment of pediatric OCD ($n=40$, ages 7–17 years) and found no differences between the two groups at posttreatment. Treatment response rates were robust for both intensive and weekly sessions: 90 % and 65 %, respectively. Unfortunately, limited access to highly trained providers makes E/RP inaccessible for many youth. Web-camera-based CBT methods have been investigated as a means for treatment dissemination. In a preliminary study, Storch et al. [148] found in a randomized, wait-list controlled study ($n=31$; ages 7–17 years) that web-camera-based CBT was superior in decreasing OCD symptoms relative to the wait-list group.

Case Follow-up

Zoe and her family participated in 12 weekly sessions of CBT with E/RP, focusing exposure on her contamination fears and prevention of her washing rituals. In session, exposures began with Zoe holding contaminated objects that she rated as producing distress levels of a 4 (on a scale of 0–10). Once she habituated to these items (provided a distress rating of 0 or 1), increasingly more difficult exposures were practiced. For example, contaminated items that she habituated to previously were now placed together to increase the level of contamination. She held these items in her hands and rubbed them along her arms and legs to enhance her anxiety and increase the difficulty level of the exposure. During these sessions she was instructed to refrain from washing her hands for the rest of the day. Between sessions, she was to practice E/RP by going into rooms that her father frequented (his bedroom, office) and to sit in the rooms until she habituated to her anxiety. After five sessions of E/RP, Zoe reported that she was ready for exposures that would cause her higher levels of distress (ratings of 8–10). In session, she practiced exposures by tossing a contaminated ball back and forth with her father. Once she habituated to the anxiety, she moved on to touching her father's arm for several minutes. By the following session, Zoe was able to hug her father with limited distress and anxiety. By the 12th session, Zoe reported an improved ability to manage her contamination fears and washing, as well as an overall decrease in anxiety. Her parents reported an increased understanding on how to react to Zoe's obsessive-compulsive symptoms and how to refrain from accommodating her symptoms. Both Zoe and her parents noted understanding on how to intervene in the future should the obsessive-compulsive symptoms reemerge.

Conclusions

OCD in children and adolescents is an impairing neuropsychiatric syndrome that, if untreated, can persist into adulthood and contribute to marked disability. Fortunately, efficacious treatments are available. Exposure and response prevention has emerged as the leading empirically supported behavioral treatment for pediatric OCD. Studies emphasizing these behavioral approaches within a family-based context appear to have more robust outcomes. Although pharmacotherapy is a more readily available efficacious treatment method than CBT, remission rates for SSRIs are lower than for CBT with E/RP, and the potential for adverse events is higher. Additionally, a substantial minority do not respond to CBT and/or pharmacotherapy. Consequently, current research seeks to better understand factors that facilitate and expedite treatment, so that increasingly individually targeted and cost-effective CBT can be disseminated. The field has already begun to examine innovative methods of treatment dissemination in children and adolescents, such as computer-administered (via web camera) E/RP [148]. However, further investigation into these novel treatment delivery options is warranted.

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Posttraumatic Stress Disorder in Children and Adolescents

Damion J. Grasso and Joan Kaufman

Abstract Roughly half of children and adolescents exposed to significant trauma develop PTSD, yet in many at-risk populations in which trauma exposure is known, PTSD is frequently under diagnosed. Most reliable identification of PTSD involves assessment of trauma exposure information and symptomatology from multiple informants. Over the past two decades, tremendous strides have been made in the assessment and behavioral treatment of PTSD in children and adolescents. More work, however, is needed to determine optimal pharmacological intervention strategies, as well as integrative treatment approaches that can address the wide range of challenges faced by families of children with PTSD. This chapter reviews the diagnostic history of PTSD, epidemiological data, state-of-the-art assessment instruments and techniques, risk factors, evidence-based treatments, and promising practices and innovations. An illustrative case example is also presented to highlight various aspects and challenges in the diagnosis and treatment of childhood PTSD.

Keywords Posttraumatic stress disorder • Acute stress disorder • Trauma exposure • Child maltreatment • Trauma-focused therapy

Case Scenario

Jovan is a 12-year-old boy, whose family has an extensive history with child protective services (CPS) involving ongoing intimate partner violence (IPV), sexual abuse of Jovan's half sister, and physical and emotional abuse of Jovan and his half brothers. In response to the most recent incident, when Jovan's stepfather stabbed his mother in the leg with a kitchen knife, CPS referred the children to a community-based outpatient treatment program. Jovan was assessed for trauma-related problems using a standard child- and parent-report measure of posttraumatic stress disorder (PTSD), as well as a more thorough semi-structured diagnostic interview. Jovan reported frequent nightmares about being chased by his stepfather, difficulty concentrating, feeling like he is on "high alert," and trying hard to avoid thinking about the abuse and family violence. The assessment indicated that trauma-focused clinical interventions would be appropriate. While Jovan's mother acknowledged some of the

D.J. Grasso
University of Connecticut Health Center, 263 Farmington Avenue, Farmington, CT 06030, USA

J. Kaufman (✉)
Yale University School of Medicine, 301 Cedar Street, PO Box 208098, New Haven, CT 06520, USA
e-mail: joan.kaufman@yale.edu

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violence, she minimized its severity and was unaware of the full extent of Jovan and his sibling's PTSD symptoms. She was initially resistant to participating in clinical interventions because she was torn between her alliance and dependence on her husband and her wish to "do right" by her children. In addition, Jovan's younger brothers completely denied the violence.

Description of the Disorder

PTSD is one of the few disorders defined in the current DSM-IV [1] with an etiology directly linked to a specific precipitating event. Physical and sexual abuse, as well as intrafamilial violence, are the most common traumatic events associated with childhood PTSD [2, 3]. Other common traumas experienced by children include natural disasters, automobile accidents, witnessing community violence, or experiencing the sudden and violent death of a loved one. By 16 years of age, most children (i.e., 67.8 % in a nationally represented survey) have been exposed to at least one traumatic event, although only a small proportion of traumatized children will develop PTSD [4].

PTSD is a relatively young diagnosis. Diagnostic criteria were not introduced until 1980, with the publication of the DSM-III [5]. In 1987, in response to new data suggesting that symptoms and distress were normative after traumatic events [6], minimum duration criteria requiring symptoms be present for at least 30 days were added to the diagnosis of PTSD [7]. This revision, however, created a dilemma such that the diagnosis of adjustment disorder was the only possible diagnosis for appreciably impairing symptomatology in the first month after significant traumas [6]. Thus, acute stress disorder (ASD) was born and included in the DSM-IV [1]. A diagnosis of ASD requires the presentation of symptoms for a minimum of 2 days and a maximum of 4 weeks posttrauma, upon which a diagnosis of PTSD would be given. An immediate diagnosis of ASD, however, is not required to meet criteria for PTSD. A diagnosis of PTSD can be specified as acute onset (symptoms begin less than 3 months after trauma), chronic (symptoms last more than 3 months), or delayed onset (symptoms emerge 6 months after trauma).

Table 1 contains the DSM-V proposed diagnostic criteria for ASD and PTSD in adults and young children (American Psychiatric Association, http://www.dsm5.org). It is noted in the following text where DSM-IV-TR and the DSM-V proposed criteria differ.

Criterion A

In DSM-IV-TR, criterion A is comprised of two parts. Criterion A1 specifies that "The person has experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others" [1]. In the proposed DSM-V, criterion A1 is changed to limit the range of experiences that qualify as relevant for the diagnosis of PTSD. This change also applies to ASD. Second, as noted in the table, the DSM-IV criterion A2, "the person's response involved intense fear, helplessness, or horror" (p. 467) [1], was eliminated from the proposed DSM-V criteria for both ASD and PTSD as it was found to have no clinical utility [8].

Criterion B (Reexperiencing)

DSM-IV defines reexperiencing symptoms as including distressing images or thoughts about the event, nightmares, dissociative episodes, physiological distress in response to reminders of the event,

Table 1 Proposed DSM-V criteria for acute stress disorder and posttraumatic stress disorder

Acute stress disorder	Posttraumatic stress disorder
A. The person was exposed to one or more of the following events: death or threatened death, actual or threatened serious injury, or actual or threatened sexual violation in one or more of the following ways: (1) Experienced the event(s) him/herself (2) Witnessing, in person, the event(s) as they occurred to others (3) Learning that the event(s) occurred to a close relative or close friend. In such cases, the actual or threatened death must have been violent or accidental (4) Experiencing repeated or extreme exposure to aversive details of the event(s) (e.g., first responders collecting body parts; police officers the event(s) (e.g., first responders collecting body parts; police officers repeatedly exposed to details of child abuse). This does not apply to exposure through electronic media, television, movies or pictures, unless this exposure is work-related	**A. The person was exposed to one or more of the following events: death or threatened death, actual or threatened serious injury, or actual or threatened sexual violation in one or more of the following ways:** (1) Experienced the event(s) him/herself (2) Witnessing, in person, the event(s) as they occurred to others (3) Learning that the event(s) occurred to a close relative or close friend. In such cases, the actual or threatened death must have been violent or accidental (4) Experiencing repeated or extreme exposure to aversive details of the event(s) (e.g., first responders collecting body parts; police officers repeatedly exposed to details of child abuse). This does not apply to exposure through electronic media, television, movies or pictures, unless this exposure is work-related
Note: DSM-IV criterion A2 has no clinical utility	**Note:** DSM-IV criterion A2 has no clinical utility
B. Eight (or more) of the following symptoms are present that were not present prior to the traumatic event or have worsened since	**B. Intrusive symptoms that are associated with the traumatic event(s) [that began after the traumatic event(s)], as evidenced by one or more of the following:**
B1. Intrusion symptoms	
(1) Spontaneous or cued recurrent, involuntary, and intrusive distressing memories of the traumatic event(s)	(1) Spontaneous or cued recurrent, involuntary, and intrusive distressing memories of the traumatic event(s). **Note:** In children, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed
(2) Recurrent distressing dreams in which the content and/or affect of the dream is related to the traumatic event(s)	(2) Recurrent distressing dreams in which the content and/or affect of the dream is related to the traumatic event. **Note:** In children, there may be frightening dreams without recognizable content
(3) Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event was recurring	(3) Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event was recurring. Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings. **Note:** In children, trauma-specific reenactment may occur in play
(4) Intense or prolonged psychological distress or physiological reactivity at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s)	(4) Intense or prolonged psychological distress or physiological reactivity at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s)
B2. Dissociative symptoms	
(5) A subjective sense of numbing, detachment from others, or reduced responsiveness to events that would normally elicit an emotional response	(5) Marked physiological reactions to reminders of traumatic event(s)
(6) An altered sense of the reality of one's surroundings or oneself (e.g., seeing oneself from another's perspective, being in a daze, time slowing	

(continued)

Table 1 (continued)

Acute stress disorder	Posttraumatic stress disorder
(7) Inability to remember at least one important aspect of the traumatic event (typically dissociative amnesia; not due to head injury, alcohol, or drugs	
Note: Reworded to make criterions more applicable across cultures	
B3. Avoidance symptoms	
(8) Persistent and effortful avoidance of thoughts, conversations, or feelings that arouse recollections of the traumatic event	
(9) Persistent and effortful avoidance of activities, places, or physical reminders that arouse recollections of the traumatic event	
B4. Arousal symptoms	
(10) Sleep disturbance (e.g., difficulty falling or staying asleep)	
(11) Hypervigilance	
(12) Irritable or aggressive behavior	
(13) Exaggerated startle response	
(14) Agitation or restlessness	
Note: Data suggest that acute posttraumatic reactions may be varied and need not necessarily include dissociative or other DSM-IV ASD symptom clusters. Reorganization and rewording address this issue	
C. The disturbance causes clinically significant distress or impairment in social, occupational, or other areas of functioning	**C. Persistent avoidance of stimuli associated with the traumatic event(s) [that began after the traumatic event(s)], as evidenced by one or more of the following:**
	(1) Avoids internal reminders (e.g., thoughts, feelings, physical sensations) that arouse recollections of the traumatic event(s)
	(2) Avoids external reminders (e.g., people, places, conversations, activities, objects, situations) that arouse recollections of the traumatic event(s)
D. Duration of the disturbance (symptoms in criterion B) is 3 days to 1 month after the traumatic event	**D. Negative alterations in cognitions and mood that are associated with the traumatic event(s) [that began or worsened after the traumatic event(s)], as evidenced by three or more (Note: two or more in children) of the following:**
Note: Altered from minimum of 2–3 days to reduce false positives	(1) Inability to remember an important aspect of the traumatic event(s) (typically dissociative amnesia; not due to head injury, alcohol, or drugs)
	(2) Persistent and exaggerated negative expectations about one's self others, or the world (e.g., "I am bad," "No one can be trusted," " I've lost my soul forever," "My whole nervous system is permanently ruined," "The world is completely dangerous")
	(3) Persistent distorted blame of self or others about the cause or consequences of the traumatic event(s)
	(4) Pervasive negative emotional state (e.g., fear, horror, anger, guilt shame)

(continued)

Table 1 (continued)

Acute stress disorder	Posttraumatic stress disorder
	(5) Markedly diminished interest or participation in significant activities (6) Feeling of detachment or estrangement from others (7) Persistent inability to experience positive emotion (e.g., unable to have loving feelings, psychic numbing)
E. The disturbance is not due to the direct physiological effects of a substance (e.g., medication or alcohol) or a general medical condition (e.g., traumatic brain injury, coma), and the symptoms are not restricted to those of brief psychotic disorder: (1) Irritable or aggressive behavior (2) Reckless or self-destructive behavior (3) Hypervigilance (4) Exaggerated startle response (5) Problems with concentration (6) Sleep disturbance (e.g., difficulty falling or staying asleep)	**E. Alterations in arousal and reactivity that are associated with the traumatic event(s) [that began or worsened after the traumatic event(s)], as evidenced by three or more (Note: two or more in children) of the following:**
F. Duration of the disturbance (symptoms in criteria B, C, D, and E) is more than 1 month	
G. The disturbance causes clinically significant distress or impairment in social, occupational, or other areas of functioning	
H. The disturbance is not due to the direct physiological effects of a substance (e.g., medication or alcohol) or a general medical condition (e.g., traumatic brain injury, coma)	

and in young children, trauma-specific play or reenactment. These largely remain intact in the proposed DSM-V. As noted in Table 1, there are a number of qualifications to the criteria for children in order to account for developmental differences in the presentation of PTSD symptoms. For example, recurrent thoughts may be evident in children, not only through verbal report, but also in play themes, e.g., a child who was sexually abused may play out scenes with sexually explicit material or may 'hump' his/her stuffed animal. A child who was physically abused may use toys to depict a parent character hurting a child character, or may hit and shout at a peer while repeating the same things a parent said to him when he was abused. Reliving the trauma can also manifest as trauma-specific reenactment in children, which might emerge, for example, as a sexually abused child initiating sexual advances towards other children or toward an adult. In addition, in children, nightmares need not specifically relate to the traumatic event to contribute towards the intrusion cluster.

Criterion C (Avoidance)

DSM-IV avoidance symptoms include deliberate efforts to avoid activities, places, or people that elicit memories of the event and avoidance of thoughts or feelings related to the event, as well as several numbing symptoms (e.g., detachment, anhedonia). As result of several confirmatory factor analytic studies [9–11], DSM-V proposes to divide avoidance symptoms into two separate clusters:

one comprised of the avoidance symptoms noted above and one including the numbing symptoms and newly proposed negative alterations in mood and cognition symptoms (e.g., a child who blames himself for not stopping the IPV). For ASD, dissociative symptoms are essentially unchanged in the proposed DSM-V criteria.

Criterion D (Hyperarousal)

Hyperarousal symptoms include sleep difficulties, irritability, concentration problems, hypervigilance, and exaggerated startle. In DSM-V, aggressive, reckless, and self-destructive behavior symptoms are also included in this category. Agitation and restlessness are new symptoms included in this cluster of symptoms for ASD.

Proposed DSM-V Criteria for Preschool Children

It is only within the past decade that the diagnosis of PTSD has been applied to infants and toddlers. Scheeringa and colleagues [12–15] have proposed new specific criteria for diagnosing PTSD in preschool children. These criteria are comprised of the same four core symptom clusters used to diagnose PTSD in older children and adults; however, items that require reports of subjective experiences were eliminated from the alternate criteria for preschoolers (e.g., foreshortened sense of future), and all remaining items were behaviorally anchored (e.g., feelings of detachment operationalized as socially withdrawn behavior). In the studies by Scheeringa and colleagues [14] examining the utility of the DSM-IV PTSD criteria with preschool children, the avoidance/numbing cluster was the set of symptoms least frequently endorsed in the very young children. Only 2 % of highly traumatized preschool children endorsed sufficient DSM-IV PTSD avoidance/numbing symptoms (e.g., three symptoms). Limiting the number of avoidance symptoms to only one resulted in approximately one-quarter of the highly traumatized children in their studies meeting diagnostic criteria for PTSD, a rate comparable to that reported in other traumatized samples of older children. Therefore, only one avoidance symptom is required for the diagnosis of PTSD in preschool children in the proposed DSM-V criteria. Sheeringa and colleagues also examined a cluster of symptoms assessing loss of previously acquired skills (e.g., toilet training), new-onset separation anxiety, and new onset of fears unrelated to the trauma, but these were not retained in the proposed DSM-V PTSD criteria for preschool children because they did not add to the diagnostic utility. However, Scheeringa and colleagues have suggested that these symptoms may be useful in dimensional assessment tools of PTSD for purposes of predicting treatment outcome, as they were among the most common symptoms observed in young children across their studies [12–15].

Prevalence

Results from large epidemiological surveys of psychiatric disorders in children and adolescents indicate that the prevalence of PTSD in the normal population ranges from 0.4 % to 3 % [4, 16]. This percentage is lower than the 6–8 % of United States adults estimated to have lifetime PTSD [17, 18]. As in the adult literature [17, 19–21], the majority of studies report that PTSD is about two times more prevalent in girls than boys (e.g., 3.7 % boys and 6.3 % girls in the National Survey of Adolescents)

[3, 22–26]. Some, but not all studies [27], have reported higher rates of PTSD in black [3, 16] and in Hispanic [3] adolescents compared to white adolescents. This may be a reflection of the greater tendency for minorities to possess other risk factors associated with PTSD (e.g., violence exposure, low socioeconomic status) [28].

Estimates of PTSD in certain populations of children are much higher than those in the general population. In a number of small-scale studies of children receiving child welfare services, 26–67 % met criteria for PTSD [29–37]. Prevalence estimates of PTSD in youth involved with the juvenile justice system range from 4.8 % to 48.9 % [38–40]. Rates ranging from 18.4 % to 33.3 % are reported in psychiatrically hospitalized samples of children [41–43]. In homeless youth, more than 80 % were found to have been physically or sexually assaulted, and 8.3–17.7 % met criteria for PTSD [44, 45]. These ranges are quite large, particularly for youth involved with the juvenile justice system. Most of the studies reporting higher rates of PTSD involved evaluators who were familiar with the participants' trauma histories prior to assessing PTSD symptoms, employed multiple methods (e.g., self-, parent, and teacher report and semi-structured interview), and utilized multiple sources (e.g., child, parent, caseworker, CPS records) to identify trauma exposure and symptoms (see Diagnosis and Assessment Section below for discussion of how these issues affect the diagnosis of PTSD).

Psychiatric Comorbidity and Differential Diagnosis

Approximately three-quarters of adults with PTSD experience one or more comorbid lifetime diagnoses, among which 37–48 % report a lifetime history of major depression [17, 46, 47]. In one-half to three-quarters of all cases, the onset of PTSD is primary. The risk for major depressive disorder (MDD) following PTSD is about the same as the risk of MDD following any other anxiety disorder and 30–40 % more likely in individuals with a history of a preexisting anxiety disorder [47]. Numerous studies also report increased risk of suicidal ideation in individuals with PTSD [48, 49]. PTSD is also highly comorbid with alcohol and substance use disorders in adolescents and adults [17, 50–52], In addition, a large national survey of 4,023 adolescents revealed a positive association between number of trauma exposures and comorbidity of PTSD with MDD and substance use disorders [52].

The diagnosis of PTSD shares numerous symptoms with multiple other common child psychiatric diagnoses. Determining the presence of PTSD and potential comorbid diagnoses requires careful assessment of the developmental timing of the onset of symptoms, the pattern of problem behaviors, the severity of difficulties across different settings, and the association of problem behaviors with trauma triggers.

PTSD and MDD have four symptoms in common, including anhedonia, insomnia, irritability, and concentration disturbance. For the diagnosis of PTSD to be given, there must be at least one intrusion symptom (e.g., flashbacks, nightmares), a cardinal feature of the disorder. For comorbid MDD to be diagnosed, beyond symptoms that overlap with the diagnosis of PTSD, there should be at least one symptom that is uniquely associated with MDD (e.g., depressed mood, suicidality).

Irritability is a very nonspecific symptom associated with many of the major child psychiatric diagnoses including mania and oppositional defiant disorder (ODD). Most symptoms of ODD involve some expression of irritability, but for a comorbid ODD diagnosis to be given, there should be evidence of a persistent pattern of defiance (i.e., actively defies or refuses to comply with adults' requests or rules). While there is general agreement that irritability is a universal feature of childhood mania, whether irritability should be characterized as episodic or chronic is highly debated [53]. In PTSD, irritability is frequently worse when the child is exposed to trauma triggers and less evident in non-emotionally charged environments. The child may also display an eagerness to please adults, which would be inconsistent with a comorbid diagnosis of ODD.

Concentration problems are part of the criteria for PTSD, mania and attention deficit hyperactivity disorder (ADHD). Concentration problems associated with ADHD and mania must have been present in childhood and exhibit a chronic course that is generally worse in a school setting. The problems are unlikely related to ADHD or mania if they emerged after the trauma and are worse at home or when exposed to trauma triggers.

Sleep disturbance is another symptom shared by PTSD and several child diagnoses. While both PTSD and mania are associated with sleep disturbances, decreased need for sleep is the cardinal feature of mania, and nightmares and insomnia (e.g., wanting to sleep, but not being able to) are the sine qua non of PTSD.

In PTSD, dissociative reactions may include hallucinations, which is a primary symptom of psychotic disorders. Visual, auditory, or tactile hallucinations have been reported to occur in 9 % of maltreated children recruited from juvenile court or pediatric clinics [54], 20 % of child sexual abuse victims on psychiatric inpatient units [55], and 75–98 % of abused children who meet criteria for a dissociative disorder [56]. These are characterized by a disruption in functions of memory, consciousness, and perception of self and one's environment [57]. Differentiating between PTSD, MDD or bipolar disorder with psychotic features, and a primary psychotic disorder has extremely important treatment implications. A number of distinctive features of psychotic-like symptoms in traumatized children facilitate this differential diagnosis. For example, hallucinations in maltreated children are frequently trauma related (e.g., hearing the perpetrator's voice), are often nocturnal [58], and frequently resolve with psychotherapeutic intervention and safety reassurances [56]. In addition, the presence of hallucinations in traumatized children is not typically associated with other psychotic symptoms that would suggest schizophrenia or another primary psychotic diagnosis. They are less likely to be associated with negative symptoms (e.g., withdrawn behavior, blunted affect) or abnormal early development as would be typical in childhood-onset schizophrenia [59]. Hallucinations in traumatized children tend to be associated with impulsive, aggressive, and self-injurious behavior, nightmares, and trancelike states and less likely to be associated with evidence of formal thought disorder [60].

Course

Studies examining the trajectory of PTSD symptoms have identified children and adolescents who present a persistent, chronic course, as well as those who appear more resilient. One study examined PTSD symptom course over 3–4 years in 125 German children with partial or full PTSD and who were part of a larger epidemiological study [61]. About a quarter of the youth in the sample presented with a chronic course, meeting criteria for PTSD at follow-up, while about half showed symptom remission, and approximately 4 % had subthreshold symptoms at baseline that worsened [61]. Symptom chronicity was predicted by exposure to new trauma between baseline and follow-up [61]. Another study examined latent class trajectories of PTSD symptoms in 201 children referred to the Navy's Family Advocacy Program due to parental sexual or physical abuse or witnessing IPV [62]. Two latent class trajectories were identified: a resilient class and a persistent symptom class comprised of older youth who reported exposure to a greater number of trauma experiences [62]. A more recent study reported similar findings in a sample of 190 children with a history of traumatic injury [63]. The authors followed these children 6–16 years post-injury and identified three distinct subtypes: children with low symptoms at both time points (57 %), children with elevated symptoms at baseline who recovered by follow-up (33 %), and children with persistent symptoms (10 %) [63]. Children in the chronic group were more likely to have had a serious injury, and younger children tended to be in the recovery group [63].

Etiology and Prognosis

The likelihood of individuals developing PTSD and its prognosis are influenced by four primary factors: genetic factors, biological factors, the nature of the trauma, and posttrauma factors. [64] Each are described in turn.

Trauma Characteristics

Beyond inherent factors, trauma factors are among the best replicated predictors of PTSD onset, severity, and persistence. These factors include unexpectedness [65], chronicity [66, 67], emotional and physical proximity to traumatic event [68, 69], and when applicable, severity of sexual [70] and physical assault [71]. Another robust predictor of PTSD is the number of types of traumas experienced. Specifically, research indicates a robust positive linear relationship between PTSD and exposure to multiple types of trauma, which has been coined poly-victimization by Finkelhor and colleagues [72]. Interestingly, experiencing multiple types of trauma is more predictive of symptom severity than is repeated exposure to the same trauma [73, 74], which suggests a mechanism that has less to do with chronicity and more to do with the cumulative burden of experiencing multiple types of trauma. Further, poly-victimization is associated with less tractable and more treatment resistant PTSD [75], as well as comorbid MDD and substance use disorders [76].

Posttrauma Factors

Factors in the posttrauma environment contribute most in determining the likelihood of PTSD becoming chronic. The absence of social supports and exposure to ongoing psychosocial adversity are the most potent predictors of PTSD chronicity [68, 69, 77]. Low parental support and a hostile and coercive parenting style, as perceived by children, is a positive predictor of PTSD severity [78]. Moreover, the presence of comorbid mood and substance use disorders is associated with worse prognosis and greater psychosocial impairment [79].

Parents' responses to their children's trauma experiences also appear to influence children's development of PTSD. In one study, greater parental distress to their children's accidental injury positively predicted children's subsequent development of PTSD [80]. In another study, maternal posttraumatic stress 6 weeks after their children's traumatic injury predicted more severe posttraumatic stress in children 7 months later [81]. Parent distress has also been found to precede more severe PTSD in children who have experienced terrorism [82]. In another study, parenting stress partially mediated the positive relationship between family violence exposure and posttraumatic stress in young children [83].

Cognitive factors posttrauma also appear to play a role in the development of PTSD. In one study, distorted cognitions (i.e., appraising reexperiencing symptoms as dangerous) and maladaptive cognitive coping strategies (i.e., avoidance-focused) assessed 2 weeks after an accident predicted greater PTSD severity 3–6 months later [84]. Others have found higher rates of PTSD in youth who report higher levels of thought suppression [85, 86] and greater negative self-attributions pertaining to the trauma [87, 88] immediately following the traumatic event.

Genetic Risk

Genetic risk can be ascertained via family studies, twin studies, and molecular genetic studies, each with unique contributions and limitations. Family studies have shown that the prevalence of PTSD is higher in relatives of probands with PTSD than in the relatives of trauma-exposed individuals without PTSD [89, 90]. Family studies, however, are limited in that they cannot differentiate whether the familial transmission of PTSD is due to genetic or environmental factors (e.g., adverse impact of living with a psychiatrically ill parent). Twin studies have revealed three key findings: (1) a so-called gene-environment correlation showing that genetic factors account for approximately 20 % of risk of exposure to assaultive traumatic events, but not non-assaultive negative life events [91, 92]; (2) genetic factors account for approximately 25–40 % of the variance in predicting onset of PTSD following trauma, statistically accounting for the influence of genetics on the probability of trauma exposure [93]; and (3) common genetic influences may contribute to the comorbidity of PTSD with other psychiatric disorders including MDD, generalized anxiety disorder (GAD), panic disorder, and alcohol and substance use disorders [93].

Unlike twin studies, molecular genetic studies can help to identify specific genetic markers of PTSD risk. Cornelis, Nugent, Amstadter, and Koenen [94] recently published a review of candidate gene association studies, identifying a total of 30 associated with the development of PTSD, 18 of which have focused on genes in the dopaminergic and serotonergic systems. Genes involved in brain development (e.g., BDNF) and stress reactivity (e.g., FKBP5) have also been implicated in the etiology of PTSD [94]. Few studies have replicated these findings; data from existing studies suggest that genes only account for a small portion of the variance in the development of PTSD. Evolving work in this area is beginning to examine gene–gene interactions, epigenetic measures, gene-behavior associations, and other relevant endophenotypes.

Neurobiological Correlates

Considerable more work has been conducted on the neurobiology of PTSD in adults than in that of children. Emerging research findings suggest the neural circuits implicated in PTSD are related to the neural circuits underlying fear conditioning [95–98]. Key brain structures involved in the fear conditioning circuit include the amygdala, hippocampus, anterior cingulate cortex (ACC), and ventromedial prefrontal cortex [99]. Fear-potentiated startle paradigms have been used to examine fear conditioning in patients with PTSD [100]. In a recent study [101], children with PTSD were found to have elevated startle reflexes, even after effective trauma-focused treatment, suggesting that abnormalities in the fear circuit may persist after symptom recovery.

Several meta-analyses have been published summarizing structural [102] and functional [103] magnetic resonance imaging (MRI) findings in adult patients with PTSD. These findings show that when compared to healthy controls, adult patients with PTSD have reduced hippocampal [102, 104, 105] and ACC [102] volumes. Findings of amygdala volumes in patients with PTSD have been mixed [102, 104], but functional data indicate increased amygdala activation during fear conditioning and emotion processing tasks in patients with PTSD compared to control participants with potential trauma exposure but without PTSD [106]. Patients with PTSD were also reported to have hypoactivation in the dorsal and rostral ACC and ventromedial prefrontal cortex [106].

Some brain findings in children are different from adults and suggest that there may be developmental differences in the neurocircuitry underlying PTSD. In terms of hippocampal findings, children and adolescents fail to show evidence of hippocampal atrophy in contrast to the findings in adults [102, 104]. One possibility is that genetic predispositions combined with early trauma and resultant effects on neural and endocrine activity interact to influence volumetric changes later in life [102].

In a recent fMRI study [107], however, children with PTSD were found to have reduced hippocampal activation during the retrieval component of a verbal declarative memory task compared to trauma-exposed children without PTSD. While far fewer studies have examined potential amygdala volume differences in children with and without PTSD, a meta-analysis [104], indicating a small effect, reported reduced total amygdala volumes in children with PTSD compared to non-traumatized children. Children with PTSD have also been found to have decreased prefrontal cortical volumes [108, 109] and reduced ACC N-acetylaspartate to creatine ratio, a marker of neuronal integrity, a finding that is also present in adults [110]. No studies to date, however, have examined fear conditioning circuitry explicitly in juvenile populations.

In addition to these neuroimaging changes, one study reports that children with PTSD have reduced medial and caudal corpus callosum area [111], and another study shows reduced fractional anisotropy, a measure of axon integrity, in this region of the corpus callosum [112]. This region contains interhemispheric projections from brain structures involved in circuits that mediate the processing of emotional stimuli and various memory functions—core disturbances associated with PTSD.

Assessment

Assessment of Trauma Exposure

Prior to assessing PTSD symptoms, an examiner must inventory a child's history of trauma exposure, a process that is often complicated by informant discrepancies. Consequently, relying exclusively on one informant to obtain information about trauma exposure increases the risk of failed detection. In Jovan's case discussed at the opening of this chapter, the evaluator obtained discrepant reports of IPV—with Jovan's half brothers completely denying these experiences. If the evaluator failed to incorporate other family members' accounts of the violence, the children's violence exposure may have been missed and PTSD not assessed.

Several reasons underlie informant discrepancies. A child's denial of trauma exposure may stem from active avoidance symptoms, a hallmark feature of PTSD, which allows the child to suppress feelings of shame, guilt, or distress that often accompany child abuse [48]. The denial may also reflect efforts to stymie CPS from filing an abuse or neglect report against a parent, taking custody of the child, or delaying family reunification. A parent may likewise underreport her child's trauma exposure in an attempt to prevent associated feelings of distress, shame or guilt, or to distance herself from details that trigger recall of her own traumatic past. A parent who is involved with the child welfare system may fear attracting unwanted scrutiny from CPS. Many parents of youth involved in juvenile justice have limited awareness of their children's trauma experiences, as supervision and monitoring are often lacking [113]. Additionally, foster or adoptive parents may simply lack critical information about the traumatic lives of the children that are committed to their care.

Given the limited reliability of the parent and child, a report of past trauma necessitates the examination of other sources when they exist. In fact, data from a study of 116 children in CPS revealed that assessors would have failed to detect 40 % of sexually abused children, 30 % of physically abused children, and 16 % of children who witnessed IPV if they had relied solely on parent and child report without access to child protective service records [32]. In these cases, PTSD symptoms would not ordinarily have been surveyed, and the diagnosis of PTSD would have been missed. Child and parent report did, however, contribute unique information. Of the various types of maltreatment, parents were most likely to report incidents of IPV and occasionally reported incidents of physical and sexual abuse that occurred in the past when the family was living in another state that their caseworkers were unaware of. These data highlight the importance of clinicians obtaining information from multiple

sources (e.g., CPS, children, parents, teachers) when making psychiatric diagnoses and delineating treatment plans for traumatized children.

As reviewed elsewhere [114, 115] and delineated in Table 2 [116–145], several instruments are available to survey trauma exposure in children and adolescents. Most of the standard semi-structured and structured child psychiatric diagnostic interviews include a survey of a variety of criterion A traumas. However, specialized measures are also available. For example, the Traumatic Events Screening Inventory (TESI) [146] and Violence Exposure Scales (VEX-R) [126] assess a wide variety of childhood traumas, and both have caregiver and child-report versions. The Child Trauma Questionnaire (CTQ) [116] provides an excellent assessment of a range of maltreatment experiences. One of the most comprehensive self-report instruments to date is the Juvenile Victimization Questionnaire (JVQ) [118], which surveys a total of 34 specific incidents of child victimization. More detailed measures of IPV can be obtained with the Revised Conflict Tactics Scale (CTS2) [125] or the Partner Violence Inventory (PVI) [147], and lastly, reliable methods have also been developed to extract and rate severity of maltreatment experiences from case records [148] and to integrate trauma data from multiple informants [149, 150].

Assessment of PTSD Symptoms

Obtaining trauma history information prior to assessing symptomatology in children permits clinicians to further query children and adolescents who deny traumatic experiences that have been substantiated by parent or caseworker report. For example, consider what the evaluator of Jovan's sister might have said if she had denied sexual abuse despite the evaluator's prior knowledge:

> You're doing such a great job. Now I wonder if you can answer some questions about something else your caseworker told me about. Your caseworker told me about the time your stepfather undressed you and touched your private sexual body parts when you were 9 years old. I don't need you to explain that to me, but I wonder if you can think about when your stepfather touched you while answering the next questions.

This method of questioning allows the child a means to endorse possible PTSD symptoms without having to detail the traumatic event, which is not something a child is expected to master before receiving treatment. Furthermore, if children are particularly reticent to talk, a clinician might begin by asking the more benign hyperarousal items (e.g., sleep difficulties, concentration problems, irritability), progress to asking about avoidance/numbing/negative mood symptoms, and then query about the more stress provoking reexperiencing items. The fact that the child initially denied the sexual abuse experiences is sufficient to warrant positive rating of the avoidance item required for the diagnosis of PTSD.

Similar to obtaining trauma exposure information, the assessment of PTSD symptomatology is also best achieved with the use of data from multiple informants. Children are the best reporters of cognitive and emotional symptoms [151]. Children are also frequently the best to report nightmares and sleeping difficulties [152]. In addition, parents and other adults who spend time with the child are good reporters of externalizing behavior problems such as anger outbursts, concentration problems, and sexual acting out [151]. If children are living in foster care or with other guardians who do not know them well, obtaining adjunctive information from birth parents and/or schoolteachers can be enormously helpful. However, parents and caregivers are notoriously poor at identifying internalizing (e.g., depression, anxiety) symptoms [151]. In fact, one study found that parent report of their children's traumatic stress was more highly correlated with parents' self-report of traumatic stress than it was with their children's self-reported symptoms [78].

Several reviews have identified a number of valid and reliable DSM-IV-based measures for the assessment of trauma symptomatology in school-aged children [114, 115, 146]. There is only one

Table 2 Standardized measures to assess trauma exposure, acute stress, and posttraumatic stress disorder in children

Measure	Format	Age group	Cost and contact information
Trauma exposure			
Childhood Trauma Questionnaire [116]	Self-report	12–18	Cost, psychcorp.com
History of Victimization Form [117]	Self-report	7–18	Free, vicky.wolfe@lhsc.on.ca
Juvenile Victimization Questionnaire [118]	Self-report	7–18	Free, unh.edu/ccrc/juvenile_victimization_questionnaire.html
Lifetime Incidence of Traumatic Events [119]	Self-/parent report	8+	Cost, sidran.org
Traumatic Events Screening Inventory [120]	Self-/parent report or interview	6–18	Free, ncptsd@ncptsd.org
Abuse and neglect			
Checklist for Child Abuse Evaluation [121]	Interview	7–18	Cost, parinc.com
Child Abuse and Neglect Interview [122]	Interview	7–18	Free, robert.ammerman@chmcc.org
Sexual abuse			
Child Sexual Behavior Inventory [123]	Parent report	2–12	Cost, parinc.com
Community violence			
Survey of Children's Exposure to Community Violence [124]	Parent report	6–10	Free, jrichter@nih.gov
Domestic violence			
Revised Conflict Tactics Scale [125]	Parent report	NA	Cost, wpspublish.com
Violence Exposure Scales [126]	Self-/parent report	4–10	Free, fox@umd.edu
Acute stress disorder			
Acute Stress Checklist for Children [127]	Self-report	8–17	Free, nikaphd@mail.med.upenn.edu
Posttraumatic stress and trauma-related symptomatology			
Adolescent Dissociative Experience Survey [128]	Self-report	11–18	Shipping, jarmstrong@mizar.usc.edu
Adolescent Self-Report Trauma Questionnaire [129]	Self-report	12–21	Free, smweine@ulc.edu
Angie/Andy Cartoon Trauma Scales [130]	Self-report	6–12	Cost, mhs.com
Child Dissociative Checklist [131]	Parent report	5–12	Free, frank.putnam@chmcc.org
Child PTSD Symptom Scale [132]	Self-report	8–18	Free, foa@mail.med.upenn.edu
Childhood PTSD Interview (Child and Parent Versions) [133]	Interview	7–18	Free, kenneth.fletcher@umassmed.edu
Children's PTSD Inventory [134]	Interview	7–18	Cost, psychcorp.com
Clinician-Administered PTSD Scale for Children and Adolescents [135]	Interview	7–18	Free, ncptsd@ncptsd.org
Computer-Administered Screen for Traumatic Stress PTSD Reaction Index for DSM-IV [136]	Computer-administered self-report	10–18	Shipping, dgrasso@psych.udel.edu
Darryl's Cartoon-Based Measure of Community-Violence Related PTSD [137]	Interview	6–10	Free, pg27@drexel.edu
Feelings and Emotions Experienced During Sexual Abuse [117]	Self-report	7–18	Free, vicky.wolfe@lhsc.on.ca
Levonn's Cartoon-Based Interview for Assessing Children's Distress [138]	Interview	6–10	Free, jrichter@nih.com
Parent Report of Posttraumatic Symptoms [119]	Interview	6–18	Cost, sidran.org

(continued)

Table 2 (continued)

Measure	Format	Age group	Cost and contact information
Pediatric Emotional Distress Scale [139]	Parent report	2–10	Free, conway.saylor@citadel.edu
Sexual Abuse Fear Evaluation [140]	Self-report	7–18	Free, vicky.wolfe@lhsc.on.ca
Trauma Symptom Checklist for Children [141]	Self-/parent report	13–16	Cost, parinc.com
Trauma Symptom Checklist for Young Children [142]	Parent report	3–12	Cost, parinc.com
UCLA PTSD Reaction Index for DSM-IV [143]	Self-/parent report	7–18	Free, Hfinley@mednet.ucla.edu
Weekly Behavior Report [144]	Parent report	<7	Free, jcohen1@wpahs.org
When Bad Things Happen Scale [145]	Self-report	10–20	Free, kenneth.fletcher@umassmed.edu

measure that specifically assesses ASD symptomatology, the 29-item Acute Stress Checklist for Children (ASC-Kids) [127]. This measure has been validated with children aged 8–17 years, is available in English and Spanish, and has an advantage over other PTSD symptom scales in assessing ASD since it surveys the full range of dissociative symptoms required for the diagnosis of ASD. There are multiple well-validated scales to assess PTSD symptomatology. These include the University of California Posttraumatic Stress Disorder Reaction Index (UCLA PTSD RI) [143], the Clinician-Administered PTSD Scale for Children and Adolescents (CAPS-CA) [135], the Trauma Symptom Checklist for Children (TSCC) [153], Levonn's Cartoon-Based Interview for Assessing Children's Distress [138], the Angie/Andy Cartoon Trauma Scales (ACTS) [130], and Darryl, a cartoon-based measure of community-violence-related PTSD in children and adolescents [137].

The UCLA PTSD RI is probably the most widely used instrument in the field; has parent- and child-report versions, as well as a nine-item abbreviated version [154]; and has validated clinical cutoffs suggestive of a probable PTSD diagnosis [155]. A computer-administered version of the UCLA PTSD RI has been developed by the Delaware Division of Prevention and Behavioral Health Services [156]. The Computer-Assisted-UCLA PTSD RI (CA-UCLA) is fully self-administered and utilizes written and spoken prompts. Unlike the paper version, the CA-UCLA specifically refers to the traumatic event when posing all questions that refer to the trauma. Particular strengths of this measure include the opportunity for youth to complete the screen in private using a laptop computer and headphones, and direct-care workers without assessment experience can more readily assess trauma exposure and PTSD.

The TSCC, Levonn, and ACTS are child self-report measures that were developed to assess a range of symptoms but are not to specifically diagnose PTSD. The Levonn and ACTS both have cartoon pictures that provide visual cues to help children understand the questions surveyed.

All of the structured and semi-structured research child diagnostic interviews also include items to assess PTSD symptomatology [157–160]. These interview schedules are comparably reliable in diagnosing PTSD. Given the differential diagnostic issues discussed previously, and the high rates of comorbidity between PTSD and other child psychiatric diagnoses, there is an advantage to using more inclusive psychiatric assessment measures when evaluating traumatized children.

Current measures of PTSD for young children (under age 6) are primarily caregiver report forms with little direct assessment of the child. Of the measures available for young children, the *Posttraumatic Stress Disorder Semi-Structured Interview and Observation Schedule* is the most comprehensive, developmentally appropriate, and well validated [115]. An additional measure for preschool children that is showing good early psychometric properties is the Preschool-Aged Psychiatric Assessment (PAPA) [161]. The PAPA is an interviewer-based, structured parental interview for the comprehensive assessment of mental health symptoms in children aged 2 through 5, which includes PTSD. The Trauma Symptoms Checklist for Young Children is also a good tool for

use with young children. It is a parent-report screening checklist that covers a broad range of symptoms, but is not meant as an independent assessment of the diagnosis of PTSD [162]. The Levonn cartoon interview was originally developed for preschoolers and has been used extensively with children this age [138].

Bearing in mind the wide range of reasonable assessment options, most critical is the use of standardized, psychometrically sound measures. Unfortunately, despite well-researched benefits and guidelines, most child health professionals do not use standardized screens for child mental health problems [163, 164]. Studies in large outpatient mental health clinics have found that unstructured interviewing underestimates the prevalence of PTSD in treatment seekers by a factor of two to seven [165]. A recent study examined diagnoses of PTSD derived from case records of children in a residential facility and those receiving outpatient treatment and compared the prevalence of PTSD in each of these groups with PTSD diagnosed via a comprehensive assessment of trauma exposure and PTSD symptoms [166]. Following a more comprehensive assessment, the authors reported a sixfold increase in PTSD prevalence in the outpatient agency and a 20-fold increase in PTSD prevalence in the residential facility [166].

Treatment

Several empirically validated treatments have been developed for children with PTSD. Central to the efficacy of each of these treatments is the importance of evaluating the child's current safety and exposure to ongoing risks, delineating strategies to minimize the impact of secondary stressors, working to strengthen and support the child's primary caregivers, and identifying trauma triggers in the environment that exacerbate clinical symptomatology (e.g., contact with the perpetrator, reminders around the home). A selection of available treatment strategies is described below.

Trauma-Focused Cognitive Behavioral Therapy

Trauma-Focused Cognitive Behavioral Therapy (TF-CBT) [167] is a 12-to-16-session intervention designed for children ages 3–18 years to reduce behavioral and emotional problems associated with child trauma exposure. During the initial phase of treatment, the therapist provides psychoeducation about trauma exposure and traumatic stress and teaches a variety of stress-reduction skills such as deep breathing, muscle-tension relaxation, emotion identification and regulation, and cognitive coping. Caregivers also receive education and guidance on effective parenting skills and behavior management. The core component of TF-CBT is implemented mid-treatment and involves development of a trauma narrative. The trauma narrative functions as a means of therapeutic exposure and facilitates emotional and cognitive processing of the event. The narrative involves identifying thoughts and feelings related to the event and correcting distorted beliefs or perceptions. After completion of the trauma narrative, the therapist helps prepare the child and caregiver to maintain future safety and healthy coping and initiates treatment termination. A focus on enhancing safety earlier rather than later in treatment may be indicated for children experiencing ongoing trauma exposure, such as community or domestic violence [168].

Clinical training on TF-CBT can be pursued via workshops conducted by certified trainers, a treatment manual, and a web-based training available at www.musc.edu/tfcbt. A link to ongoing web-based consultation is available following completion of the web-based training. Further, a clinical workbook developed by the Delaware Division of Prevention and Behavioral health Services and distributed to providers throughout the state has been designed to accompany the TF-CBT manual (electronic copies available on request) [169].

The efficacy of TF-CBT has been demonstrated in a number of randomized controlled trials and has been deemed "supported and efficacious" based on current standards [154]. Significantly greater improvements in PTSD, internalizing symptoms, dissociation, sexualized behavior, and social competence in sexually abused children have been observed in children who received TF-CBT compared to wait-list controls and child-centered therapies [170–178]. In one such study, 79 % of 89 sexually abused children (ages 8–14 years) who received TF-CBT no longer met criteria for PTSD posttreatment compared to only 54 % of 91 children who received client-centered therapy [172]. Moreover, therapeutic effects of TF-CBT are maintained over time [170, 175]. In one study, 41 children (ages 8–15 years) showed significantly greater improvement on a number of symptom measures at 6- and 12-month follow-up compared to 41 children who received nondirective therapy [170]. In a noncontrolled study, 100 sexually abused children receiving TF-CBT showed a 48 % reduction in symptoms from pre- to posttreatment [179], and the 64 children that followed-up 2 years later showed an additional 26 % reduction in symptoms [175]. Similar positive results were obtained in the treatment of children and adolescents with PTSD secondary to a single-incident trauma who were provided an alternate but conceptually similar model of CBT [180].

Deblinger and colleagues have recently established a variant of the standard 16-session treatment that is reduced to eight sessions. One rationale for this was to accommodate families at risk for dropping out of treatment [181]. The study was conducted with sexually abused children, 4–11 years of age. While both variants led to significant reductions in PTSD symptoms, children who received 16 versus eight sessions had significantly fewer reexperiencing and avoidance symptoms [181]. Similar results were found in a recent randomized controlled trial of eight-session TF-CBT for children exposed to IPV. TF-CBT was found to be superior to a standard, client-centered treatment as evidenced by 75 % remission in the TF-CBT group compared to 45 % remission in the comparison group [182]. The latter study also extends the evidence base on TF-CBT by demonstrating that it can be effective in reducing symptoms of PTSD secondary to nonsexual trauma, as the majority of efficacy studies have focused on childhood sexual abuse.

In addition to investigating the efficacy of the eight sessions compared to the 16-session treatment, Deblinger et al. [181] examined each version with and without inclusion of the trauma-narrative component and found noteworthy group differences. First, children in the 16-session and eight-session trauma-narrative versions showed a significantly greater reduction in abuse-related fear posttreatment than children in the nonnarrative versions. The authors interpreted these differences as reflecting the greater focus on habituation of trauma responses in the narrative versions and concluded that the shortened course of TF-CBT may be sufficient in reducing PTSD symptoms for some children [181]. Second, parents in the longer nonnarrative version reported greater improvements in parenting practices than those in the trauma-narrative version. Relatedly, children in both nonnarrative versions showed a greater reduction of externalizing behavior problems [181]. The authors interpreted these findings as reflecting the greater amount of time spent on parent education and behavior modification in the nonnarrative versions. This raises the question of whether the standard model could provide more in the way of managing externalizing behavior problems and parent education. Specifically, though the standard model touches upon behavior management skills, the nonnarrative course allows for expansion of topics pertaining to increasing positive parent–child interaction, reinforcing positive behavior, ignoring less severe behavior problems, being directive, and using consequences effectively [182]. Further, there is more time to implement exercises and role-play towards increasing parent and child competencies in these areas.

For children with co-occurring traumatic stress and significant behavior problems, Cohen et al. [183] suggest incorporating a functional behavioral analysis to determine the function of the behavior and to focus in on the problems most pertinent to the family. Although working with the parent to develop a problem list for managing and prioritizing the family's concerns is not a new concept [184], the practice is sometimes lost in more directive, evidence-based treatments with preselected standardized measures of symptoms and specific milestones already laid out. A recent study found that the

problem list, or top problems approach, as established with the parent and adolescent yielded client-driven priorities that were clinically relevant; corresponded to items on the Child Behavior Checklist and Youth Self-Report; and complemented these standardized measures by adding clinically relevant specificity [185].

There have been remarkable efforts to implement and test TF-CBT within community-based mental health systems. In a community-based benchmarking study, which is a noncontrolled effectiveness study that compares effect sizes to those achieved in efficacy studies, TF-CBT led to significant reductions in symptoms of PTSD and internalizing behavior problems in children ages 7–17 years exposed to a variety of trauma types and referred from child welfare, juvenile justice, crisis services, and other sources [186]. Bigfoot and Schmidt [187] developed and validated an adaptation of TF-CBT for American Indians and Alaska Natives, called Honoring Children, Mending the Circle (HC-MC), which blends traditional native teachings with the model components. Finally, De Arellano et al. [188] has modified office-based TF-CBT to be delivered as a community-based treatment, in or near the home, to help underserved populations who face significant barriers to treatment and over-represent families who drop out. The program is called the Community Outreach Program-Esperanzo (COPE), with a client base largely comprised of ethnic minorities and rural residents. The case example in the current chapter is based on a family that received COPE services.

Cognitive-Behavioral Therapy for Sexually Abused Preschool Children (CBT-SAP), which shares the main principles of TF-CBT, was designed by Cohen and Mannarino to accommodate younger children [178]. In a study of 77 sexually abused preschool children randomly assigned to CBT-SAP or nondirective supportive therapy (NST), children who received CBT-SAP showed significant reductions on a variety of parent-report measures, whereas children in the comparison group did not show significant change [178]. A follow-up of 43 of the children from this study revealed that children who had received CBT-SAP continued to show significant reductions in symptoms over the course of a year, while the NST group showed less change [177].

More recently, Scheeringa, Weems, Cohen, Amaya-Jackson, and Guthrie [189] adapted TF-CBT for children ages 3–6 years and tested it in a randomized controlled trial. This 12-session protocol was designed to implement developmentally appropriate components of TF-CBT including psychoeducation about PTSD, identification of feelings, coping skills, and exposure to trauma-related reminders using drawing, imaginal exposure, and in vivo exposures, as well as safety planning [189]. Parents participated in three conjoint sessions, observed all child sessions on a monitor in another room in order to simultaneously learn the material, and met with therapists individually. The manual and assessments used are available online at http://www.infantinstitute.com. The authors found that the TF-CBT group showed a greater reduction in PTSD symptoms than the wait-list control group post-treatment and at 6-month follow-up; however, the effects were not significant for symptoms of depression, separation anxiety, ODD, or ADHD [189]. The wait-list control group ultimately received treatment and combined with the treatment group, symptoms of depression, separation anxiety, and ODD showed significant reductions at the 6-month follow-up with large effect sizes.

Prolonged Exposure

Prolonged exposure (PE) [190], which has been highly effective for adult PTSD [191], has been modified for use with adolescents. PE is a manualized treatment, distinct from TF-CBT, consisting of nine to twelve sessions each lasting 90 min. Introductory sessions include psychoeducation about PTSD and treatment rationale. The remainder involves repeated imaginal exposure in-session and assignment of in vivo exposure to avoided trauma cues during the week. Adolescents (12–18 years) were randomly assigned to PE or dynamic therapy. Both groups showed decreased symptoms of PTSD and depression; however, PE resulted in the greatest reduction of symptoms, with approximately

two times as many youth no longer meeting criteria for PTSD posttreatment [192]. In addition, treatment gains were maintained at 6- and 17-month follow-ups. There is a manual available for using PE with adolescents [193]. Training in PE is conducted via intensive workshops that are listed on the Center for the Treatment and Study of Anxiety at the University of Pennsylvania (http://www.med.upenn.edu/ctsa/workshops_ptsd.html).

Relationship-Based Therapy

Another evidence-based treatment has emerged in recent years specifically for preschool children. *Child–parent psychotherapy* (CPP) [194] was developed to address the needs of preschool children exposed to family violence. It is a 52-week dyadic treatment. CPP integrates modalities derived from psychodynamic, attachment, trauma, cognitive-behavioral, and social learning theories. The parent–child relationship is used as a vehicle for improving the child's emotional, cognitive, and social functioning through a focus on safety, affect regulation, the joint construction of a trauma narrative, and engagement in developmentally appropriate goals and activities. CPP is based on the following premises:

(1) The attachment system is the main organizer of children's responses to danger and safety in the first years of life;
(2) Early mental health problems should be addressed in the context of the child's primary attachment relationships;
(3) Child outcomes emerge in the context of transactions between the child and environmental protective and risk factors;
(4) Interpersonal violence is a traumatic stressor with pathogenic repercussions on its witnesses as well as its recipients;
(5) The therapeutic relationship is a key mutative factor in early mental health treatment;
(6) Cultural values must be incorporated into treatment [194].

In a randomized controlled trial of CPP, 75 young children (ages 3–5 years) exposed to IPV and exhibiting parent-reported emotional and behavioral problems were randomly assigned to receive CPP or case management [195]. Results indicated significant reductions in both child and parent internalizing and externalizing symptoms posttreatment and at 6-month follow-up compared to standard treatment in the community [195]. A reanalysis of these data found that children who had four or more trauma experiences showed significantly greater improvement in PTSD symptoms, as well as internalizing and externalizing behavior problems, than children with fewer trauma experiences [196]. CPP has also been effective in improving attachment, parent–child relationship problems, and emotional and behavioral problems in children in randomized controlled trials [197, 198], although to date, it has not been tested with preschool children diagnosed with PTSD.

Group Therapy

Several models of group therapy have been developed for the treatment of PTSD. Most are based on CBT interventions. Multimodality Trauma Treatment (MMTT) [199] is an 18-week, manualized, group CBT intervention for children exposed to single event traumas. The treatment includes psychoeducation, exposure through trauma narratives, muscle relaxation, breathing exercises, interpersonal problem solving for anger control, development of positive self-talk, and relapse prevention. Evaluation of the treatment resulted in a 57 % reduction in the diagnosis of PTSD posttreatment and

an 86 % reduction at 6-month follow-up. Stein and colleagues [200] studied a shorter 10-session CBT group therapy for PTSD conducted within the school setting. Posttreatment assessments revealed an 86 % reduction in PTSD symptoms for those in the intervention group. These data suggest that group treatment can be an effective intervention for PTSD secondary to single event traumas.

There are also several school-based approaches. The structure, consistency, and potential support available at school make it an attractive place to implement group-based interventions. A recent review identified 16 studies, nine of which were randomized controlled trials [201]. Most had effect sizes ranging from medium to large in treating PTSD symptoms. The most rigorous of the studies were examining the efficacy of Cognitive Behavioral Intervention for Trauma in schools (CBITS) compared to either wait-list controls or office-based TF-CBT [201]. The latter comparison revealed a higher completion rate in the CBITS, relative to the TF-CBT condition: 91 % versus 15 %, respectively [202]. The authors attributed these findings to the familiarity and close proximity of schools to the families of the children [202]. The limitations of a school-based setting, however, prevent a more individual approach to treating PTSD (e.g., developing a trauma narrative), which may be necessary for the recovery of children with multiple trauma exposures and a more complex symptom presentation [201].

Finally, Trauma Affect Regulation: Guidelines for Education and Therapy for Adolescents and Pre-Adolescents (TARGET-A) is a versatile four to twelve-session group intervention designed to treat symptoms of posttraumatic stress in youth with substance use disorders and co-occurring trauma symptoms secondary to interpersonal victimization [203]. Key components include developing self- and affect-regulation skills, interpersonal problem solving, stress management, and social information processing. In a randomized controlled trial, TARGET was equivalent to a trauma-informed outpatient addiction treatment in reducing posttraumatic stress, depression, generalized anxiety, and substance use but was superior in sustaining sobriety self-efficacy [204]. TARGET has also been successfully implemented and examined in a number of juvenile justice facilities and other youth agencies; however, data are not yet available for report.

Preventative Approaches

The Child and Family Traumatic Stress Intervention (CFTSI) is a secondary prevention program for trauma-exposed youth, ages 7–17 years, at risk of developing PTSD. CFTSI is a 4-session intervention provided to children and parents with the goal of optimizing social and family support and coping skills shortly after trauma exposure. Specific objectives are to (1) provide psychoeducation about the effects of trauma and common trauma symptoms; (2) improve child and parent communication about feelings, symptoms, behaviors, and in turn, increase parent support of the child; and (3) to facilitate development of skills to cope with symptoms, including guided imagery, thought stopping, and distraction techniques [205]. In a randomized pilot study, 53 youth were assigned to CFTSI and 53 to a supportive comparison condition. Children who received CFTSI had fewer full and partial PTSD diagnoses and greater reduction in posttraumatic stress and generalized anxiety than the comparison group at the 3-month follow-up [205].

Integrative Approaches

Consistent with the notion that childhood victimization and adversity do not exist in isolation [206], treatment providers must look beyond the referral problem and consider aspects of the family or community environment that may be maintaining the problem or compromising effective treatment.

Identifying and conceptualizing the multifarious challenges faced by families inform patient engagement strategies [207], as well as the treatment approach; however, most manualized treatments are not designed to accommodate many of the coexisting problems faced by families of victimized children. For example, parental substance abuse, mental health problems, and IPV are common problems in families of children involved in child welfare [208, 209] and juvenile justice [210].

There are few interventions that aim to address both childhood PTSD and parent behavior/symptoms. Multisystemic Therapy for Child Abuse and Neglect (MST-CAN) is a hybrid of traditional MST designed for physically abused children and their families. Like traditional MST, treatment is delivered in multiple contexts including home, school, and community and at rates between two and five times per week depending on the family's needs. A comprehensive assessment of strengths and needs of the child and systems in the family's social ecology informs treatment planning. MST-CAN differs from the traditional model in that it involves establishing a safety plan based on a functional analysis of physical abuse incidents, works primarily with CPS rather than juvenile justice, and incorporates a clarification process in which the parent accepts responsibility for the abuse and apologizes to the child and family [211]. MST-CAN also provides several cognitive-behavioral interventions to address problems, as needed, including anger management, conflict resolution, and prolonged exposure therapy [212] for parents presenting with PTSD symptoms [211]. A randomized effectiveness trial of MST-CAN compared to enhanced outpatient treatment demonstrated a greater reduction in PTSD symptoms and internalizing behavior problems, as well as parent psychiatric distress, neglectful and physically abusive behavior, and significant improvements in social support [211].

MST-CAN has been further adapted to address parental substance abuse by incorporating Reinforcement-Based Treatment (RBT) [213, 214]. Untreated parental substance abuse has been associated with more severe childhood PTSD, MDD, substance dependence [215], juvenile delinquency [216], as well as longer out-of-home placements for children and reduced likelihood of successful family reunification [217]. Addressing both parental substance abuse and child maltreatment concurrently minimizes the placement of children in out-of-home care, while their parents undergo substance abuse treatment, which has been standard practice [214]. The feasibility of this model, referred to as Building Stronger Families (BSF), has been examined in a 4-year implementation study conducted in Connecticut and yielded a 93 % successful completion rate as indicated by sustained sobriety, stable mental health, permanent placement of children, and reliable housing [214]. Additional data have not yet been published.

Other opportunities for integrative treatments include combining trauma-focused treatment for childhood PTSD with interventions to address children's exposure to IPV [218]. One published effort described comparisons among a 10-week group treatment program for children exposed to IPV, a 10-week program offering child and parent group sessions, and a wait-list control group [219]. While assessment and treatment of child PTSD symptoms was not reported, the child and parent group program produced a greater reduction of child externalizing symptoms than the child-only groups and the wait-list control [219].

Integrative treatments focusing on reducing child PTSD secondary to IPV, as well as parent distress and/or psychopathology associated with IPV, would be a valuable contribution to child welfare. In many child welfare samples, the majority of CPS reports are the result of children witnessing IPV [220], which is sometimes documented as emotional abuse, and in other cases, physical neglect, depending on the state. In our case example, Jovan's family may have benefitted from such an intervention. Jovan's mother had been largely nonparticipatory until mid-treatment, when she became more aware of the consequences her children suffered because of the abusive partner and her involvement with him. This epiphany was likely the result of the therapist's outreach, as he had made several attempts to connect with the mother, share the trauma narratives, and challenge some of her distorted cognitions, including that she was the only victim of the IPV and that she could not effectively parent her children without a partner. Sharing the trauma narratives allowed Jovan's mother to better understand her children's feelings and thoughts about the IPV and abuse, whereas the children

did not volunteer this information and she did not have the insight to elicit it. The therapist also encouraged Jovan's mother to seek professional help for her depression, which she initiated by the end of treatment.

Psychopharmacological Intervention

Very few studies have examined the pharmacological treatment of ASD and/or prevention of PTSD, and there are currently no FDA-approved pharmacological treatments for PTSD in children or adolescents. The available research has recently undergone two reviews [221, 222], highlighting the lack of randomized controlled studies.

A randomized pilot study in children with severe burns and ASD reported that a 1-week low-dose treatment of imipramine resulted in remission of symptoms in twice as many children as those in the placebo group, who received chloral hydrate to assist with sleep [223]. In contrast to adult studies, two randomized controlled pilot studies examined the use of sertraline to treat childhood PTSD and found null results [224, 225]. To note, however, two uncontrolled open trials of citalopram reported significant symptom reduction in children and adolescents with PTSD [226, 227]. Atypical antipsychotics have been used in children with PTSD and profound hyperarousal symptoms [228, 229]. A case series examining the use of quetiapine to treat six adolescent boys in juvenile detention for 6 weeks with doses ranging from 50 to 200 mg/day reported a significant reduction of PTSD symptoms as measured by the TSCC posttreatment [230]. A case series of risperidone administered to three physically abused preschool-age children diagnosed with ASD secondary to serious burns found significant improvement in symptoms posttreatment [231]. In addition, six sexually abused adolescents with chronic PTSD with associated psychotic features showed symptom improvement after a course of clozapine [232]. A few studies have examined the effect of antiseizure medication on PTSD symptoms in children and adolescents. One study reported on a subsample ($N = 12$) of conduct disordered youth with PTSD who were part of a double-blind, randomized controlled trial in which 71 boys with conduct disorder were assigned to a high or a low dose of divalproex sodium (Depakote), reporting that youth in the high-dose condition showed a greater reduction in PTSD symptoms [233]. Harmon and colleagues [234] administered clonidine over several weeks to seven preschool-age children with PTSD enrolled in a day hospital and found significant improvements in PTSD symptoms. In an explorative study, Loof et al. [235] administered carbamazepine (Tegretol) to 28 sexually abused children and adolescents with PTSD and reported that 22 of the youth were asymptomatic at the end of treatment, with the remaining six showing symptom reduction. A pilot study of children with PTSD suggests some benefit with propranolol. Using a B-A-B (off-on-off) medication design in a clinical setting, children exhibited significantly fewer symptoms when receiving medication [236]. Open trial studies show some efficacy for clonidine and guanfacine in the treatment of PTSD in children and adolescents [237], but RCTs are needed. In summary, studies of pharmacological treatment for childhood PTSD have been fewer in number and reveal mixed data. There are many promising agents that require more rigorous evaluation. In general, there is a paucity of RCTs, especially in the child and adolescent literature.

It is evident from these reviews that the extant data do not support the use of selective serotonin reuptake inhibitors as first-line treatments for PTSD in children and adolescents, and there is limited evidence that the brief use of antiadrenergic agents, second-generation antipsychotics, and several mood stabilizers may attenuate PTSD symptoms in youth [221, 222]. However, controlled trials of these agents in children and adolescents with PTSD are needed. To date, pharmacological treatment choice is best guided by the comorbid diagnostic profile of the child and ideally used to augment evidenced-based trauma psychotherapeutic treatments.

Novel pharmacological agents that target neurophysiological processes underlying memory formation are currently being investigated in preclinical and clinical trials. This work is based on research indicating that acute glucocorticoid release plays a key role in enhancing emotional memory consolidation and fear conditioning extinction-based learning [238]. Consolidation of memory requires glucocorticoid release and beta-adrenergic receptor activity in the basolateral nucleus of the amygdala (BLNA) [238]. While this mechanism is not fully understood, research suggests that it may be associated with stimulation of NMDA receptors in the BLNA by increasing calcium conductance and calcium channel subunit expression [238]. NMDA receptor agonists, particularly D-cycloserine (DCS), have been shown to facilitate fear conditioning extinction learning when administered just before extinction trials [239]. This has been demonstrated in exposure-based treatment for several anxiety disorders [238]. Similarly, yohimbine, which increases noradrenergic activity, has been show to enhance therapeutic learning during in vivo sessions to treat claustrophobia [240]. Unfortunately, DCS in conjunction with exposure-based treatment for PTSD has not shown beneficial results [241]. One small-scale RCT compared DCS and placebo and reported that remission of PTSD symptoms was comparable between groups [242]. Other studies are pending.

Given the previous discussion, there is risk that antidepressants and benzodiazepines, which inhibit glucocorticoids, and reduce cortisol and noradrenergic activity, may attenuate the therapeutic learning sought during exposure-based treatment [238]. Indeed, preclinical studies have shown that the influence of antidepressant and anxiolytic on the amygdala and hippocampus disrupt memory consolidation in rodents [238]. To note, a recent review of four trials examining potential benefits of combined psychotherapy and SSRI treatment, one in which involved children and adolescents, failed to find evidence that combining the two enhanced treatment outcomes [243]. Future research is needed to further investigate this potential treatment interference.

Case Follow-Up

Jovan and his sister received a total of 16 sessions of TF-CBT provided in the community. Both children showed significant symptom reduction from pre- to posttreatment and no longer met full criteria for PTSD. Jovan's mother was initially not engaged in her children's therapy; however, she became increasingly engaged as sessions progressed. Both children completed trauma narratives and opted to share them with their mother. Whereas Jovan's sister wrote a story about her sexual abuse, Jovan's narrative was less conventional and involved a graphical representation of what had happened. During the conjoint session, Jovan's mother offered praise and support, and she developed a deep appreciation of the impact of the family violence on Jovan and his siblings. During the course of treatment, Jovan's mother separated from her husband. Although she was still communicating with her ex-husband, Jovan's mother was more independent, sought her own mental health treatment, and took steps to further remove herself from the abusive partner. At a 3-month follow-up, the children remained asymptomatic, and CPS had closed the case.

Summary

Over the past two decades, tremendous strides have been made in the assessment and behavioral treatment of PTSD in children and adolescents. More work is needed to determine optimal pharmacological intervention strategies and to devise integrative treatment approaches that can address the range of challenges experienced by families of children with PTSD.

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Selective Mutism

Courtney P. Keeton

Abstract Selective mutism (SM) is an impairing behavioral disorder of childhood characterized by persistent failure to speak in specific social situations despite the ability to speak in other situations. SM typically begins during the preschool years but is usually not identified until the early school years. The disorder occurs in 0.11–2 % of children and persists for most children if untreated. SM is most often conceptualized as an anxiety disorder and is considered by many to be an early-onset or developmental variant of social phobia. The treatment literature is dominated by case reports and a few controlled studies. The most common treatments are those that are also used for pediatric anxiety, namely, cognitive, behavioral, and pharmacological interventions. Cognitive and behavioral strategies are recommended as the first-line treatment. Selective serotonin reuptake inhibitors are suggested in cases of treatment resistance and/or high symptom severity or impairment. It is often necessary to involve the child's teacher or other school personnel in the treatment plan.

Keywords Selective mutism • Anxiety • Social phobia • Speech problem • Language problem • Exposure treatment • SSRI treatment

Case Scenario

Naila is a 5-year-old East Indian girl whose parents sought an evaluation out of concern that Naila did not speak in preschool or currently in kindergarten. They indicated that Naila has an impressive vocabulary and expressive language skills that she mostly showcases at home with immediate family. However, they said she seems "like an entirely different child" when at home compared to school and other places.

Naila's parents described her as timid in social situations. At age 3 years, she did not sing along or dance with same-age children during story times at the local library, "froze" when an unfamiliar child or adult attempted to engage her in play or conversation, and participated in her soccer lessons only minimally and with much encouragement from her father. Towards the end of the school year, when the preschool teacher informed the parents that Naila did not talk or sing in class, they were surprised that she had not "warmed up" by then. Also, the teacher report was inconsistent with their observations given that Naila was consistently excited about school, always talked about the other

C.P. Keeton (✉)
Department of Psychiatry and Behavioral Sciences, Division of Child and Adolescent Psychiatry,
Johns Hopkins Medical Institution, Baltimore, MD, USA
e-mail: ckeeton@jhmi.edu

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kids, and recited songs and other things she had learned. In addition, Naila had occasional playdates with one of the kids in her preschool class and was fully verbal during those visits in her home.

Naila's lack of speech continued to cause significant impairment through age 5. They noticed, for example, that Naila's juice box from her lunch had been untouched on numerous occasions because she could not insert the straw and was unable to ask someone for assistance. Another time, she had fallen on the playground and had fractured her arm, but had not reported to a teacher that she was injured and waited until she got home to tell her parents. At the time of the evaluation, Naila's mother had stopped working in order to address Naila's speech problems.

Description of the Disorder

Selective mutism (SM) is an impairing disorder of early childhood in which children who are capable of speech withhold it in some situations where speech is expected, such as at school or in social situations involving unfamiliar people. The lack of speech is disruptive to school functioning or social communication. Persistence of the disorder must occur for at least one month excluding the first month of school when lack of speech, high anxiety, and difficult adjustment could be normative. Lack of speech cannot be due to lack of familiarity with the language and cannot be better accounted for by a communication disorder, such as withholding speech to avoid stuttering, pervasive developmental disorder, schizophrenia, or psychosis.

SM was originally described as a deliberate refusal to speak. In 1877, the disorder was termed *aphasia voluntaria* emphasizing a voluntary capacity to limit speech. In 1934, the disorder was named elective mutism, still inferring that children acted volitionally to withhold speech. SM first appeared in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) as "elective mutism." The term was revised in subsequent versions of the DSM to "selective mutism" to emphasize that speech is context dependent or selective. It is currently included in the "Other Disorders of Childhood and Adolescence" diagnostic category; however, SM is being considered as a specifier for social phobia (SOP) for DSM-5 (www.dsm5.org). In the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [1], the term "elective mutism" (F94.0) is used and falls in the category "Disorders of social functioning with onset specific to childhood and adolescence." The DSM-IV-TR and ICD-10 define similar criteria, but the ICD-10 specifies that the child must be within two standard deviations on standardized tests of language expression and comprehension.

Lack of Speech

The hallmark feature of children with SM is a clear discrepancy between a child's speech abilities and their speech performance across situations. Most children with SM are like any other child in the home environment; they speak freely to parents and siblings, laugh, sing, argue, yell, narrate their own play, and respond to as well as initiate speech. In social contexts such as school and public forums, there is a marked contrast in speech behavior, and the usually verbose child shows silence or reduced speech and may show visible distress, reduced affect, and withdrawn behavior [2]. This discrepancy explains why many parents go months or even years without realizing there is a problem. In extreme instances, a child has bouts of reducing or withdrawing speech even with parents [3]. Many children with SM communicate using gestures such as nodding and pointing. Some communicate using short (monosyllabic) utterances or speak in an altered voice such as a "baby" voice or making grunts. Others withhold nonverbal gestures and appear "frozen" with regard to physical presentation and affect [4, 5].

Variability of Speech

SM is a heterogeneous disorder with variability of speech patterns across and within affected children [2]. Compared to speech at home, children with SM tend to speak less to familiar individuals in public and rarely speak to unfamiliar individuals in public or at school [6]. Whereas some children may not smile, laugh, or participate nonverbally at school, others are creative in communicating and participating fully in the absence of speech. Some children may be silent in the school context but speak openly in public, whereas others may reduce speech in most social forums. Likewise, some children may speak openly to select individuals, including a new clinician, and withhold speech with others, and there is not necessarily a recognizable explanation or pattern. A child may speak to specific individuals on some occasions, but not other times. It is not uncommon for a child to enjoy a birthday party including verbal participation and to withdraw entirely at another birthday party without identifying a reason for the difference. Thus, there is a generous range of speech behaviors among affected children.

Social Skills Deficits

Compared to typically developed peers, children with SM show lower social competence such as social assertion, social responsibility, and verbal and nonverbal social skills [7, 8]. Compared to children with mixed anxiety, children with SM were rated by observers as lower on verbal social skills and higher on social anxiety [9]. In another study, children with SM were rated similarly to children with SOP and scored lower than normal controls with regard to social skills [10].

Impairment

SM is disabling to children's social, academic, language, and personal/emotional development. Socially, children with SM tend to withdraw and isolate themselves, which leads to reduced opportunities for friendship formation and extracurricular opportunities, as well as acquisition or mastery of social skills including pragmatic communication and leadership abilities [6, 8, 11, 12]. Peer rejection and bullying are also possible because of the SM child's inability to protest maltreatment by peers [13]. Academically, children with SM are unlikely to participate verbally at school, including answering or asking questions about content and assignments, and this can interfere with a teacher's ability to evaluate achievement [14]. Indeed, school is typically the first setting in which significant functional impairment is evident, and some children are held back from promotion to the next grade due to failure to speak in school [15]. Avoidance of social conversation may also lead to language deficits over time [16]. Affected children may also feel insecure about themselves, leading to decreased autonomy and self-doubt [3]. Failure to voice a need can result in other functional impairments or personal humiliation, e.g., the child who does not request a bathroom pass and subsequently has an accident in the classroom. Overall, SM is a serious condition that can significantly impair the functioning of young children.

Physiological Findings

Only two studies have been published on the physiological mechanisms of SM. In the first study, 16 individuals aged 5–16 years with SM and matched controls were tested for speech reception thresholds,

speech discrimination of phonetically balanced monosyllabic words, and efferent auditory activity using measures of middle-ear acoustic reflex (MEAR) thresholds, MEAR decay function, and suppression effect of transient evoked otoacoustic emissions [17]. Afferent auditory function was assessed using auditory brainstem response. As a group, children with SM displayed reductions in auditory efferent activity; however, 25 % of the group did not display these abnormalities. In a follow-up study, nine children with SM and abnormal auditory efferent activity showed impaired auditory processing during a vocalization task [18]. Findings of the two studies provide some evidence that children with SM who have difficulty processing incoming auditory information while speaking may cope with this difficulty by resorting to speech avoidance.

Another study has compared psychophysiological arousal in 10 children with SM (aged 7 ± 1.8 years) to 11 children with SOP (aged 8.8 ± 2.0 years) and 14 non-disordered children (aged 8.9 ± 1.5 years) [19]. They compared heart rate, blood pressure, and skin conductance during role play and read-aloud tasks. There were no differences in heart rate or blood pressure changes across the three groups. Contrary to the authors' hypothesis, the SM group, like the control group, showed low levels of arousal (skin conductance) during the social interaction tasks suggesting a lack of heightened anxiety or that speech avoidance was used as an emotion regulation tactic keeping arousal low. Given the small sample size of this study, additional research is needed to draw firm conclusions.

Prevalence and Course

Estimates of SM prevalence vary based on whether the sample is clinical or community based, with higher rates generally found in community samples. Relatively lower prevalence rates in treatment settings support the notion that a high percentage of affected children are never seen for treatment [20]. The prevalence of SM has not been assessed in the majority of existing large-scale epidemiological studies of childhood psychopathology. Studies in primary care and psychiatry clinics estimate the prevalence in these treatment settings at 0.5 % and 0.11 %, respectively [21, 22]. A community study conducted in the United States estimated a prevalence of 0.71 % in children attending kindergarten through second grade [14]. Similarly, a study conducted in West Jerusalem using similar methodology found a prevalence rate of 0.76 % in children ages 4–6 years [23]. A higher rate of 1.9 % was reported in a study conducted in Finland with 2nd grade teachers [24]. In comparison, a lower prevalence rate of 0.18 % was found in Sweden; this sample was somewhat older (7–15 years) and also utilized teacher reports. Another study conducted in the United States using a primary care sample of children, ages 8–17 years, estimated a rate of 0.5 % for SM [22]. According to Bergman et al. [14], SM occurs at rates that are comparable to, or greater than, other well-understood childhood psychiatric disorders such as obsessive-compulsive disorder, autism, major depressive disorder, and Tourette syndrome.

Age of Onset

Age of onset is typically before age 5. The mean age of onset of SM ranges from 2.7 to 4.1 years [3, 7, 20, 23, 25]; however, the average age of referral to treatment is 6–9 years of age [26]. The disorder either may not be discovered until the child enters school, or parents and/or doctors expect the child to "grow out of it" when signs of the problem are evident during the preschool years [4]. In most cases, onset is insidious, with children being described as having a behaviorally inhibited temperament throughout their early development [20]. However, there are cases when onset is abrupt, such as in response to a stressful event [3, 27], and these cases may be transient in relation to those with a gradual onset [2].

Demographic Distribution

The literature is somewhat inconsistent regarding a gender difference. It is suggested that SM is slightly more common in females, showing ratios of 1:1.5–1:1.9 for example [3, 20, 25]. Given that others have documented comparable prevalence among the sexes [14], the suspected gender difference may result from research limitations such as small sample sizes [28].

Rates of SM appear to be higher in children who have immigrated from one country to another, and there is a change in native language [23, 29]. For example, one study reported a prevalence rate of 2.2 % for children who had immigrated to West Jerusalem (mostly from other Israeli cities, and for whom Hebrew was not the primary language) and a rate of 0.47 % in native children. There appear to be no differences in SM prevalence by socioeconomic status [3, 30] or race [31].

Course

SM does not appear to resolve spontaneously. One community-based case-controlled study found that 27 % of elementary school children with SM showed some improvement at a six-month follow-up but that the majority remained significantly impaired compared to their unaffected peers [14]. A retrospective study of 153 children and adults affected by SM indicated that many continue to suffer from social anxiety even if SM resolves [2].

Follow-up data of clinically referred and treated individuals suggests that children with SM continue to experience communication deficits, social withdrawal, anxiety disorders, and psychosocial impairment into adulthood. One follow-up study of 45 young adults who were diagnosed with SM as children found that 16 individuals (39 % of sample) showed complete remission, 12 individuals (29 %) showed remarkable improvement, eight individuals showed mild improvement, and five showed no improvement [32]. Many individuals in the "remission" group reported other problems such as mood problems. There is one controlled, long-term outcome study of SM in young adulthood; the mean follow-up period was 13 years, and there was a remission rate of 58 % [33]. At follow-up, only 18 % of the sample had slightly improved. In this study, there were high rates of phobic disorders and other diagnoses at follow-up, even when SM had remitted. In these long-term follow-up studies, high rates of familial mutism and shyness predicted unfavorable outcomes [32, 33]. In another study, 17 children (mean age 8 years) were evaluated 6 to 8 months following the initiation of treatment, and all but one of them continued to meet diagnostic criteria despite significant symptomatic improvement [34].

Comorbidity

SM most commonly co-occurs with anxiety disorders, elimination problems, disruptive behavior, and communication disorders.

Anxiety

Children with SM score high on measures of social anxiety and shyness [3, 7, 10]. Rates of SOP in children with SM are high, with comorbidity estimates in some samples of SM up to 97–100 % [6, 9, 20, 35]. Although children with both SOP and SM do not endorse higher levels of anxiety than children with SOP only, blind observers, clinicians, and parents have rated them as having more severe symptoms [9, 14, 19, 36]. Other common comorbid anxiety disorders include separation anxi-

ety (31.5 %), specific phobia (13 %), and GAD (13 %) [25]. Some studies document high rates of physical symptoms, which are also consistent with anxiety disorders; children with SM, for example, scored significantly higher than controls on the somatic subscale of the Screen for Child Anxiety Related Disorders measure [37], and these results were demonstrated in an earlier study that used the Revised Ontario Child Health Study scales [7].

Given the high levels of social anxiety in SM, many consider this disorder a relative of SOP. Some suggest SM is an extreme form of SOP, whereas others consider SM a developmental variant of SOP [20, 31]. Prior suggestions that SM could be classified as a subtype of SOP [20, 38] and recent recommendations that "refusal to speak" is a behavioral symptom of social avoidance, similar to school refusal [31], have led the DSM-V Task Force to consider SM as a specifier of SOP rather than maintaining it as a distinct disorder (www.dsm5.org).

Elimination Disorder

Several studies suggest high rates of toileting problems in children with SM, including constipation, enuresis, and encopresis. In their sample of 30 children, Black and Uhde [20] reported that 17 % had enuresis and 7 % had encopresis. Steinhausen and Juzi [3] reported that 33 % of their sample ($n = 100$) had enuresis and/or encopresis. Other studies have compared rates of lifetime elimination disorder in an SM group relative to healthy controls. Kristensen [25] studied 54 children with SM and reported a rate of 31.5 % of elimination disorder compared to 9.3 % in the control group. In another study of 70 children with SM, rates of enuresis were 14.3 % compared to 6.5 % in the control group, but in this case the difference was not statistically significant [39].

Disruptive Behavior

Data is mixed with regard to the frequency of disruptive behavior in the SM population. Many studies describe 10–90 % of children with SM as oppositional, aggressive, or controlling without necessarily fulfilling diagnostic criteria for a disruptive behavior disorder [3, 6, 20, 40, 41]. Some studies show no differences in parent-reported or teacher-reported externalizing behaviors such as ADHD, ODD, and CD among children with SM and healthy controls [7, 14, 37, 42]. In contrast, when compared to children with SOP, parents of children with SM and SOP reported significantly higher (though in the nonclinical range) scores on the delinquency and aggression scales [9]. Another study found that 29 % of children with SM and SOP had comorbid oppositional defiant disorder, in comparison to 5 % of those with SOP only [43]. Finally, a latent profile analysis of 130 children with SM, ages 5–12 years, resulted in three distinct groups including an exclusively anxious group, an anxious-communication-delayed group, and an anxious-mildly oppositional group [41].

Some oppositionality such as arguing or refusing may be explicitly related to an anxiety-provoking situation rather than generalized disruptive behavior [44]. Children with SM may appear oppositional in the settings where speech is withheld if they are perceived to be remaining silent as an act of defiance. However, many children with SM (like anxious children) are cooperative and reluctant to draw attention to themselves through acts of misbehavior.

Communication Disorders

The DSM specifies that SM should not be diagnosed if the lack of speech is better accounted for by a communication disorder. Although children with this disorder generally have normal language skills,

there may occasionally be an associated communication disorder (e.g., Phonological Disorder, Expressive Language Disorder, or Mixed Receptive-Expressive Language Disorder) or a general medical condition that causes abnormalities of articulation. Many studies show evidence of delayed speech acquisition or poor articulation in the SM population, and the percentage of language or communication problems in children with SM varies widely, ranging from 11 % to 65 % [3, 25, 30, 45]. When compared to children with SOP, children with SM performed worse on nonverbal tests of language [46]. Thus, speech delays and other language problems are not uncommon in the SM population.

Etiology

Views on the etiology of SM have changed over recent decades. Older conceptualizations of SM implicated factors such as trauma, stressful events, or family dysfunction as etiological variables [45, 47–50]. Current conceptualizations, which are discussed further here, are based on symptom overlap with SOP and suggest that multiple variables are associated with SM including behavioral inhibition, genetics, and environmental factors.

Behavioral Inhibition

Behavioral inhibition (BI) is a temperament characterized by shyness, apprehension, and withdrawal in novel situations. Reluctance to speak has been described as a defining feature of BI [51]. Much of the support for BI as an etiological variable stems from the association between SM and SOP for which there is a clearly established link with BI [52]. However, there are only a few studies that empirically address temperament and SM. In one study, individuals with SM had temperaments characterized by difficulty responding to novel situations and difficulty handling transitions and change [2]. In many reports, children with SM are consistently described as having behavioral or personality characteristics that resemble BI, such as a lifetime history of shyness or slow-to-warm-up temperament [6, 52, 53]. Descriptive reports of children with SM also show that they tend to score high on the "withdrawn/depressed" or "internalizing" scales of socioemotional and behavioral checklists [14, 42, 54, 55].

Familial/Genetic Vulnerability

The co-occurrence of SM and social anxiety in families suggests a possible genetic etiology. Poor language production, extreme shyness, and speech and language disorders occurred in 78 % of first-degree relatives in one sample, with concordance rates of SM of up to 18 % in first-degree relatives [32]. Another study reported that about 70 % of first-degree relatives of children with SM had a history of social anxiety and shyness, and 37 % of first-degree relatives had a history of SM [20]. The rates of avoidant personality disorder (17.5 %) and lifetime generalized SOP (37 %) among parents of children with SM are higher compared to parents of children without any disorder (4.7 % and 14.1 %, respectively) [39].

Only one study has looked at genetic susceptibility factors for SM; the sample included 106 individuals with SM, and results indicated an association between SM and the *CNTNAP2* gene, more specifically the rs2710102 single nucleotide polymorphism (SNP) [56]. The rs2710102 SNP of *CNTNAP2* has been implicated in the developmental language delay component of autism. Findings

of this study therefore provide preliminary evidence of a potential shared genetic etiology for autism spectrum disorders and SM. Without replication, however, it is premature to consider variation of the *CNTNAP2* gene as a risk factor for SM.

Environmental Vulnerability

Families of children with anxiety disorders and SM have been rated by parents as less socially active and less involved in recreational activities as compared to families of unaffected children [42]. In a recent study of parent-child interactions, parents of children with SM were rated as significantly more controlling compared to parents of anxious or unaffected groups [57]. In another study, parents of children with SM demonstrated higher degrees of monitoring based on a clinician-rated interview, but there were no differences on self-reported parenting styles among parents with SM and parents with unaffected children [37]. Clinician-rated measures may therefore be more sensitive to picking up on impactful parenting behaviors.

One common tendency that contributes to or maintains SM is accommodation by others [55]. Common accommodation behaviors include "mind-reading" or guessing the child's response instead of waiting for a verbal response, assuming the child will not answer independently, developing non-verbal communication habits with the child, labeling the child as shy, and avoiding facilitating social opportunities such as playdates and camps. Such behaviors reinforce the absence of speech and limit opportunities to develop, practice, and master social skills.

The behavior of other individuals in the child's environment may contribute to further silence through a process of negative reinforcement. When a child is faced with an anxiety-provoking situation, the behavioral response is speech withdrawal (a form of avoidance or escape). Avoidance or escape of the situation results in reduced distress, which reinforces the lack of speech. Additionally, reduced requests for speech over time negatively reinforce the silence. If a child repeatedly does not respond when a peer says "hello" or asks a question, the peer may stop interacting and soliciting responses, which negatively reinforces the lack of responding (while also unfortunately reducing social opportunities).

Assessment

A multi-informant, multi-method approach is recommended for the assessment of SM [4]. Since the child may not speak much or at all to the clinician, the primary caregiver is typically the main informant. Information from a daycare provider or teacher is helpful. Assessment methods include observational methods, interviewing, pencil-and-paper questionnaires, and speech and language assessment.

Observational Methods

An audio or video file of the child speaking comfortably is useful for verifying the child's capacity for age-appropriate speech and for evidence of possible communication problems [4]. Many parents are willing to bring a recording to the evaluation; however, some children protest about showing the video. In these instances, viewing the video (with or without the child present) can be added to the exposure hierarchy in behavioral treatment.

Observing the child in person provides valuable information about symptoms and severity. It is helpful to observe the extent that the child speaks to parents in the waiting room prior to being greeted by a clinician and to observe changes in behavior upon being greeted. One can also access other indicators of anxiety such as fidgetiness, tenseness, closeness with caregiver, and social skills or comfort with the social interaction including eye contact and quality of communication with the examiner.

Although some children speak comfortably with the examiner or at least answer questions indirectly by whispering responses to a parent, most are not expected to initiate speech or offer responses. The examiner may avoid direct communication with the child initially in order to reduce the child's anxiety; for example, the examiner could offer a child some crayons and paper and invite her to draw without asking any questions. Direct questions about the child ("What is your name?" "What grade are you in?") that are natural in forming a rapport may be less helpful in this instance when the child does not cope well with being in the spotlight. One alternative strategy is to explain to the child that the parent will be answering many questions and the child is welcome to talk at any time, especially if the parent says something that is incorrect.

Some studies have utilized social interaction tasks to code the child's anxiety severity and related behaviors. For example, two groups of investigators used blinded observers to rate children's anxiety levels and social effectiveness during videotaped experimental role plays and reading tasks involving same-age peers and unfamiliar adults [9, 19].

Interviews

The clinical interview is an opportunity to assess the family and developmental history, complete a functional assessment, determine the presence of comorbid problems, and rule out alternative explanations for the problem. It is essential to rule out and/or assess for organic problems (hearing loss, brain injury) or speech problems that explain the mutism because a diagnosis of SM cannot be given unless other causes of lack of speech are ruled out. Structured interviews are valuable for obtaining a thorough impression of the clinical symptoms including likely comorbidities such as SOP or elimination problems. Two structured interviews that contain modules specific to SM include the Anxiety Disorders Interview Schedule for DSM-IV [58] and the Preschool Age Psychiatric Assessment [59].

Disorder-Specific Questionnaires

The Selective Mutism Questionnaire (SMQ) is a 17-item parent-report measure designed to assess the child's speaking behaviors across three social settings (i.e., school situations, social situations with family members, and situations outside of school not involving family) [60]. On this measure, parents respond to questions such as how frequently their "child talks to most peers at school," by indicating whether that behavior occurs always, often, seldom, or never. The SMQ has shown excellent internal consistency and strong convergent and discriminant validity [60, 61]. Scores range from 0 to 51 and higher scores reflect age-appropriate speaking behavior. Some data suggests that the average summed total score of a child diagnosed with SM is about 13 [60]. The SMQ has been used to demonstrate changes in symptoms as a function of treatment [34, 62].

The School Speech Questionnaire (SSQ) was adapted from the SMQ to collect information from teachers regarding students' speaking behaviors at school [14]. It includes 10 items rated on the same 0 ("never") to 3 ("always") scale as the SMQ, and six of the items are used to compute a total sum score. Psychometric data on this measure is limited, although the internal consistency in the original

sample was good [14]. The SSQ was helpful in showing treatment effects in at least one published treatment study in which mean scores raised significantly from 0.59 at baseline to 2.68 at the 6-month follow-up of a behavioral intervention for preschoolers [63].

Speech-Language Assessment

Since assessing for communication problems is an important consideration in SM, it may be necessary to refer the child for a formal assessment by a speech and language pathologist. Often nonverbal language assessments can be effectively used to screen for problems and help determine if a referral for additional testing is needed. Two examples include the Peabody Picture Vocabulary Test (PPVT-IV) [64] and the Children's Communication Checklist (CCC-2) [65]. The PPVT-IV assesses receptive vocabulary and yields a standardized score based on the child's age. Administration involves presenting a group of pictures to the child, saying a word that describes one of the pictures, and then asking the child to point to the picture that the word describes. The CCC-2 is a 70-item parent-report measure that screens for communication problems and identifies pragmatic language impairments.

Treatment

Although SM is most often conceptualized as an anxiety disorder, significantly less is known about effective treatments for SM relative to more common anxiety disorders. Most of what we know about the treatment of SM comes from retrospective record reviews, uncontrolled case studies, single-case experiments, and a few controlled studies. There are increasing data showing that psychosocial and pharmacological treatments can be effective with this vulnerable population. Most of these studies were conducted in small samples that were clinically referred and are more likely to be severe or difficult to treat compared to the general population of children with SM. Additionally, the majority of studies have been conducted in school-aged or adolescent populations despite the preschool age of onset of SM. The goals of treatment are to reduce anxiety and increase the quality and quantity of speech across people and situations. Remission is achieved when speech gains generalize to real-world situations and the child demonstrates spontaneous, age-appropriate conversational speech across contexts.

Psychosocial Treatments

A variety of approaches have been used in the treatment of SM including any combination of behavioral, cognitive behavioral, psychodynamic, speech-language, and family systems therapies. Behavioral and cognitive behavioral treatment approaches have received the most research support, produce positive end-state functioning in children, and are therefore considered the first-line treatment [53, 66]. The high degree of anxiety in the SM population contributes to an underlying rationale for using cognitive and behavior modification approaches in the treatment.

Treatment duration varies by the study, but the consensus is that psychosocial treatment is likely to last several months and can be longer than treatment for common anxiety disorders [13]. Since a child may not speak at all for several treatment sessions, a great deal of time is spent establishing rapport and ways of communicating. When a child does begin speaking, it is a slow and gradual process whereby she may speak a few words per session, and it takes many sessions to achieve more fluid or

spontaneous speech and to assist with generalizing those gains to the real world. Commonly used specific treatment techniques are discussed below.

Graduated Exposure, Shaping, and Stimulus Fading

These exposure-based techniques are based on the theory that mutism is a learned avoidant behavior that is reinforced by removal of distress following mutism. Exposure is the most often cited technique in the literature [53, 66]. Graduated exposure targets the problem by teaching approach behavior (rather than avoidance) to overcome the distress. Exposure involves having the child face anxiety-provoking or feared speech situations in a gradual way, starting with the least distressing situations and moving toward increasingly distressing situations. There are two books available that guide parents on collaborating with the school to assist the child in working through a gradual hierarchy [67, 68].

A related technique, shaping, involves reinforcement for successive approximations of behaviors that resemble speech. Stimulus fading involves gradually increasing the number of people in a speaking situation, or gradually removing protective factors such as a parent, and has been successful in increasing the amount of speech and the number of people spoken to across varied settings [69, 70]. Often these strategies are used concomitantly.

Sample in-office exposures include talking openly in clinician's office to parent without clinician and gradually fading in clinician and fading out parent, mouthing brief responses through play followed by whispering some or all of the response with subsequent increases in volume (e.g., mouthing/verbalizing "go fish" during card game), showing clinician a home video of self-talking or singing, answering "yes/no" questions first with gestures followed by progressively louder verbalizations, and reciting the alphabet or favorite songs. Outside of session, specific daily speech exposures for social situations including daycare or school are assigned. Sample out-of-session exposures include mouthing words to the morning song with rest of the class, whispering one word to assigned buddy in response to teacher's question, voicing a need to teacher, ordering drink at restaurant, and asking an unknown child his name at a public playground.

Exposure exercises may be problematic for children for whom direct discussion of the mutism or its treatments is extremely anxiety provoking such that it may be aversive and produce increased anxiety or an oppositional response. In these instances, other behavioral strategies should be prioritized.

Contingency Management

This strategy, typically used in conjunction with exposure exercises, involves the use of rewards to reinforce efforts and gains toward treatment goals. Rewards range from positive attention, praise, privileges, to tangible items. Experiential and tangible rewards should be age appropriate, desirable, and commensurate with the "size" of the completed behavior (i.e., small rewards for small steps and big rewards for big steps). Examples include sitting in the clinician's chair, playing a game, going to the theater, or getting prizes (e.g., stickers, sugarless gum, hair accessory, or craft activity). This strategy also involves using consequences to reduce the mute behavior. Consequences may range from ignoring the mutism (while attending to speech attempts) to enforcing a punishment as a result of failed speech in a situation when speech was expected. While there is some evidence that this strategy results in treatment gains, most clinicians caution against using coercive or aggressive tactics which will likely exacerbate the problem [2]. Thus, ignoring the mutism while focusing on rewarding speech attempts is likely a more effective strategy for many children, compared to issuing more serious consequences such as privilege removal. Contingency management is often used in conjunction with exposure-based practices in order to reward a child's progress and enhance motivation toward realizing continued treatment gains. In one small study comparing exposure-only to contingency management-only, exposure was considered relatively more effective [35].

Relaxation Training and Systematic Desensitization

Relaxation training involves teaching the child diaphragmatic breathing and progressive muscle relaxation in order to target autonomic arousal and related physiological responses associated with anxiety. When paired with exposure, the goal is for the child to learn to tolerate increasing levels of anxiety. This strategy has resulted in positive outcomes such as increased verbalizations at school and number of individuals spoken to, school attendance, and involvement in extracurricular activities [12].

Self-Modeling

This technique involves splicing an audio or video recording to depict a child speaking in a context in which she is mute. Also referred to as "audio feedforward" and "video feedforward," this technique requires the child to listen to or view the recording several times. The goal is that the child develops beliefs about her ability to speak as depicted in the recording, followed by actual speaking behaviors. Published case reports on children aged 5–9 years have paired self-modeling during the course of treatment with techniques such as stimulus fading, reinforcement including "mystery motivators," and fluoxetine [71, 72]. Positive findings were reported including developmentally appropriate speech that generalized beyond the scenario depicted in the recordings. However, feedforward techniques were not successful for some children who refused to make the recording [71].

Parent Training

This strategy targets environmental variables associated with the problem. The parents may be encouraged to reduce accommodation behaviors, increase opportunities for social interaction outside of the home, apply reinforcement for the child's speech outside of the home, model self-exposure to social-evaluative situations, or model positive self-talk or other coping strategies [54].

Cognitive Restructuring

This technique involves identification of maladaptive thoughts and teaching realistic, coping-focused thinking. A child who is able to articulate specific worries such as thinking that her voice will sound funny is in a position to develop positive self-talk or challenge the irrational components of specific thoughts through Socratic questioning. This technique is best suited toward older children who have the cognitive maturity to identify anxiety-enhancing thoughts; however, a simplified version for younger children focused on reflection on past successes with exposures could be helpful [73].

Innovative Psychosocial Strategies

Although there are no published treatment manuals specific to SM, some researchers have adapted existing evidence-based psychosocial treatments to suit the individual needs of children with SM. One such manual is Social Effectiveness Therapy for Children (SET-C), a social skills group treatment with demonstrated efficacy for youth with social anxiety [74]. In a case study of a 10-year-old with SM, SET-C sessions were adapted to begin with a shaping/warm-up exercise requiring repeated vocalization of a sound, a word, and then a sentence, followed by learning a new social skill (e.g., eye contact, greetings, topic transitions), role playing the new skill, and completing an exposure task. Treatment also included several parent training sessions and school-based interventions. Although there were a

number of challenges associated with the case, the authors concluded that SET-C could be appropriate for school-age or adolescent youth who have SM and obvious social anxiety and/or social skills deficits [54]. Similarly, the Coping Cat manual for child anxiety [75] and modular CBT for child anxiety [76] are evidence-based treatments that have been applied to SM. The Coping Cat is an individual treatment that involves teaching the child emotion recognition, cognitive restructuring, problem solving, and relaxation, followed by graduated exposure. In one case example, this treatment was adapted for an 8-year-old by increasing parental participation in treatment; after completing the manual, the child no longer met criteria for SM [77]. Another case report of an 8-year-old utilized a modular CBT treatment including a focus on psychoeducation, cognitive restructuring, exposure, and relapse prevention, and resulted in resolution of SM after 21 sessions [55].

The majority of treatment studies have limited representation of preschool children, and a need for early intervention has been identified because of the early age of onset of SM as well as data showing more favorable outcomes for younger children [53, 78]. There is one recent behavioral treatment study that involved seven children with SM aged 3–5 years [63]. This study is further set apart from others in the emphasis on the importance of treatment setting and a behavioral strategy the authors termed "defocused communication." First, treatment started in the home where the child was most comfortable and then moved to the kindergarten where symptoms were most impairing. Second, the clinician, parents, and teacher utilized communication strategies such as sitting beside rather than across from the child, creating joint attention using an activity the child enjoys rather than focusing on the child, and thinking aloud rather than asking the child direct questions. These strategies were paired with psychoeducation, stimulus fading, and rewards for weekly or twice-weekly sessions for a maximum of 6 months. At the six months, six out of seven children spoke in all kindergarten settings. At the one year follow-up, five out of seven children spoke freely in the classroom. This study provides evidence that behavioral treatment can be favorable for the youngest children diagnosed with SM and articulates strategies involving treatment setting and communication style that could influence outcome.

Other newly emerging, innovative treatment approaches for SM involve Web-based and group formats. There is one case of Web-based CBT program used for a 7-year-old that resulted in significant reductions in anxiety and overall SM symptom severity [79]. One 8-week group treatment focused on psychoeducation, relaxation exercises, gradual exposure, and rewards resulted in significant increases in speech production across settings for the five participants (mean age 6.1 years) [62]. Another cognitive behavioral group-based format emphasizing exposure, social skills training, and speech and language techniques has resulted in speech inside and outside of treatment for the majority of children treated [80]. Finally, pilot data on nine children aged 4–7 years shows promise regarding an intensive 1-week group behavioral treatment. This program, "Brave Buddies," uses a simulated classroom for children to practice speech and has resulted in increases in spontaneous speech and improvement on the SMQ school subscale [81].

There is one NIMH-funded randomized controlled trial that tests a 20-session integrated behavioral therapy for children aged 4–8 years, but the results are not yet available (Bergman RL. Personal Communication, 2011).

Pharmacologic Treatments

Pharmacotherapy is recommended in the treatment of SM generally when psychosocial interventions are ineffective or when symptoms are chronic and severe [78, 82]. There are currently no medications that are approved by the United States Food and Drug Administration (FDA) for the treatment of SM. No large-scale studies of pharmacotherapy for SM have been conducted, and medication effects as described in the literature tend to be variable. Despite limited data regarding the use and safety of drugs in the treatment of SM, at least one survey study showed that child and adolescent psychiatrists

commonly prescribe psychotropic agents, usually antidepressants, for children with SM [21]. SSRIs are considered the first-line pharmacologic treatment for SM because of the predominance of reports in the literature and due to the relative safety and established efficacy of these agents in other childhood psychiatric disorders [82]. Since most drug studies have utilized fluoxetine, this is the preferred agent for children with SM. The choice of agent, however, may be impacted by the presence of comorbid conditions.

Fluoxetine

Fluoxetine is the most studied SSRI for the treatment of SM. Notably, there is one double-blind, placebo-controlled treatment study involving 15 children, aged 6 to 11 years [83]. Treatment occurred for 12 weeks, and the mean maximum dose of fluoxetine was 21.4 mg/day. Fluoxetine-treated subjects showed significant improvement across ratings of mutism and anxiety; however, they remained highly symptomatic at the end of 12 weeks, and comparisons with the placebo group were not statistically significant except for parent-reported global improvement. The authors concluded that short-term fluoxetine was well tolerated and showed benefit but that 12 weeks may be too short a period to find significant changes. Also, they speculated that early changes may be less evident at school compared to elsewhere (such as in the neighborhood) and that starting treatment during the summer or early in the school year, before patterns of nonspeaking in the school context have become too entrenched, may be most beneficial. Additionally, dosing may have been conservative given the severity of the patient population.

An open trial study of fluoxetine with 21 children, ages 5–14 years, found that an optimal response at the end of 9 weeks was achieved with 20 mg/day [84]. Significant pre- to posttreatment changes were found across self- and parent-rated social behavior and anxiety symptoms and clinician-rated global assessment of functioning and overall improvement. Younger children showed the greatest improvements. Several case reports focused on fluoxetine described positive outcomes and few side effects in children [82]. Time to response and treatment duration within the case reports is variable, with some children beginning to speak after only 2 weeks of fluoxetine treatment and others requiring 6–12 weeks to achieve some benefit.

Sertraline

Sertraline was studied in one double-blind, placebo-controlled multiple baseline trial with five children, aged 5–11 years, with SM [85]. Children were given 50 mg/day for 2 weeks followed by 100 mg/day for 8–12 weeks (depending on randomly assigned placebo phase length). Although the internal validity of the multiple baseline design was not demonstrated (because increased talking behaviors did not always correspond to the randomly determined onset of medication initiation), all participants showed rapid improvements in talking behavior in home and community settings, and two of five demonstrated improved speech in the school context. The two children who no longer met diagnostic criteria at the end of the 16-week study were the youngest. Children continued to make gradual gains with continued sertraline treatment post-study.

Paroxetine

A case report study of an 8-year-old girl with SM, SOP, and separation anxiety treated with paroxetine 5 mg/day at bedtime demonstrated an increase in speaking behaviors following 2–3 weeks of

treatment according to parent and teacher report [86]. SOP and separation anxiety resolved as well. There were no adverse events. The child was treated for 3 years without relapse of symptoms.

Phenelzine

There are two case report studies of phenelzine examining a total of five children (one aged 5 years 6 months, four aged 7 years) [87, 88]. Maximum doses ranged from 22.5 to 30 mg daily. Treatment duration ranged from 18 weeks to 15 months. The children began talking freely during treatment and maintained gains following medication discontinuation. One child was followed 8 years after medication discontinuation and remained free of SM symptoms. The most common side effects included constipation, insomnia, and weight gain. The authors concluded that phenelzine is effective in treating SM but should be considered after SSRIs and behavioral treatment because of the possibility of food and drug interactions. The authors also concluded that phenelzine could be helpful when weight gain is desirable and that it could help target comorbidities such as enuresis, obsessive-compulsive symptoms, and mood symptoms.

Comparative Treatment Studies

There is one study that compared different serotonergic medications to various nonmedication treatments for 17 youth with SM. Children treated with medication were rated by parents and clinicians as showing superior gains on measures of global functioning and SM symptom severity [34]. Results of this study should be interpreted with caution due to methodological constraints such as small sample size, lack of randomization, and heterogeneity of therapies received by the children. However, the "real-world" treatment design is a feature that lends support to the use of SSRIs as an effective treatment for SM.

Case Follow-up

Behavioral therapy involving Naila, her parents, and teacher was initiated. A functional assessment conducted with each adult identified behaviors that could unintentionally maintain the mutism, and alternative adaptive behaviors were identified. For example, rather than continuing to remove privileges from Naila in the absence of speech, the mom agreed to offer Naila labeled praise and rewards for speech efforts. With the input of Naila's teacher, the parents and clinician constructed an exposure hierarchy to begin shaping increased speech within the school context. A contingency management program was developed such that Naila earned a "brave talk buck," paper money that she could redeem for special prizes, each time a step on the hierarchy was completed. The concept of shaping was modeled in weekly sessions with the clinician, and the parents created daily speech opportunities for Naila in public.

By the end of the school year, Naila had attended 16 treatment sessions. She had made significant progress; she spoke while on the playground at school, often whispered responses to the teacher when one on one, and consistently whispered to select peers. Outside of school, she started playing and talking with unfamiliar kids in public play areas, spoke some at a birthday party, talked normally with a librarian and her dentist, and began saying "thank you" or "bye" to store clerks.

However, she continued to meet criteria for selective mutism. The family planned to continue the behavioral strategies through the summer and consult with a psychiatrist regarding medication treatment if she regressed or failed to make additional progress.

Summary

SM is a disabling disorder of childhood that typically onsets during the preschool years and persists for most children without treatment. SM is best conceptualized as an anxiety disorder and shares many overlapping features with SOP. Multimodal assessment involving parents, teachers, and the child is critical. Scientifically rigorous studies are lacking, but the literature indicates that exposure-based strategies are recommended as the first-line treatment, and treatment with a selective serotonin reuptake inhibitor is suggested in instances of treatment resistance and/or high symptom severity or impairment. Evidence from retrospective reports, follow-up studies, and treatment studies suggests that younger age and lower rates of shyness and familial psychopathology may contribute to more favorable outcomes. Controlled treatment-outcome studies with well-characterized samples including young children and standardized diagnostic and treatment procedures are needed to further elucidate the most effective treatment strategies for children with SM.

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Part III
Assessment and Treatment

Assessment of Anxiety Disorders: Categorical and Dimensional Perspectives

Yasmin Rey, Carla E. Marin, and Wendy K. Silverman

Abstract This chapter provides an overview of evidence-based instruments for the assessment of pediatric anxiety disorders from both categorical and dimensional perspectives. The chapter begins with a brief discussion of a categorical perspective to pediatric anxiety assessment and how interview schedules best capture this perspective. This is followed by a summary of the most widely used interview schedules to assess pediatric anxiety, including the evidence base for accomplishing specific assessment goals (i.e., diagnosis and treatment evaluation). The chapter follows with a brief discussion on a dimensional perspective and how rating scales best capture this perspective. This is followed by a summary of the most widely used rating scales for assessing pediatric anxiety, including research support for their use across contexts (i.e., identifying and quantifying anxiety, screening, and treatment evaluation). Next is a brief summary of objective measures of pediatric anxiety. The chapter concludes with a discussion of future research directions.

Keywords Child • Adolescent • Anxiety • Assessment • Evidence base

Pediatric anxiety disorders are among the most common psychiatric disorders affecting children and adolescents, with prevalence rates ranging from 11 % to 12.3 % in community samples [1] and from 4 % to 45 % in clinical samples [2]. They are associated with significant personal distress and interference in functioning (e.g., academic, family, peers) [3]. If left untreated, pediatric anxiety disorders can lead to other psychopathologic conditions including depression and substance abuse [4–6].

One of the greatest challenges is the appropriate assessment of these disorders both in research and clinical settings, particularly in light of their high comorbidity with one another and with other diagnoses. Over the past two decades there has been much attention paid to the development of evidence-based assessment approaches. Evidence-based assessment is important to ensure that treatment is targeted to address the most impairing concern, such as anxiety, and that symptoms can be reliably tracked over time [7].

This chapter provides an overview of evidence-based methods and instruments for the assessment of pediatric anxiety disorders. Both categorical and dimensional perspectives are considered.

Author Note: All authors affiliated with the Child Anxiety and Phobia Program at the Center for Children and Families of the Department of Psychology at Florida International University.
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Y. Rey (✉) • C.E. Marin • W.K. Silverman
Florida International University, 11200 SW 8th Street, Miami, FL 33199, USA
e-mail: yrey@fiu.edu

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Categorical measures are designed to ascertain appropriate diagnosis or diagnoses. For this purpose, structured and semi-structured diagnostic interview schedules, administered to the child or adolescent (from here on referred to as child) and their parents, are used. Dimensional measures assess anxiety as a continuous measure, providing quantitative information about frequency and severity of symptoms. Rating scales, completed by multiple informants including the child and his/her parents, are the most commonly used dimensional measures. For most purposes including initial assessment and treatment evaluation, the combination of the two is recommended, thereby incorporating both perspectives.

Interview schedules and rating scales are emphasized in this chapter because they are the most widely used assessment approaches. We provide an evaluative narrative as well as comprehensive tables that summarize reliability, validity, and utility information. However, such subjective verbal reports have limitations and do not directly capture two additional aspects within the tripartite conceptualization of anxiety [8], namely, (1) avoidance of anxiety-provoking situations or objects and (2) physiological reactions such as rapid heartbeat and sweating. To assess behavioral avoidance, other assessment methods need to be considered such as direct observations. To assess physiological reactions, psychophysiological measurements such as heart rate or galvanic skin response need to be considered. Thus, we include a brief section on these objective measures. There also is growing interest in assessment methods that are at the crossroads of neuroscience and clinical science such as brain imaging and laboratory tasks in attention biases. We refer the interested reader to Chap. 2, as well as Field et al. [9] and Pine [10], for further information on these methods.

It is important to note that all of the categorical and dimensional anxiety measures included in this chapter have been developed based on the revised third or fourth editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R; DSM-IV) [11, 12]. The advent of the fifth edition of the DSM will likely have implications for existing measures of pediatric anxiety which might require revision and psychometric reevaluation.

Multi-method and Multisource Assessment of Pediatric Anxiety

It is generally recommended that a multi-method (e.g., diagnostic interviews, rating scales, observations, physiological measures) and multisource (e.g., children, parents, teachers) assessment approach be pursued whenever possible [13]. A multi-method assessment approach is recommended for pediatric disorders, including anxiety, because symptoms typically manifest across different response systems including the behavioral, the subjective/cognitive, and physiological [8]. The rating scales and diagnostic interview schedules summarized in this chapter capture these three aspects via subjective verbal reports and therefore do not directly capture behavioral and physiological reactions of anxiety. However, more objective measures of these responses are obtained through direct observations and physiological assessment which are summarized later in this chapter.

A multisource assessment approach is also recommended for pediatric disorders, including anxiety, because different respondents typically have different perspectives [14]. It is common practice to obtain information from the child and parent(s) when assessing anxiety. Despite this, there is often low agreement between child and parent reports [15]. This low agreement has been found for both dimensional [15] and categorical measures of pediatric anxiety. For example, studies using the Anxiety Disorders Interview Schedule: Child and Parent versions (ADIS: C/P) [16, 17] have yielded poor estimates of agreement between children and parents regarding the presence of anxiety diagnoses [18–20], although child–parent agreement is higher at the symptom level, especially for observable symptoms [21]. It is less common to obtain information from teachers given the logistical challenges and the lower reliability of internalizing symptom detection in the school setting [22].

Certain factors (e.g., sex, age, parent psychopathology) have been shown to be related to child–parent agreement and the relative reliability of respondents' reports, though these findings have

been inconsistent [23]. Edelbrock [24] found parent reports of internalizing symptoms to be more reliable than young children's self-reports, but older children's self-reports of symptoms were more reliable than parents' reports. In contrast, Silverman and Eisen [25] did not find age differences in parent or child reliability estimates of anxiety symptom reports. In light of these mixed findings, there is clearly a need to advance our understanding of the conceptual and clinical meaning of child and parent discordance [26]. However, despite this, it is generally recommended that information be obtained from both the child and his/her parents in the assessment of pediatric anxiety to obtain as full and accurate a diagnostic picture as possible.

Categorical Perspective in the Assessment of Pediatric Anxiety Disorders

Consistent with a medical model [27], the categorical perspective is the dominant approach used in clinical psychology and psychiatry. Clinical disorders are defined by a specific set of symptoms and criteria, based on the DSM-IV (text revision) [28] or the International Classification of Diseases (ICD-10) [29]. These diagnostic labels are useful because they provide the field with a common language to describe psychopathological conditions. This "present/absent" approach implies that individuals either meet criteria for a disorder or do not and provides less information about subthreshold symptoms that lead to significant impairment [30]. Information about such symptoms may be important for treatment planning [30]. This is where dimensional measures can be useful, as discussed in the following section.

Semi-Structured and Structured Diagnostic Interview Schedules

In clinical practice, diagnostic interviews are most often unstructured. Clinicians ask a series of questions that they either learned during their training or have developed over time, aimed at identifying whether the child meets criteria for any DSM diagnoses. However, in research, semi-structured and structured interviews are the norm for both initial diagnosis and treatment evaluation [31]. These standardized interviews have been designed to limit the variability inherent in unstructured clinical interviews by asking the same questions of all informants and using specific methods to capture the data and record responses. In addition to the standard questions, semi-structured interviews allow interviewers to ask follow-up questions to clarify informants' responses regarding the presence or absence of symptoms. They require administration by clinically trained interviewers who are knowledgeable in the DSM and/or ICD. In contrast, structured interviews require that each question be asked verbatim and additional questions cannot be used to clarify informant responses. Thus, they can be administered by lay persons and require minimal knowledge of the DSM and/or ICD.

Table 1 [17, 20, 25, 32–47] presents a summary of the most widely used and researched semi-structured and structured interview schedules, including, when available, reliability estimates obtained from initial psychometric studies. All of the interview schedules have respective child and parent versions, which are administered separately. Most can be administered to children between the ages of 6 and 18 years. The interview schedules' formats are generally similar. They begin with an introductory section, which includes questions requesting a brief description of the presenting problems, as well as questions about school, activities, friendships, and family. This is followed by sections or modules designed to assess for specific disorders, which typically begin with a small number of screening questions. If an informant responds "yes" to a screening question, the entire set of questions for that section is administered, which includes obtaining frequency, intensity, and interference ratings of endorsed symptoms. If an informant responds "no" to all screening questions, the diagnostic

Table 1 Structured and semi-structured diagnostic interview schedules

Diagnostic interview	Ages, years	DSM anxiety diagnoses	Interrater reliability (κ [kappa])			Test–retest reliability (κ [kappa])			Studies
			Child	Parent	Combined	Child	Parent	Combined	
Semi-structured									
Anxiety Disorders Interview Schedule for DSM-IV: Child and Parent versions	6–18	Generalized Anxiety Disorder	0.72–0.82	0.78–0.82	0.80–0.90	0.63	0.72	0.80	Lyneham et al. [32]
		Obsessive- Compulsive Disorder	…	0.91	0.91–0.96	…	…	…	Rapee et al. [20]
		Separation Anxiety Disorder	0.70–0.81	0.66–0.86	0.59–0.89	0.78	0.88	0.84	Silverman and Eisen [25]
		Social Phobia	0.80–0.87	0.63–0.87	0.77–0.82	0.46–0.71	0.54–0.86	0.73–0.92	Silverman and Nelles [17]
		Specific Phobia	0.59–1.00	0.33–0.87	0.63–1.00	0.76–0.80	0.65–0.80	0.81–0.84	Silverman et al. [33]
Child and Adolescent Psychiatric Assessment	9–17	Generalized Anxiety Disorder	…	…	…	0.79	…	…	Angold and Costello [34] Angold and Costello [35]
Diagnostic Interview for Children and Adolescents	6–18	Separation Anxiety Disorder	…	…	0.94	0.32–0.75	…	…	Boyle et al. [36]
		Specific Phobia	…	…	0.98	0.65	…	…	Kebede et al. [37] Reich [38]
Schedule for Affective Disorders and Schizophrenia for School-Age Children	6–18	Generalized Anxiety Disorder	…	…	1.00	…	…	0.78	Ambrosini [39]
		Obsessive-Compulsive Disorder	…	…	…	…	…	0.67–0.74	Ambrosini et al. [40]
		Post-traumatic Stress Disorder	…	…	…	…	…	0.60–0.67	Kaufman et al. [41]
		Separation Anxiety Disorder	…	…	0.65–1.00	…	…	…	Shahrivar et al. [42]
		Specific Phobia	…	…	0.64–0.75	…	…	0.80	
Structured									
NIMH Diagnostic Interview Schedule for Children Version IV	9–17	Generalized Anxiety Disorder	…	…	1.00	0.38	0.65	0.58	Breton et al. [43]
		Obsessive- Compulsive Disorder	…	…	…	0.63	0.84	0.79	Ho et al. [44].
		Panic Disorder (Agoraphobia)	…	…	…	0.20	…	…	Roberts et al. [45]
		Separation Anxiety Disorder	…	…	1.00	0.27–0.72	0.44–0.58	0.49–0.80	Schwab-Stone et al. [46]
		Social Phobia	…	…	…	0.25–0.44	0.45–0.54	0.44–0.48	Shaffer et al. [47]
		Specific Phobia	…	…	…	0.42–0.68	0.55–0.96	0.86	

section may be skipped. Sections covering developmental, medical, and psychiatric history also are contained in most of the parent versions of the schedules.

Diagnoses are obtained after the separate administration of the child and parent interviews. Both interviews contain questions that correspond to each criterion required to meet a given diagnosis. If the required number of criteria is met for a particular diagnostic section in either the child or parent interview schedule, then a diagnosis is warranted. Separate diagnoses for the child and parent versions are obtained using diagnostic algorithms completed either by the clinician (e.g., Schedule for Affective Disorders and Schizophrenia for School-Age Children, [K-SADS]) [39] or by computer (e.g., The National Institute of Mental Health Diagnostic Interview Schedule for Children for DSM-IV [NIMH DISC-IV]) [47]. These diagnoses are then combined for a final diagnosis using rules derived either by the developers of the interview (e.g., ADIS: C/P) [16] or by computerized algorithms (e.g., DISC-IV) [47].

The *ADIS: C/P* [16] is the most widely used semi-structured interview in pediatric anxiety disorders research, including randomized clinical trials. This is likely because it has the most comprehensive coverage of the DSM anxiety disorders [7]. The ADIS: C/P also includes modules for other common DSM disorders, such as major depressive disorder (MDD) and dysthymia, as well as externalizing disorders (e.g., attention deficit hyperactivity disorder, oppositional defiant disorder).

In addition to acquiring information regarding DSM-IV diagnostic criteria, the ADIS: C/P contains clinician severity rating scales to assess the child's level of distress and/or impairment in functioning relating to each disorder using a 0- (*none*) to 8 (*very much*)-point scale [7]. The severity ratings derived by the clinicians are based on the information obtained from both the child and parent interviews. Severity ratings of 4 or higher suggest a DSM diagnosis, assuming all diagnostic criteria are met. When criteria for multiple disorders have been met, the most severe and interfering disorder, based on the severity rating scale, is considered the primary diagnosis, followed by a ranking of the other severity ratings (e.g., secondary, tertiary). The ADIS: C/P severity rating scales are also used to obtain ratings from children and parents of the severity of the child's fear and/or avoidance in specific situations. In this way, clinicians can ascertain which symptoms/situations are most severe and should be targeted in the child's treatment.

The *Child and Adolescent Psychiatric Assessment (CAPA)* [35] is a semi-structured interview that assesses the frequency, duration, and intensity of symptoms associated with over 30 psychiatric disorders, including the anxiety disorders, according to the DSM-IV and ICD-10. It also covers a number of disorders that were part of DSM-III-R but are no longer included in the DSM-IV (e.g., overanxious disorder [OAD], avoidant disorder [AVD]). The CAPA assesses symptoms of psychiatric disorders that have occurred over the past 3 months, referred to as the *primary period*. It uses a modular format, allowing interviewers to administer specific diagnostic modules independently from the entire interview. Unique to the CAPA is the inclusion of a glossary that provides descriptions of symptoms reported by the child or parent to aid the interviewer in determining the presence or absence of symptoms. Also included in the glossary are instructions for coding symptom severity levels.

The *Diagnostic Interview for Children and Adolescents (DICA)* [38] was designed originally as a highly structured interview to be administered by lay interviewers; however, successive versions have rendered the DICA more semi-structured [38]. In addition to a parent version, the DICA has a version for children ages 6–12 years old and a version for adolescents ages 13–18 years old. The DICA covers over 20 psychiatric disorders, including all of the anxiety disorders, using DSM-IV criteria. Similar to the CAPA, the DICA also covers a number of disorders that were part of DSM-III-R but are no longer included in the DSM-IV (e.g., OAD, AVD). Diagnoses based on the ICD-10 can be derived using computer algorithms. The DICA assesses both current psychiatric diagnoses and lifetime diagnoses.

The *(K-SADS)* [39] is a semi-structured interview that assesses over 30 psychiatric disorders, including the anxiety disorders. At present, there are three versions available: the K-SADS-Present

State (K-SADS-P-IVR), K-SADS-Epidemiologic (K-SADS-E), and K-SADS-Present and Lifetime (K-SADS-P/L). The K-SADS-P-IVR assesses frequency and severity of symptoms of psychiatric disorders, both currently and over the past 12 months, based on the DSM-IV, DSM-III-R, and the Research Diagnostic Criteria (RDC) [48]. The authors of the current K-SADS-P-IVR also included the Clinical Global Impressions Scales [49], which are used to measure symptom severity and symptom improvement. The K-SADS-E (fifth version) and K-SADS-P/L both assess current and lifetime diagnoses based on the DSM-IV and DSM-III-R. The K-SADS-P/L (version 1.0) is unique in its inclusion of an 82-symptom screening interview. If a child or parent responds "yes" to the presence of a given symptom, a supplement with the remaining symptom criteria for the specific disorder is administered. If a child or parent responds "no" to the screening symptoms, the specific diagnostic supplemental section is skipped, shortening administration time.

The *NIMH DISC-IV* [47] was originally designed for epidemiological use, but successive versions have been used in clinical studies and as an aid to diagnosis in service settings. The DISC-IV is a structured interview that assesses over 30 psychiatric disorders, including the anxiety disorders, based on the DSM-IV and ICD-10. The DISC-IV assesses the presence of current diagnoses (within the past 4 weeks at the time of the interview) and diagnoses occurring within the past 12 months. It also includes an optional module for lifetime diagnoses.

Reliability

Table 1 summarizes the interview schedules' reliability estimates (kappa coefficients) for specific anxiety disorders when study sample sizes were sufficient to allow these analyses. Kappa coefficients (κ[kappa]) greater than 0.74 are considered excellent, κ[kappa]s between 0.59 and 0.74 are considered good, κ[kappa]s between 0.40 and 0.58 are considered fair, and κ[kappa]s <0.40 are considered poor [50].

As Table 1 shows, estimates of reliability between clinicians (or interrater reliability) have generally been found to be good to excellent for generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), separation anxiety disorder (SAD), social phobia (SOP), and specific phobia (SP) (κ[kappa]: 0.63–1.00) using the latest version of the ADIS: C/P for DSM-IV [16] and its previous version for DSM-III-R [17] according to child, parent, and combined child and parent reports (see Table 1) [17, 20, 32]. The previous version of the ADIS: C/P for DSM-III-R has shown somewhat lower reliability estimates for some anxiety disorders examined, such as SAD (κ[kappa] = 0.59) found anywhere in the diagnostic profile using combined child and parent reports, and poor to fair estimates for SP as the primary diagnosis and as a diagnosis anywhere in the profile using child and parent reports, respectively (κ[kappa]: 0.33–0.59) [17, 20].

Test–retest reliability estimates (7–14 day retest interval) for specific anxiety diagnoses using the ADIS: C/P for DSM-IV and its previous version have generally been found to be good to excellent for GAD, SAD, SOP, and SP (κ[kappa]: 0.63–0.92) according to child, parent, and combined reports (see Table 1) [25, 33]. However, one study [25] using the previous version of the ADIS for DSM-III-R [17] found fair reliability estimates for SOP according to child and parent reports (κ[kappa]: 0.46 and 0.54, respectively) (see Table 1).

The reliability of diagnoses has been examined using several versions of the K-SADS (K-SADS-P-IIIR and K-SADS-IV-R, K-SADS-E, and K-SADS-P/L) in both clinic and community samples [39–42]. Findings show that interrater and test–retest reliability estimates for anxiety diagnoses based on combined child and parent reports vary from good to excellent (see Table 1).

One study examined interrater reliability of a number of disorders, including some anxiety disorders, using the DISC-R [51]. Reliability estimates for the anxiety disorders examined, namely, GAD

and SAD, were excellent (see Table 1). This finding is not surprising given the highly structured nature of the DISC. Retest reliability of diagnoses using the latest version of the DISC (DISC-IV), as well as previous versions (i.e., DISC-R, DISC 2.1, and DISC 2.3), has been examined in both clinic and community samples [43–47]. Retest intervals ranged between 1 and 23 days. As Table 1 shows, reliability estimates in the good to excellent range were found for OCD using child, parent, and combined reports (κ[kappa]: 0.63–0.84) [44]. Poor to fair retest reliability estimates were found across studies for SOP and panic disorder (PD) with agoraphobia using child, parent, and combined reports (κ[kappa]: 0.20–0.54) [45, 47]. Test–retest reliability estimates for GAD, SAD, and SP using the DISC vary across studies and informants. Test–retest reliability estimates for GAD have been found to be good using parent report (κ[kappa] = 0.65) [46] but poor to modest for child and combined reports (κ[kappa]: 0.38–0.58) [45, 47]. Retest reliability estimates for SAD have been excellent for child and combined reports in one study (κ[kappa] = 0.72 and 0.80, respectively) [46], but other studies have found poor to fair estimates for SAD using child, parent, and combined reports (κ[kappa]: 0.27–0.58) [43, 45, 47]. Good to excellent reliability estimates were found for SP using child, parent, and combined reports in one study (κ[kappa]: 0.68–0.96) [47], but other studies reported only fair reliability estimates for SP using child and parent reports (κ[kappa]: 0.42–0.55) [43, 45].

Less research has been conducted on the reliability of anxiety diagnoses using the CAPA and DICA [34–38]. Overall, studies show good to excellent (κ[kappa]: 0.65–0.98) interrater and retest reliability estimates [34, 35, 37, 38], except for one study on the child-report version of the DICA, which found a poor retest reliability estimate of 0.32 for SAD [36]. More research is needed given the absence of interrater reliability estimates on CAPA- derived anxiety diagnoses and the availability of retest reliability estimates for child-reported GAD only. Further, interrater and retest reliability estimates are available for a couple of DICA-derived anxiety diagnoses (i.e., SAD, SP) based on combined child and parent reports or child report only.

Validity

Relative to studies examining reliability, fewer studies have examined the validity of anxiety diagnoses using interview schedules. Wood et al. [52] examined concurrent validity of ADIS: C/P diagnoses of GAD, PD, SAD, and SOP in 186 children (ages 8–17 years) referred to an anxiety disorders clinic. Children and their parents were administered the ADIS: C/P and completed the Multidimensional Anxiety Scale for Children (MASC) [53]. Findings showed strong convergence between the ADIS: C/P anxiety diagnoses (except for GAD) and the MASC subscale scores corresponding to the respective disorders. Findings also supported divergent validity of the ADIS: C/P in the predicted direction. For example, MASC Social Anxiety subscale scores, but no other subscale scores, were significantly elevated for children meeting *DSM-IV* SOP.

Studies of the validity of anxiety diagnoses obtained using the DICA and K-SADS have not shown such positive results [36, 54]. For example, in a study of 30 clinic-referred children (ages 7–16 years), poor to modest convergence was found for the presence of any DSM-III anxiety disorder between the K-SADS and Child Assessment Schedule [54, 55]. In a community sample of 2,317 children (ages 6–16 years), poor convergence was observed between the DICA-R DSM-III-R anxiety diagnoses of SAD and OAD and subscales corresponding to these disorders on the revised Ontario Child Health Study Scales [56] (κ[kappa] = 0.37 and 0.31, respectively) [36]. Although these findings fail to support the concurrent validity of these two widely used interviews, it should be noted that the K-SADS findings were likely impacted by the small sample size and both studies are based on previous editions of DSM; validity studies using DSM-IV diagnoses and measures are needed.

Alternative Formats

The semi-structured and structured interview schedules summarized above have been most commonly administered face to face with the interviewer recording the interviewees' responses using a hard paper copy of the interview. Several of the interview schedules are available in alternative formats, though research on these formats is relatively scant.

The DISC-IV (C-DISC-4.0) [47] and the DICA [38], for example, are available in computerized formats. With the C-DISC-4.0, interviewers read questions from a computer screen and key in responses given by the child and/or parent. Scoring algorithms are built into the computer program, which generates a diagnostic report immediately after completion of the interview, thus minimizing interviewer error. The administration of the DISC-IV is not necessarily straightforward for clinicians (e.g., clinicians must follow specific skipping instructions and keep track of informants' responses to a number of symptoms to determine if follow-up questions about onset and impairment are warranted). As a consequence, the DISC authors recommend that interviewers using more than a single diagnostic module employ the C-DISC-4.0 to aid interview administration [47]. Reliability of diagnoses using the C-DISC-4.0 was examined in one study [57] using the Spanish version of the interview. Test–retest reliability estimates for the anxiety disorders examined, namely, SAD, GAD, and SOP, were fair to good (κ[kappa]: 0.47–0.66) based on parent report only. Reliability estimates for lifetime diagnoses of SAD, GAD, and SOP based on parent report were poor to excellent (κ[kappa]: 0.27–0.75).

The computerized DICA can be administered by an interviewer or be self-administered. Children and/or their parents read the interview questions from the computer screen and answer them on their own. The DICA authors recommend that an interviewer administer the computerized DICA for younger children, as well as older children or parents with reading difficulties [38]. Only one study examined the retest reliability (over a 1 week retest interval) of diagnoses using the self-administered computerized DICA in a sample of clinic-referred children 6–18 years old [58]. Results revealed poor to modest kappa coefficients for the anxiety disorders examined, namely, OAD, SAD, and post-traumatic stress disorder (PTSD) (κ[kappa]: 0.35–0.50).

In addition to computerized formats, interview schedules can be administered via the telephone. Telephone assessments are useful when assessing families who reside in geographically distant locations as well as those with demanding schedules and/or transportation difficulties. Telephone assessments can also be useful for conducting posttreatment or follow-up evaluations. The parent version of the ADIS:C/P has been used in a telephone format. Lyneham and Rapee [59] compared agreement between diagnoses (present/absent) derived using a telephone administration of the parent ADIS to diagnoses derived from standard face-to-face administration of the ADIS:C/P. Kappa coefficients of agreement were in the good to excellent range for anxiety diagnoses examined, GAD, SAD, SOP, and SP (κ[kappa]: 0.63–0.86). These findings suggest anxiety disorders can be diagnosed using a less resource-demanding alternative to face-to-face assessments [59]. Similar studies are needed for other interview schedules, as well as other delivery formats including web-based formats (i.e., Internet DISC-IV [60]).

Summary

The primary aim of the interviews described above is to diagnose psychiatric disorders as well as to evaluate diagnostic status at posttreatment. Thus, it is critical that the anxiety diagnoses derived from these interviews are reliable and valid. The ADIS: C/P is well researched with respect to reliability, with several studies reporting overall good to excellent retest and interrater reliability estimates. The DISC is the next most researched interview in terms of retest reliability, with findings generally

showing fair estimates for most of the anxiety disorders examined. Less research has been conducted on the reliability of anxiety diagnoses using the K-SADS, CAPA, and DICA, but the findings generally show good reliability estimates for most anxiety disorders examined. Validity data have also been obtained for the ADIS: C/P, DICA, and K-SADS. The ADIS: C/P has demonstrated strong convergence between anxiety diagnoses examined (i.e., SAD, SOP, PD) and corresponding subscales of the MASC. In contrast, findings for the DICA and K-SADS have shown poor to modest convergence between anxiety disorders examined and other measures of anxiety, but these studies were conducted using previous versions of the DSM and require updating.

Overall, the ADIS: C/P is currently considered the "gold standard" and the most highly recommended interview for the diagnosis of pediatric anxiety disorders. Given most of the ADIS: C/P evaluative research has been conducted in anxiety disorders specialty clinics, more research is needed using the interview in community clinics where base rates for anxiety disorders are lower than in anxiety clinics. Also needed is research on the reliability of pediatric anxiety diagnoses with relatively low base rates such as OCD, PD, and PTSD. Finally, more research is needed on the evaluation of interview schedules administered in alternative formats.

Dimensional Perspective in Assessment of Pediatric Anxiety Disorders

Within a dimensional perspective, emotional and behavioral problems occur along a continuum of severity, instead of falling into distinct disorders [61]. As such, the differences between normal and disordered behaviors are viewed as quantitative rather than qualitative. Within this perspective, symptoms of disordered behavior as well as the threshold between normal and disordered behaviors are derived statistically from large representative samples of children and may vary according to child sex, age, and, in some cases, ethnicity.

Child and Parent Anxiety Rating Scales

Rating scales are the primary dimensional measure of pediatric anxiety. They are commonly used as screening tools to identify the presence of anxiety in children and to assess treatment response by quantifying the degree to which anxiety symptoms or anxious behaviors are present before and after treatment. Table 2 [62–123] presents the most widely used and researched rating scales for the assessment of pediatric anxiety. Also included in the table are reliability and validity estimates from psychometric studies.

All of the rating scales included in Table 2 are completed by children and/or adolescents, and most also have accompanying versions that can be administered to parents. The parent versions are identical to the child versions except the item stems have been changed (e.g., "I" modified to "My child"). These rating scales yield a total score, as well as subscale scores with higher scores indicating greater anxiety. Additionally, most have recommended clinical cutoff scores that suggest the presence of an anxiety diagnosis. (The utility of these clinical cutoffs is discussed later in the chapter.) The scales are now summarized below.

The *MASC* [53] contains 39 items that assess major areas of anxiety in children ages 8–19 years. A parent-report version (parent MASC) has also been examined for parents of children 7–13 years old [64, 75]. Children rate the frequency of experiences such as "I get scared when my parents go away" and "I worry about doing something stupid or embarrassing" using a 4-point scale (i.e., *never, rarely, sometimes, often)*. The MASC contains four subscales: Physical Symptoms, Social Anxiety, Harm Avoidance, and Separation/Panic. The MASC also contains an Inconsistency Index, to identify

Table 2 Youth and parent anxiety rating scales

Rating scale	Internal consistency (α)	Test–retest reliability	Convergent validity (r)	Divergent validity (r)	Studies
Youth scales					
Multidimensional Anxiety Scale for Children (MASC)	Total: 0.84–0.94 Physical Symptoms (PS): 0.77–0.89 Social Anxiety (SA): 0.66–0.91 Harm Avoidance (HA): 0.53–0.82 Separation/Panic (S/P): 0.58–0.81	3 weeks (ICCs) Total: 0.79–0.88 PS: 0.80–0.92 SA: 0.79–0.84 HA: 0.34–0.76 S/P: 0.85–0.89 1 month (ICCs) Total: 0.73–0.86 PS: 0.73–0.85 HA: 0.60–0.73 SA: 0.75–0.90 S/P=0.74 3 months (ICCs) Total=0.93 PS=0.83; HA=0.72 SA=0.83; S/P=0.93 12 months (*r*s) Total=0.52 PS=0.47; HA=0.48 SA=0.54; S/P=0.55	With RCMAS, STAIC, SCARED, SCAS Total: 0.60–0.81 PS: 0.44–0.76 SA: 0.54–0.73 HA: −0.13 to 0.43 S/P: 0.27–0.58	With Abbreviated Symptom Questionnaire [62] and Children's Depression Inventory (CDI) [63] Total: −0.15 to 0.60 PS: 0.07–0.66 SA: −0.01 to 0.59 HA: −0.04 to 0.32 S/P: 0.18–0.33	Baldwin and Dadds [64] Fincham et al. [65] Grills-Taquechel et al. [66] Ivarsson [67] Kingery et al. [68] March et al. [69] March et al. [70] Muris et al. [71] Olason et al. [72] Osman et al. [73] Rynn et al. [74] Villabø et al. [75] Yao et al. [76]. Yen et al. [77]
Revised Child Anxiety and Depression Scales (RCADS)	Generalized Anxiety Disorder (GAD): 0.77–0.86 Obsessive-Compulsive Disorder (OCD): 0.73–0.83 Panic Disorder (PD): 0.79–0.88 Separation Anxiety Disorder (SAD): 0.76–0.79 Social Phobia (SOP): 0.82–0.87	1 week (ICCs) GAD=0.79; OCD=0.65 PD=0.76; SAD=0.75 SOP=0.80	With RCMAS: GAD: 0.65–0.73 OCD: 0.49–0.67 PD: 0.59–0.69 SAD: 0.58–0.62 SOP: 0.62–0.73	With CDI GAD: 0.05–0.64 OCD: 0.12–0.64 PD: 0.20–0.60 SAD: 0.06–0.44 SOP: 0.14–0.60	Chorpita et al. [78] Chorpita et al. [79] de Ross et al. [80]

Revised Children's Manifest Anxiety Scale (RCMAS); RCMAS-2	Total: 0.85–0.92 Physiological Anxiety (PA): 0.67–0.75 Worry (W): 0.77–0.86 Social Concerns/Concentration (SC): 0.67–0.72 Social Anxiety (SA) = 0.80	1 week (*r*s) Total: 0.76–0.88 PA: 0.73–0.75 W: 0.71–0.85 SC = 0.85 SA = 0.64 2 weeks (*r*s) Total = 0.68 PA: =0.61; W = 0.66 SA = 0.61 5 weeks (*r*s) Total = 0.77 PA = 0.78; W = 0.63 SC = 0.60 9 months (*r*) Total = 0.68	With MASC, SCARED, SCAS, and STAIC Total: 0.58–0.88 PA: 0.59–0.85 W: 0.73–0.84 SC: 0.64–0.73	With CDI Total: 0.56–0.74 PA = 0.61 W = 0.66 SC = 0.69	Ang et al. [81] Muris et al. [71] Reynolds [82] Reynolds [83] Reynolds and Richmond [84] Varela and Biggs [85] Winsniewski et al. [86] Wolfe et al. [87]
Screen for Child Anxiety Related Emotional Disorders (SCARED)	Total: 0.89–0.94 Somatic/Panic (S/P):0.70–0.88 Generalized Anxiety (GA): 0.77–0.88 Separation Anxiety (SA): 0.54–0.75 Social Phobia (SOP): 0.72–0.89 School Phobia (ScP): 0.43–0.86	2 weeks ICCs (*r*s) Total = 0.57 (0.61) S/P = 0.77 (0.82) GA = 0.50 (0.52) SA = 0.46 (0.51) SOP = 0.53 (0.55) ScP = 0.65 (0.66) 5 weeks ICCs Total = 0.86 Subscales: 0.70–0.90 3 months ICCs (rs) Total = 0.50 (0.57–0.70) S/P = 0.67 (0.58–0.69) GA = 0.46 (0.50–0.62) SA = 0.51 (0.55–0.69) SOP = 0.24 (0.29–0.83) ScP = 0.52 (0.46–0.53) 6 months (*r*s) Total = 0.47 S/P = 0.38; GA = 0.48 SA = 0.19; SOP = 0.47 ScP = 0.36	With MASC, SCAS, STAIC, RCMAS, Internalizing (INT) and Anxious/ Depressed (AD) scales of the Youth Self-Rating Scale (YSR) [88] Total: 0.61–0.87 S/P: 0.59–0.78 GA: 0.61–0.84 SA: 0.47–0.66 SOP: 0.36–0.66 ScP: 0.36–0.58	With CDI, Conners Attention Deficit Hyperactivity Disorder-Adolescent Version [89], and Externalizing (EXT) scale of the YSR [88] Total: 0.13–0.71 S/P: 0.07–0.65 GA: 0.21–0.69 SA: 0.20–0.37 SOP: 0.08–0.43 ScP: 0.06–0.53	Birmaher et al. [90] Birmaher et al. [91] Boyd et al. [92] Crocetti et al. [93] Essau et al. [94] Hale et al. [95] Haley et al. [96] Linyan et al. [97] Muris et al. [98] Muris et al. [71] Muris et al. [99] Weitkamp et al. [100]

(continued)

Table 2 (continued)

Rating scale	Internal consistency (α)	Test–retest reliability	Convergent validity (r)	Divergent validity (r)	Studies
Spence Children's Anxiety Scale (SCAS)	Total: 0.88–0.94 Separation Anxiety (SA): 0.61–0.85 Generalized Anxiety (GA): 0.61–0.86 Social Anxiety (SOC): 0.70–0.80 Obsessions/Compulsions (O/C): 0.58–0.84 Panic/Agoraphobia (P/AG): 0.74–0.89 Fears of Physical Injury (PI): 0.53–0.90	2–4 weeks (rs) Total: 0.76–0.86 SA: 0.69–0.76 GA: 0.69–0.78 SOC: 0.67–0.79 O/C: 0.64–0.77 P/AG: 0.67–0.78 PI: 0.72–0.83 12 weeks (rs) Total = 0.63 SA = 0.52; GA = 0.66 SOC = 0.75; O/C = 0.69 P/AG = 0.51; PI = 0.59 6 months (rs) Total = 0.60 SA = 0.57; GA = 0.56 SOC = 0.57; O/C = 0.53 P/AG = 0.45; PI = 0.54	With RCMAS, MASC, SCARED, STAIC, and YSR INT and AD scales Total: 0.71–0.92 SA: 0.49–0.68 GA: 0.58–0.76 SOC: 0.41–0.73 O/C: 0.52–0.66 P/AG: 0.56–0.73 PI: 0.40–0.63	With CDI and Depression Self-Rating Scale [101] Total: –0.03 to 0.72 SA: –0.12 to 0.58 GA: 0.01–0.60 SOC: –0.09 to 0.70 O/C: –0.02 to 0.57 P/AG: –0.01 to 0.66 PI: –0.21 to 0.53	Brown-Jacobson et al. [102] Essau et al. [94] Hernandez-Guzman et al. [103] Ishikawa et al. [104] Mellon and Moutavelis [105] Muris et al. [71] Muris et al. [99] Spence [106] Spence et al. [107] Whiteside and Brown [108]
State-Trait Anxiety Inventory for Children (STAIC)	Trait (T): 0.59–0.91 State (S): 0.73–0.94	1 week (ICCs) S: 0.32–0.79 15 days (rs) T = 0.81; S: 65–0.67 3 weeks (ICCs) T = 0.85; S = 0.55 6 weeks (rs): T: 0.65–0.71; S: 0.31–0.47	With RCMAS, MASC, SCARED, and SCAS: T: 0.58–0.88 S: 0.24–0.35	With CDI: T: 0.36–0.74	Chayawat and Brown [109] Cross and Huberty [110] Li and Lopez [111, 112] Muris et al. [71] Nelson et al. [113] Papay and Hedl [114] Papay and Spielberger [115] Psychoutaki et al. [116] Reynolds [82] Schisler et al. [117] Spielberger [118]
Parent scales					
Multidimensional Anxiety Scale for Children-Parent Version (MASC-P)	Total = 0.87–0.90 Physical Symptoms (PS) = 0.77–0.85 Harm Avoidance (HA) = 0.70–0.74 Social Anxiety (SA) = 0.86–0.89 Separation/Panic (SP) = 0.72–0.77	12 months (rs) Total = 0.70 PS = 0.66 HA = 0.56 SA = 0.68 S/P = 0.70	With SCAS subscales Subscales: 0.16–0.74	…	Baldwin and Dadds [64] Villabø et al. [75]

Revised Child Anxiety and Depression Scale- Parent Version (RCADS-P)	Total = 0.95 Total Anxiety = 0.94 Generalized Anxiety Disorder (GAD): 0.82–0.88 Major Depressive Disorder (MDD): 0.80–0.83 Obsessive-Compulsive Disorder (OCD): 0.74–0.84 Panic Disorder (PD): 0.71–0.81 Social Phobia (SOP): 0.84–0.88 Separation Anxiety Disorder (SAD): 0.72–0.83	2 weeks (*r*s) GAD = 0.81 MDD = 0.83 OCD = 0.75 PD = 0.69 SOP = 0.79 SAD = 0.89	With CBCL subscales (i.e., INT, AD, and AP): Total Anxiety: 0.62–0.76 GAD: 0.71–0.73 OCD = 0.40 PD: 0.57–0.60 SOP: 0.60–0.65 SAD: 0.59–0.69	With DSM Affective Problems scale of CBCL Total Anxiety: 0.55–0.56 GAD = 0.53 OCD = 0.32 PD = 0.47 SOP = 0.46 SAD = 0.42	Ebesutani et al. [119, 120]
Screen for Child Anxiety Related Emotional Disorders-Parent Version (SCARED-P)	Total = 0.90	…	…	…	Birmaher et al. [91]
Spence Children's Anxiety Scale-Parent Version (SCAS-P)	Total: 0.89–0.93 Separation Anxiety (SA): 0.74–0.90 Generalized Anxiety (GA): 0.67–0.91 Social Anxiety (SOC): 0.74–0.92 Panic/Agoraphobia (P/AG): 0.61–0.92 Fear of Physical Injury (PI): 0.47–0.83 Obsessions/Compulsions (O/C): 0.74–0.92	…	With Negative Affectivity and Physiological Arousal subscales of Affect and Arousal Scale (AFARS) [121] and CBCL INT scale Total: 0.37–0.59 SA: 0.28–0.36 GA: 0.38–0.40 SOC: 0.38–0.48 P/AG: 0.25–0.27 PI: 0.12–0.28 O/C: 0.16–0.19	With AFARS Positive Affectivity subscale and CBCL EXT scale Total: –0.21 to 0.33 SA = –0.14 GA = –0.22 SOC = –0.27 P/AG = –0.18 PI = 0.03 O/C = –0.13	Brown-Jacobson et al. [102] Nauta et al. [122] Whiteside and Brown [108]
State-Trait Anxiety Inventory for Children- Parent Report-Trait Version (STAIC-P-T)	Total: 0.84–0.91	8 weeks (ICCs) Total: 0.71–0.75 12 months (ICCs) Total: 0.68–0.76	With CBCL AD Scale Total: 0.50–0.65	With CBCL AB and Delinquent Behavior scales Total: –0.03 to 0.21	Southam-Gerow et al. [123]

inconsistencies in responses. In addition, the MASC contains two embedded subscales: a 12-item Anxiety Disorders Index and a 10-item short form (MASC-10). The 12-item Anxiety Disorders Index was empirically derived to discriminate between children with anxiety disorders from children with other disorders. Studies have found that children with anxiety disorders score significantly higher on the Anxiety Disorders Index than children with other psychiatric disorders (e.g., depressive disorders) [66, 72]. The MASC-10 was designed for purposes such as treatment monitoring and evaluation [70]. Norms for the MASC based on a large school sample of children ($N = 2698$; 8–19 years old) are available separately for each sex and three age groups (8–11 years, 12–15 years, and 16–19 years). A *T*-score above 65 on the MASC total indicates clinically significant levels of anxiety [53]. There are no norms or suggested clinical cutoff scores available for the parent MASC.

The *Screen for Child Anxiety Related Emotional Disorders (SCARED)* [90, 91] contains 38 items and can be administered to children ages 8–19 years (and to parents of children 6–18 years for the parent SCARED) [91]. Children rate the frequency of experiences over the past 3 months such as "It is hard to talk with people I don't know well" and "I follow my mother or father wherever they go" using a 3-point scale (i.e., *not true or hardly ever true, somewhat true or sometimes true, very true or often true)*. In addition to the total scale, the SCARED contains five subscales: Somatic/Panic, Generalized Anxiety, Separation Anxiety, Social Phobia, and School Phobia. The original SCARED was subsequently revised to include an additional 3 items because the Social Phobia Scale did not discriminate between children with SOP from children with other anxiety disorders [91]. There are no norms available for the SCARED. However, one study using a sample of 190 clinic-referred children (9–19 years old) and their parents determined that a cutoff score of 25 optimally discriminated between anxiety and non-anxiety, anxiety and depression, and anxiety and disruptive disorders [91]. There are no norms or suggested clinical cutoff scores available for the parent SCARED.

In addition to the revised 41-item SCARED, there is another revised version of the SCARED that contains 66 items [124]. In this version, the School Phobia subscale was removed (i.e., these items were added to the Separation Anxiety subscale) and five additional subscales were added: SP-Animal type, SP-Blood Injection Injury type, SP-Situational Environment type, PTSD, and OCD. The 66-item revised version of the SCARED has been used less frequently than the 38- and 41-item versions. (See Muris et al. [124] and Muris and Steerneman [125] for examples of studies evaluating the 66-item version.)

The *Spence Children's Anxiety Scale (SCAS)* [107, 126] contains 44 items and can be administered to children ages 7–18 years (and to parents of children ages 6–18 years using the parent SCAS) [122]. Thirty-eight of the items assess symptoms of anxiety; six are filler items to reduce negative response biases. Children rate the frequency of experiences such as "I worry that I will do badly at my schoolwork" and "I am scared of the dark" using a 4-point scale (i.e., *never, sometimes, often,* and *always*). In addition to the Total Anxiety scale, the SCAS contains six subscales: Separation Anxiety, Generalized Anxiety, Social Anxiety, Obsessions/Compulsions, Panic/Agoraphobia, and Fears of Physical Injury (which maps onto SP). Norms for the SCAS based on a large school sample of Australian children ($N = 4{,}916$) are available separately by sex and two age groups (8–11 years; 12–15 years). A *T*-score of 65 on the SCAS total or subscales indicates clinically significant levels of anxiety. Norms based on a Dutch school-based sample of 745 parents of children ages 6–18 years are available for the parent SCAS, separated by sex, two age groups (6–11 years and 12–18 years), and by anxiety disorder status (with vs. without) [122]. Although norms are available, there are no suggested clinical cutoffs for the parent SCAS.

The *Revised Child Anxiety and Depression Scale (RCADS)* [78, 79] contains 47 items and can be administered to youth ages 6–18 years (and to parents of children ages 6–18 years using the parent RCADS) [119, 120]. Children rate the frequency of experiences such as "I am afraid to talk in front of class" and "I feel nothing is much fun anymore" using a 4-point scale (i.e., *never, sometimes, often, always*). In addition to the total scale and Total Anxiety scale, the RCADS contains six subscales: SAD, SOP, GAD, PD, OCD, and MDD. The RCADS is a revised version of the SCAS designed to

broaden the assessment beyond anxiety disorders to depressive disorders by including an MDD subscale. In addition to an MDD subscale, an important difference between the RCADS and the original SCAS is the GAD subscale: Items were added to the RCADS (replacing items from the original SCAS) that are more consistent with DSM-IV GAD criteria. Another important difference between the RCADS and SCAS is that the RCADS does not contain a Fear of Physical Injury subscale.

Norms based on a school sample ($N = 1887$) are available for the RCADS, separated by sex and grade [79]. Clinical cutoff scores on the subscales were derived using a sample of 513 clinic-referred children [78]. A score of 10 or higher on the SOP subscale indicates a diagnosis of SOP; a score of 7 or higher on the GAD subscale indicates a diagnosis of GAD; a score of 5 or higher on the SAD or OCD subscale indicates a diagnosis of SAD and OCD, respectively; and a score of 12 or higher on the PD subscale indicates a diagnosis of PD. Norms based on a school-based sample of 967 parents of children ages 6–18 ($N = 1,887$) are available for the parent RCADS, separated by sex and grade [120]. Clinical cutoff scores on the subscales were derived using a sample of 490 parents of clinic-referred children ages 6–18 [119]. A score of 12 or higher on the SOP subscale indicates a diagnosis of SOP; a score of 6 or higher on the GAD subscale indicates a diagnosis of GAD; a score of 4 or higher on the SAD or OCD subscale indicates a diagnosis of SAD and OCD, respectively. A cutoff score for the PD subscale was not derived in this study.

The *Revised Children's Manifest Anxiety Scale (RCMAS)* [84] has a long history in pediatric anxiety assessment and treatment evaluation research. The RCMAS is a revised version of the original Children's Manifest Anxiety Scale [127], a downward extension of the Manifest Anxiety Scale for adults [128]. The RCMAS contains 37 items and can be administered to children ages 6–19 years. Respondents indicate "yes" or "no" to items such as "I often worry about something bad happening to me" and "I am afraid of a lot of things." In addition to the Total Anxiety scale, the RCMAS contains three subscales: Physiological Anxiety, Worry/Oversensitivity, and Social Concerns. The RCMAS also contains a Lie Scale consisting of 9 items (e.g., "I am always good"). High Lie Scale scores may call into question the validity of the ratings and suggest the consideration of alternative sources of information. The Lie Scale also can be viewed as an indicator of social desirability [84, 129, 130]. Norms based on a large community sample of children ($N = 4,972$; ages 6–19 years) are available separately by sex, age (6–8 years, 9–14 years, 15–19 years), and race (white and black). A *T*-score on the Total Anxiety scale greater than one standard deviation above the mean ($T > 60$) indicates clinically significant levels of anxiety [84].

Recently, the RCMAS was revised from its previous 37-item version to a 49-item version (RCMAS-2) [131]. Like the RCMAS, the RCMAS-2 has a "yes/no" response format and yields a Total Anxiety score. The RCMAS-2 also contains three subscales: Physiological Anxiety, Worry, and Social Anxiety. The latter subscale replaced the RCMAS Social Concerns subscale. The RCMAS-2 also includes a new 10-item content-based cluster that assesses performance anxiety. In addition, by administering only the first 10 items, the RCMAS-2 can be used as a short form, which takes about 5 min to complete.

The RCMAS-2 eliminated the 9-item RCMAS Lie Scale and now contains a "Defensiveness Scale." The Defensiveness Scale consists of 9 items that assess whether children's responses have been given in a defensive manner, with the aim of presenting themselves in a positive light (i.e., social desirability). Higher scores on this scale indicate higher levels of defensiveness. The RCMAS-2 also contains a newly added Inconsistent Responding Index, which assesses inconsistency in responses to nine pairs of items. More pairs of inconsistent items suggest greater likelihood that the child or adolescent is responding randomly or without regard to the item's content.

Norms based on a large representative US sample of children ($N = 3,086$; 6–19 years old) are available for the RCMAS-2, separately by sex and age (6–8 years; 9–14 years; 15–19 years) [131]. A *T*-score on the Total Anxiety scale greater than 1 standard deviation from the mean ($T > 60$) indicates clinically significant levels of anxiety. The reliability and validity of the RCMAS-2 were evaluated using the same sample of children from which the norms were derived as well as a school sample

of children from Singapore [81]. Findings thus far show the RCMAS-2 yields similar reliability and validity estimates as the previous version.

Similar to the RCMAS, the *State-Trait Anxiety Inventory for Children (STAIC)* [118] has a long history. A downward extension of the adult State-Trait Anxiety Inventory [132], the 20-item STAIC assesses chronic (trait) and acute (state) symptoms of anxiety in children ages 8–15 years. An example of an item that assesses trait anxiety is "I worry about things that may happen." An example of an item that assesses state anxiety is "I feel like crying." Children rate the frequency of these experiences using a 3-point scale (i.e., *hardly ever, sometimes, often*). Norms based on a large US school sample ($N = 1{,}551$, 9–12 years old) are available, separately for sex and each grade (4th–6th grade) [118]. A *T*-score greater than 1 standard deviation above the mean ($T > 60$) indicates clinically significant levels of anxiety [118]. Unlike the anxiety rating scales summarized thus far, the STAIC is mainly used for the assessment of trait anxiety instead of clinical symptoms of anxiety. As such, it is not as widely used in the assessment of treatment outcomes as the other measures.

The parent STAIC [123] includes only the Trait scale (STAIC-P-T) and can be administered to parents of children ages 7–15 years old. The STAIC-P-T includes six additional questions that assess several child anxiety-related physiological responses (e.g., dry mouth, jittery, headaches) from the parent's perspective. Currently, there are no norms or suggested clinical cutoff scores available for the parent STAIC-P-T.

Reliability

Table 2 summarizes the internal consistency and retest reliability estimates found across studies for the child and parent rating scales described above. Internal consistency (alpha) coefficients provide a measure of how well the items on a particular measure are related to one another and are likely to be assessing the same or similar constructs. Alpha coefficients >0.80 are generally considered high; alphas between 0.70 and 0.80 are moderate; and alphas <0.70 are low [133].

As Table 2 shows, alpha (α) coefficients for the self-report scales' total scores are generally above 0.80. Most subscales have been shown to have internal consistency alpha coefficients between 0.70 and 0.94, although alphas lower than 0.70 have been reported for subscales of the MASC, RCMAS, SCARED, SCAS, and STAIC (see Table 2). Alpha coefficients for the parent scales' total scores are all above 0.80; for most of the subscales, alpha coefficients range from 0.70 to 0.92, though alphas lower than 0.70 have been reported in some studies for the Generalized Anxiety, Panic/Agoraphobia, and Physical Injury subscales of the parent SCAS (see Table 2). Overall, all of these pediatric anxiety scales appear to have a reasonable degree of internal consistency.

Test–retest reliability refers to the consistency of a given measure across time. Estimates used to examine retest reliability of dimensional measures include the intraclass correlation coefficients (ICCs) and/or Pearson's *r;* both estimates indicate the strength of correspondence between scores on a given measure administered to the same individuals across two different points in time. ICCs >0.74 are excellent, ICCs between 0.59 and 0.74 are considered good, ICCs between 0.40 and 0.58 are fair, and ICCs <0.40 are poor [50]. Pearson's *r* values > than 0.50 are considered large in magnitude; values between 0.30 and 0.50 are moderate; values < 0.30 are small [134]. ICCs and *r*s have been reported for the child rating scales in Table 2 using retest intervals of varying lengths (e.g., RCMAS intervals have ranged from 1 week to 9 months). As Table 2 shows, ICCs for the child rating scales' total and subscale scores are generally in the good to excellent range across retest intervals, and Pearson's *r* values are generally large in magnitude (above 0.50). More modest estimates have been reported in several studies for the SCARED total score and some subscales of the SCARED, MASC, and SCAS (see Table 2).

Retest reliability estimates (ICCs or Pearson's *r*) are available only for the parent MASC, RCADS, and STAIC (Trait scale), with estimates ranging from 0.56 to 0.89 for the total scores and subscale

scores across different retest intervals (i.e., 2 weeks, 8 weeks, and 12 months) (see Table 2). Overall, scores obtained on the child and parent rating scales listed in the table are generally reliable, which is desirable given that clinical levels of untreated child anxiety would not be expected to change over time. Additionally, good retest reliability is essential if measures are to be used to assess treatment-related changes over time.

Convergent and Divergent validity

Table 2 summarizes convergent and divergent validity estimates found across studies. Convergent validity refers to the degree to which a given measure is correlated with other measures that assess related constructs. Convergent validity is supported when scores on two related measures (e.g., two anxiety rating scales) yield large correlation (*r*) coefficients. Divergent validity refers to the degree to which a given measure is not correlated with measures that assess unrelated constructs. Divergent validity is supported when measures of unrelated constructs (e.g., an anxiety rating scale and an aggression rating scale) show relatively lower correlations than measures of related constructs (e.g., two anxiety rating scales).

As Table 2 shows, all of the child rating scales exhibit adequate convergent validity in that the total scales and most of the subscales correlate significantly with other measures of anxiety (e.g., RCMAS, SCAS, SCARED) (*r*s usually exceed 0.50) (see Table 2). The MASC's Harm Avoidance scale, however, has consistently yielded low or nonsignificant correlations with other measures of anxiety (*r*s: −0.13 to 0.43) [64, 69, 71]. The parent rating scales also exhibit convergent validity in that the total scales and most subscales significantly correlate with other parent anxiety scales (*rs:* 0.16–0.76) (see Table 2). Similar to the child MASC, the Harm Avoidance subscale of the parent MASC has shown relatively low correlations with the parent version of the SCAS (*rs*: 0.16–0.28) [64] (see Table 2). It is therefore not recommended that clinicians use this specific subscale as the sole measure of child anxiety.

In terms of divergent validity, Table 2 shows the MASC's and SCARED's total scales and subscales have yielded low or nonsignificant correlations with child-report measures of externalizing symptoms (*r*s: −0.01 to 0.24) [69, 92] (see Table 2). However, divergent validity of the child scales has been limited in regard to depressive symptoms, which is likely due to the substantial symptom overlap between anxiety and depression. Significant correlations (often exceeding *r*s of 0.50) have been found between most child anxiety rating scales and self-report measures of depression (see Table 2). Although more research is needed, the RCADS may be a more useful measure than other anxiety rating scales for distinguishing between anxiety and depressive symptoms in that nonsignificant correlations have been found between the RCADS anxiety subscales (except PD scale) and the Children's Depression Inventory (CDI) [63, 78]. The parent SCAS and STAIC (Trait) have shown good divergent validity as evidenced by low or nonsignificant correlations with parent rating scales of child-externalizing symptoms (*r*s: −0.03 to 0.33) [108, 122, 123]. The parent RCADS total anxiety scale and subscales, however, have shown significant correlations with parent measures of depression (*r*s: >0.50) suggesting poorer divergent validity (see Table 2) [119, 120]. Divergent validity estimates have not been reported for the parent MASC or SCARED.

Discriminant Validity

The terms divergent and discriminant validity are often used interchangeably in the literature. In this chapter, however, divergent validity is evidenced by lower correlations with measures of unrelated constructs than with measures of related constructs. Alternatively, discriminant validity is used when referring to a measure's ability to discriminate, or differentiate, children with different pediatric disorders. The availability of rating scales that can discriminate pediatric anxiety disorders from other

disorders is important given anxiety disorders are highly comorbid with other anxiety, depressive, and externalizing disorders [6].

Discriminant validity has been examined for all of the self-rating scales and some of the parent rating scales, with varied findings. For example, the RCMAS and STAIC have been found to discriminate between children with anxiety disorders from children with no disorders, and children with externalizing disorders, but not children with depressive disorders [135]. The MASC and SCARED total scales and subscales (except the MASC Physical Symptoms subscale) discriminate between children with anxiety disorders and those with no disorders [75]. The MASC total scale and subscales (except Harm Avoidance and Separation/Panic subscales in one study [80]) have been shown to discriminate between children with anxiety disorders and those without anxiety disorders [66, 77]. In addition, the MASC total scale and subscales (except Physical Symptoms subscale) can discriminate between children with anxiety disorders and those with depressive disorders [74]. The SCARED total scale and subscales also can discriminate children with anxiety disorders from those with disruptive disorders (except the Separation Anxiety subscale in one study [91]) and depressive disorders (except the Generalized Anxiety and School Phobia subscales in one study [97]) [90, 91, 97].

The total scale and subscales of the parent MASC (except the Separation/Panic subscale) and parent SCAS also have been shown to discriminate between children with anxiety disorders and those with no disorders [75, 108, 122]. Similar to the child SCARED, the parent SCARED also discriminates children with anxiety disorders from those with other psychiatric disorders. Specifically, the parent SCARED total scale and Somatic/Panic and Separation Anxiety subscales discriminate between anxiety and depressive disorders [91]. The parent SCARED total scale and subscales (except the Social Phobia subscale) also discriminate well between children with anxiety disorders and those with disruptive disorders [91].

Some of the MASC, SCARED, and SCAS subscales and all of the RCADS disorder-specific subscales show good discriminant validity between children with specific anxiety disorders and healthy comparisons [52, 66, 78, 90, 102]. Findings have been inconsistent for some subscales of the MASC and SCARED. For example, the MASC Harm Avoidance subscale was found to discriminate children with GAD from children without GAD in one study [66] but not others [52, 75]. Similarly, Birmaher et al. [90] found the SCARED Somatic/Panic, Generalized Anxiety, and Separation Anxiety subscales discriminated between children with PD, GAD, and SAD, respectively, from children without these disorders. Although findings regarding the Somatic/Panic and Generalized Anxiety subscales were replicated in Birmaher et al. [91], discriminant validity of the Separation Anxiety subscale was not found. Instead, the Social Phobia subscale showed good discrimination between children with SOP from children without SOP, which had not been demonstrated previously.

Some of the parent MASC, SCARED, and SCAS subscales have also been found to discriminate between children with specific anxiety disorders corresponding to the respective subscales and those without the disorders. For example, the parent MASC Separation/Panic subscale can discriminate between children with SAD and those without SAD; the Social Anxiety subscale can also discriminate between children with and without SOP [75]. In addition, the parent SCARED Somatic/Panic subscale can discriminate between children with and without PD, and the Separation Anxiety subscale can discriminate between children with and without SAD [91]. Similar to the child version, the Separation Anxiety, Social Anxiety, and Obsessions/Compulsions subscales of the parent SCAS discriminate well between children with the anxiety disorders corresponding to the respective subscales (i.e., SAD, SOP, OCD) from those without these disorders [102, 122]. The parent RCADS anxiety subscales also have been found to discriminate children with specific anxiety disorders corresponding to the respective subscales, as well as children with depressive disorders [119]. Research is needed to examine the discriminant validity of the parent STAIC (Trait).

In sum, both the RCMAS and STAIC are useful scales to discriminate between children with anxiety disorders from children with no disorders. However, to discriminate between children with anxiety disorders from children with other disorders, including externalizing and depressive disorders, the

child and parent versions of the MASC and SCARED are recommended. Further, the child and parent MASC and SCARED, as well as the child and parent SCAS and RCADS, can discriminate among specific pediatric anxiety disorders. Caution is warranted, however, in drawing conclusions about the discriminant validity of certain subscales of the child MASC (e.g., Harm Avoidance subscale) and child SCARED (e.g., Separation Anxiety subscale) given the inconsistencies across studies.

Screening

Anxiety rating scales are often used to screen for clinical levels of anxiety in children. As such, it is important that studies evaluate the accuracy of anxiety rating scales in identifying children with an anxiety diagnosis. However, few studies have examined anxiety rating scales' sensitivity and specificity for screening purposes. Sensitivity refers to the percentage of children with an anxiety diagnosis who scored at or above a specified cutoff score on an anxiety rating scale. Specificity refers to the percentage of children without an anxiety diagnosis who scored below the clinical cutoff score on an anxiety rating scale. Even less research attention has been paid to positive and negative predictive power of these scales. Positive predictive power refers to the percentage of children who score at or above the clinical cutoff score who received an anxiety diagnosis. Negative predictive power refers to the percentage of children who score below the clinical cutoff score on an anxiety measure who did not receive an anxiety diagnosis.

The scant research conducted on the screening utility of anxiety rating scales suggests that the cutoff scores provided by the older anxiety rating scales, namely, the RCMAS and STAIC, are less likely to correctly identify children with an anxiety disorder than the newer anxiety rating scales [136, 137]. For example, in a sample of inpatient children (6–13 years old), Hodges [137] found the cutoff scores ($T>60$) of the RCMAS and STAIC total scales yielded sensitivity rates of 34 % and 42 %, respectively.

Recent research using the child and parent versions of the SCAS in a clinic-referred sample [102] revealed that, on average, the subscales' cutoff scores ($T>65$) yielded a sensitivity rate of 64 % and 74 %, respectively, which was higher than rates obtained in studies using the STAIC or RCMAS. However, both the child and parent SCAS subscales on average yielded a relative positive predictive value of 43 %. Thus, about 57 % of children who had scored at or above the clinical cutoff score on the child and parent SCAS subscales did not receive an anxiety diagnosis.

Several screening evaluation studies have used receiver operating characteristic (ROC) analyses. ROC analyses yield an area under the curve (AUC), which is an estimate of a rating scale's overall diagnostic accuracy across the whole range of scores on the scale. Generally, AUC values between 0.50 and 0.70 indicate low accuracy, values between 0.70 and 0.90 indicate moderate accuracy, and values 0.90 or greater indicate high accuracy [138]. Because the whole range of scores on a given measure are considered, ROC analyses can also identify clinical cutoff scores on individual rating scales that maximize both sensitivity and specificity.

Several studies using ROC analyses have been conducted with the MASC in samples of community and clinic children [73–75, 139, 140]. Overall, the child and parent MASC total scores have low to moderate diagnostic accuracy in identifying children with anxiety disorders (AUCs: 0.60–0.82). One study of adolescent inpatients found that the total score had high accuracy for screening children with any anxiety disorder (AUC = 0.91) [73]. The child and parent MASC subscales also have shown low to moderate diagnostic accuracy in identifying children with specific anxiety disorders corresponding to the respective subscales (AUCs: 0.51–0.84) [75, 140]. Together, the MASC may be more useful for screening children with more severe levels of psychopathology than children with less severe levels of psychopathology.

Less research using ROC analyses has been conducted on the RCMAS and the child and parent versions of the SCARED and RCADS, and there have been no studies using ROC analyses on the

child and parent versions of the SCAS or STAIC. One study that used ROC analyses on the RCMAS in a community sample of adolescents found that the Total Anxiety score had low accuracy in identifying the adolescents with anxiety disorders (AUCs: 0.51–0.67) [139].

In terms of the SCARED, Birmaher et al. [90] found that total score and subscale scores had moderate accuracy for discriminating children with an anxiety disorder from those without anxiety disorders (AUCs: 0.66–0.86) and from those with disruptive disorders (AUCs: 0.68–0.78). The SCARED had low accuracy for discriminating between anxiety and depressive disorders (AUC = 0.60). In a subsequent study, Birmaher et al. [91] used ROC analyses to determine the cutoff score that would maximize both specificity and sensitivity. A cutoff score of 25 yielded a sensitivity rate of 71 % and specificity rates that ranged from 61 % to 71 % for discriminating between children with anxiety disorders and those with depressive and disruptive disorders. The parent SCARED has been found to discriminate pediatric anxiety from disruptive disorders, but not depression (AUC = 0.59) [91].

In terms of the RCADS, Chorpita et al. [78] used ROC analyses to identify cutoff scores that maximize sensitivity and specificity. Cutoff scores identified for each of the RCADS anxiety scales yielded sensitivity rates of 59–78 % and specificity rates of 64–92 % for screening specific anxiety disorders corresponding to the subscales. Using ROC analyses to examine the parent RCADS, Ebesutani et al. [119] showed that the cutoff scores identified for the RCADS-P anxiety subscales yielded sensitivity rates ranging from 71 % to 92 % and specificity rates ranging from 73 % to 86 % for screening specific anxiety disorders corresponding to the subscales.

In summary, the older scales such as the RCMAS and STAIC have limited utility for screening anxiety disorders in children. The newer scales such as the child and parent SCAS, SCARED, and child and parent RCADS have reported higher sensitivity rates than the RCMAS and STAIC. However, when overall diagnostic accuracy of a rating scale has been evaluated using ROC curves, findings generally show that the rating scales examined (i.e., RCMAS, MASC, SCARED) have low to moderate accuracy in screening anxiety disorders in children. Given these findings, the evidence is not firm that the scales summarized are useful for screening purposes. However, the rating scales do provide essential dimensional information about child anxiety and should be used as part of a comprehensive battery, which also includes administration of a diagnostic interview to ensure that no children who have a diagnosis are missed if only an anxiety rating scale is used.

Measuring Treatment Effects

The RCMAS has been used in most of the pediatric anxiety clinical trials and has been consistently found to be sensitive to treatment change [7]. As indicated earlier, the STAIC has not been used as frequently as the RCMAS for treatment evaluation because it focuses on trait anxiety rather than clinical anxiety symptoms. The newer scales such as the MASC, SCAS, SCARED, and RCADS have been used frequently in recent pediatric anxiety trials and also show sensitivity to treatment change [141–144]. Similarly, the parent versions of the SCARED, SCAS, and MASC have been used in several pediatric anxiety clinical trials, with findings generally showing good sensitivity to treatment-related changes [141, 143, 145]. The parent RCADS has not been included in any anxiety clinical trials to date.

Clinician Rating Scales

Clinician rating scales are useful as a supplement to child and parent rating scales, especially given research showing response biases in child and parent reports [7]. The only clinician rating scale specific to pediatric anxiety disorders is the *Pediatric Anxiety Rating Scale (PARS)* [146].

The PARS contains a 50-item symptom checklist and 7 severity items that assess frequency, severity, and impairment related to symptoms of DSM-IV SAD, SOP, and GAD in children ages 6–17 years. The PARS is administered by interviewing the child and parent separately or together. The PARS symptom checklist contains six subscales: Separation, Social Interactions or Performance Situations, Generalized, Specific Phobia, Physical Signs and Symptoms, and Other Symptoms. Each symptom is rated by the clinician as present/absent based on the "yes" or "no" responses elicited from the child, parent, or both. There appears to be an inconsistency across studies, or information is vague on the source upon which clinicians' PARS ratings were obtained.

Integrating information obtained from both children and parents, clinicians then rate the severity of the anxiety symptoms endorsed as presented by the child and/or parent along seven dimensions using a 6-point scale (0 for none and 1–5 for minimal to extreme) for each dimension. The seven dimensions include number of symptoms, frequency, severity of distress associated with anxiety symptoms, interference at home, severity of physical symptoms, and avoidance. Scores of 3 or greater on each dimension indicate clinically significant severity, avoidance, or interference. A total score is also calculated by summing five of the seven dimensions (not including number of symptoms and severity of physical symptoms). Higher scores indicate higher severity of anxiety symptoms.

The reliability and validity of the PARS have been evaluated [146, 147]. Internal consistency alpha coefficients for the PARS total score have varied, with alphas ranging from 0.64 to 0.91 across studies [146, 147]. Modest test–retest reliability estimates (24-day interval) have been reported for the total score and dimensional scales (ICCs: 0.35–0.59) [146]. However, excellent interrater reliability estimates have been reported for the total score and dimensional scales (ICCs: 0.78–0.97) [146].

The PARS has support for convergent validity in that significant correlations have been found between the PARS and clinician rating scales, such as the Clinician Global Impressions (Severity Scale) [49] and the Hamilton Anxiety Rating Scale [148] (*r*s: 0.49–0.61). The PARS has support for divergent validity in that low or nonsignificant correlations have been found between the PARS and a clinician rating scale of depressive symptoms (*r*s: 0.18–0.33) [146, 147]. ROC analyses have indicated that the PARS total score has high accuracy in identifying children with anxiety disorders (AUC = 1.00), with a cutoff score of 11.5 resulting in a sensitivity rate of 100 % and specificity rate of 98.8 % [147]. The PARS also has been found to be sensitive to treatment change. Specifically, change in the PARS total score has been found to be significantly correlated with pre- to posttreatment changes in global clinician rating scales (*r*s: 0.41–0.78) [146].

Global Psychopathology Scales

In addition to child and parent anxiety rating scales, there are a few rating scales designed to assess a broad range of symptoms in children, including anxiety symptoms. These include the *Achenbach System of Empirically Based Assessment (ASEBA) for School-Age Children* [88] and the *Behavior Assessment Scale for Children (second edition) (BASC-2)* [149]. Both scales have a long history in the pediatric assessment area; however, the ASEBA scales are more widely used in the area of pediatric anxiety. Both the ASEBA and BASC-2 contain child, parent, and teacher versions. Below we summarize both of these rating scales. We also summarize the available reliability, validity, and utility information of the scales, with an emphasis on the anxiety subscales.

The ASEBA scales are designed to assess competencies, adaptive functioning, and problem behaviors in children and adolescents. The ASEBA scales include the Child Behavior Checklist (CBCL), Youth Self-Report (YSR), and Teacher Report Form (TRF). Both CBCL and TRF are administered to parents and teachers, respectively, of children ages 6–18 years old, and the YSR is administered to children ages 11–18 years old. The ASEBA scales contain 118 items that assess a range of problem behaviors. Respondents rate the frequency of each problem behavior (e.g., "too fearful or anxious,"

"temper tantrums," and "cries a lot") using a 3-point scale (*not true, somewhat or sometimes true, very true or often true*). The majority of the problem behavior items are the same across the ASEBA scales (CBCL, YSR, TRF), though there are a few differences (e.g., YSR contains items that assess social desirability that are not included in the CBCL or TRF).

In addition to the Total Problems scale, ASEBA scales (i.e., CBCL, YSR, TRF) contain two broadband and eight narrowband subscales. The Internalizing broadband subscale and the Anxious/Depressed narrowband subscale include items that assess anxiety symptoms in children. The CBCL's Internalizing and Anxious/Depressed subscales in particular have been used in most of the pediatric anxiety clinical trials and are sensitive to treatment change (see Silverman and Ollendick) [7]. Recently, six DSM-Oriented subscales were included in the ASEBA scales to provide a closer link with the DSM-IV [150]. The DSM Anxiety Problems subscale specifically assesses for symptoms of DSM-IV GAD, SAD, and SP, though it has been rarely used in the clinical child anxiety literature. The ASEBA scales were standardized using a national US probability sample of children. Norms are available for the CBCL and TRF separately by sex and age (6–11 years and 12–18 years), and norms are available by sex for the YSR. A *T*-score of 64 or higher on the broadband subscales (e.g., Internalizing) and a *T*-score of 70 or higher on the narrowband (e.g., Anxious/Depressed) and DSM-Oriented subscales (e.g., Anxiety Problems) are considered clinically significant [88].

The BASC-2 [149] is designed to assess adaptive and clinical dimensions of behavior in children. It includes parent rating scales (PRS), teacher rating scales (TRS), and a self-report of personality (SRP). The PRS and TRS have specific versions to assess children across three age ranges: 2–5 years old, 6–11 years old, and 12–21 years old. Each version of the PRS contains 160 items and each version of the TRS contains 139 items. The SRP contains 185 items and is administered to children ages 6 through 25 years. Respondents rate the frequency of behaviors using a four-point scale (from "never" to "almost always"). All of the BASC-2 scales (i.e., PRS, TRS, SRP) include a number of clinical subscales, including an anxiety subscale. Norms based on a nationally representative sample of children are available for the BASC scales separately by sex, age, and clinical status. A *T*-score of 70 or higher on the clinical subscales (e.g., Anxiety subscale) falls in the clinical range [149].

Reliability

Alpha coefficients for the ASEBA Internalizing, Anxious/Depressed, and DSM Anxiety Problems subscales range from 0.72 to 0.90 [88, 151], though an alpha of 0.67 was reported for the DSM Anxiety Problems subscale of the YSR [88]. Alpha coefficients for the BASC clinical subscales (including the Anxiety subscale) are above 0.80 [149].

Retest reliability (r) estimates for the Internalizing, Anxious Depressed, and Anxiety Problems subscales range from 0.68 to 0.91 for the CBCL and YSR over an 8-day retest interval and from 0.73 to 0.86 for the TRF over a 16-day retest interval [88, 151]. Retest reliability (r) estimates for the BASC clinical subscales (including the Anxiety subscale) are above 0.70 [149].

Validity

The ASEBA Internalizing, Anxious/Depressed, and DSM Anxiety Problems subscales have evidence for convergent validity with other related measures. For example, the CBCL and TRF Internalizing, Anxious/Depressed, and Anxiety Problems subscales have demonstrated significant correlations (*r*) with respective parent and teacher ratings on the BASC Anxiety subscales (*r*s: 0.46–0.83), thus supporting the convergent validity of the BASC as well [88]. The YSR Anxious/Depressed and DSM Anxiety Problems subscales also have demonstrated significant correlations with the anxiety subscales of the RCADS (*r*s: 0.49–0.59) [152].

Information on discriminant validity of the Internalizing, Anxious/Depressed, and DSM Anxiety Problems subscales is available only for the CBCL. The CBCL Internalizing subscale has been found to discriminate between children with anxiety disorders and those with externalizing disorders, but not children with depressive disorders [135]. The CBCL Anxious/Depressed subscale has been found to discriminate between children diagnosed with specific anxiety disorders (i.e., SAD, GAD, SP) from children without these disorders and from children with depressive disorders [153]. The CBCL DSM Anxiety Problems scale also has been found to discriminate children with specific anxiety disorders (i.e., PD, SAD, SOP, PTSD, GAD, SP, OCD) from those without anxiety disorders and those with depressive disorders [151, 153]. Information on the discriminant validity of the BASC Anxiety subscales is not available.

Screening

Information on the screening utility of the Internalizing, Anxious/Depressed, and DSM Anxiety Problems subscales is only available for the CBCL and YSR. In terms of the CBCL, Aschenbrand et al. [154] used ROC analyses in a sample of parents of anxious and non-anxious children and found that CBCL Internalizing and Anxious/Depressed subscales had moderate to good accuracy (AUCs: 0.84–0.94) for screening children with any anxiety disorder (i.e., SAD, SOP, GAD) but low to moderate accuracy for screening children specifically for GAD (AUCs: 0.65–0.73) and SOP (AUCs: 0.40–0.44). The CBCL DSM Anxiety Problems subscale was found to have low accuracy for screening children with any anxiety disorder as well as children with specific anxiety disorders (SAD, GAD, and SP) from those without these anxiety disorders (AUCs: 0.60–0.70) in a sample of parents of clinic-referred children [155].

In a recent study using a sample of parents of clinic-referred children, Ebesutani et al. [153] found the CBCL Anxious/Depressed and DSM Anxiety Problems subscales had moderate accuracy for identifying children with SAD, GAD, and SP, respectively, from children without these disorders and from children with depressive disorders (AUCs: 0.72–0.84). Comparisons of the two subscales also revealed the Anxiety Problems subscale (AUCs: 0.82–0.84) yielded significantly greater AUC values than the Anxious/Depressed subscale (AUCs: 0.72–0.80). Thus, the Anxiety Problems subscale fares better than the Anxious/Depressed scale for screening children with anxiety disorders from children with depressive disorders. However, one study using the YSR in a sample of children referred to an anxiety and depression clinic [155] found that both the Anxious/Depressed and Anxiety Problems subscales had low accuracy in identifying children with any anxiety diagnosis (AUCs: 0.64–0.68). Information on the screening utility of the BASC Anxiety subscales is unavailable.

Summary

Overall, there are a number of widely used dimensional rating scales available for the assessment of pediatric anxiety. Additionally, global psychopathology rating scales commonly used in clinical child assessment contain subscales used to assess pediatric anxiety. The rating scales summarized possess adequate evidence with respect to internal consistency and retest reliability, though retest reliability estimates are lacking for the parent SCARED and SCAS. Most of the rating scales also show evidence for convergent validity with other anxiety scales. However, most anxiety rating scales have shown strong convergence with measures of depression, providing only partial support for the divergent validity of the scales. More work is needed on the convergent and divergent validity of the parent SCARED and the divergent validity of the parent MASC.

With respect to discriminating between anxiety and other clinical disorders, the child and parent SCARED and MASC are recommended. The child and parent SCARED, MASC, and SCAS subscales, as well as the child and parent RCADS anxiety subscales, are useful for discriminating among specific anxiety disorders. However, caution is warranted when using some of the subscales of the child MASC and SCARED. In terms of screening utility, the majority of the rating scales summarized (except the PARS) have low to moderate accuracy in identifying children with anxiety disorders. Therefore, when screening children for anxiety disorders, it is recommended that clinicians not rely solely on rating scales and include other methods of assessment, such as a diagnostic interview schedule.

Preschool Assessment

All of the categorical and dimensional measures summarized thus far are applicable for assessing children of school age (6–18 years old). In recent years, there has been growing recognition that anxiety is prevalent in children of preschool age [156, 157]. For example, in community samples of preschool children, a prevalence rate of 9.4 % was reported for the presence of "any anxiety disorder" [156]. Therefore, identification of anxiety at this young age is important for treatment and prevention of later difficulties [158].

There are only a few evidence-based instruments designed specifically for the assessment of anxiety in preschool children. All are completed by parents and/or teachers, because the reliability of young children's self-reports of anxiety is suspect [24]. The *Preschool Age Psychiatric Assessment (PAPA)* [159, 160] is an interview schedule that covers a number of disorders, including anxiety disorders in preschool children. The *Preschool Anxiety Scale (PAS)* [161] is a rating scale designed specifically for assessing anxiety in preschool children. There are two other rating scales that assess a broad range of symptoms in preschool-age children that contain subscales for assessing anxiety: the *Children's Moods, Fears and Worries Questionnaire (CMFWQ)* [162] and the *ASEBA Scales for Preschool Age Children* [163]. As indicated earlier, the BASC-2 TRS and PRS also include versions to assess children ages 2–5 years [149].

The PAPA [159, 160] is a parent semi-structured interview based on the parent version of the CAPA [34, 35]. The PAPA is similar to the CAPA, but some of the content and structure has been revised to improve its utility with preschool-age children (2–5 years old). The PAPA assesses frequency, intensity, and duration of symptoms of 16 psychiatric disorders, including anxiety, based on several classification systems (i.e., DSM-IV-TR, ICD-10, RDC-Preschool Age [RDC-PA] [158], and Diagnostic Criteria: Zero to Three [164]). Additional symptoms and behaviors commonly exhibited by young children are assessed (e.g., sleep and eating behaviors, toileting history). Impairment ratings can also be obtained in 30 areas, such as the child's relationships with others (i.e., parents, other adults, siblings, peers), as well as the child's functioning at home, school or daycare, and out of home.

Only one study has examined the reliability of the PAPA. Egger et al. [160] examined the test–retest reliability of a number of psychiatric disorders (including anxiety disorders) using the PAPA in a sample of parents of preschoolers (2–5 years old) recruited from a pediatric clinic. Findings showed reliability estimates were poor for GAD (κ[kappa] = 0.39) and SP (κ[kappa] = 0.36), fair for SOP (κ[kappa] = 0.54), good for SAD (κ[kappa] = 0.60), and excellent for PTSD (κ[kappa] = 0.73). No studies have evaluated the validity of diagnoses using the PAPA.

The PAS [161] is a 28-item parent-report rating scale designed specifically to assess a range of anxiety symptoms based on the DSM-IV in preschool-age children (2–6 years old). Parents rate the frequency of their child's experiences such as "is afraid of the dark" and "is afraid of meeting or talking to unfamiliar people" using a 5-point scale (from *not true at all* to *very often true)*. In addition to the Total score, the PAS contains five subscales: Separation Anxiety, Generalized Anxiety, Social

Anxiety, Obsessive-Compulsive, and Physical Injury Fears. Recently, the PAS was revised (PAS-R) [165] to a 30-item version to better reflect the range of common symptoms of anxiety in this age group as well as to provide a clear distinction between the Separation Anxiety and Generalized Anxiety subscales. Norms for the original PAS based on an Australian community sample ($N = 510$) of mothers of preschool-age children are available separately by sex and each age (3–5 years old). A *T*-score of 60 or higher on the PAS total or subscales indicates clinically significant levels of anxiety.

In terms of internal consistency, alpha (α) coefficients for the PAS and PAS-R total scores are above 0.80. Alpha coefficients for the PAS Generalized Anxiety and Social Anxiety scales are above 0.75, though alphas lower than 0.70 have been reported for the Separation Anxiety, Physical Injury Fears, and Obsessive-Compulsive subscales (α: 0.59–0.66) [166]. All the PAS-R subscales, however, yielded alphas over 0.70 (α: 0.72–0.89) [165]. Retest reliability estimates (over 12 month interval) for the PAS-R total and subscale scores are large in magnitude (*r*s: 0.60–0.76) [165].

The PAS and PAS-R evidence convergent validity in that the total scales and subscales correlate significantly with other parent rating scales (i.e., CBCL Internalizing subscale, CMFWQ, and Emotional Symptoms subscale of the Strengths and Difficulties questionnaire [167]) (*r*s: 0.50–0.77) [161, 165, 166]. However, the Obsessive-Compulsive and Physical Injury Fears subscales have yielded relatively lower correlations with parent rating scales of anxiety (*r*s: 0.35–0.49) compared to the other PAS/PAS-R subscales [161, 165, 166].

The PAS/PAS-R also exhibits adequate divergent validity in that the total scale and subscales have yielded low or nonsignificant correlations with parent measures of externalizing symptoms (i.e., CBCL Externalizing scale, SDQ Conduct Problems scale, SDQ Hyperactive Inattention scale) (*r*s: −0.01 to 0.28) [161, 165]. In terms of discriminative validity, the total score of the PAS-R can discriminate between children (ages 3–5 years old) with anxiety diagnoses from children without diagnoses, and the subscales (except Obsessive-Compulsive) can discriminate between children with specific anxiety diagnoses corresponding to the subscales from children without these respective diagnoses [165].

The CMFWQ [162] is a 60-item parent-report rating scale specifically designed to assess a broad range of internalizing symptoms, including anxiety, in children ages 2–6 years old. Parents rate the frequency of their child's experiences such as "Fears strangers" and "Looks sad, miserable, and unhappy" using a 5-point scale (from *almost never* to *almost always)*. In addition to the Total score, the CMFWQ contains three subscales: Anxiety Problems, Inhibition/Solitary Play, and Mood Problems. Currently, there are no norms available for the CMFWQ. Internal consistency (α) coefficients for the CMFWQ total score and subscales are above 0.80 [162, 166]. Retest reliability (*r*) estimate (over 2-year interval) for the total scale is 0.56 [162]. The CMFWQ total scale and subscales correlate significantly with a parent rating scale of temperament (i.e., Short Temperament Scale for Toddlers [168]) ($r = 0.42$) and with the PAS total score (*r*s: 0.56–0.75) [166].

In addition to the scales for school-age children, the ASEBA contains scales for preschool-age children [163]. The ASEBA preschool scales include the CBCL for ages 1½–5 years (CBCL/1½ –5) and the Caregiver-Teacher Report Form (C-TRF). The ASEBA scales for preschool-age children are similar to the school-age scales in content and structure, and respondents rate the frequency of each problem behavior using a 3-point scale (*not true, somewhat or sometimes true, very true or often true*), similar to the school-age forms.

The ASEBA preschool scales (i.e., CBCL/1½–5, C-TRF) include the same broadband, narrowband, and DSM-Oriented scales found in the school-age forms, though three subscales are included in the preschool scales that are not included in the school-age scales (i.e., Emotionally Reactive, Sleep Problems, and DSM-Oriented Pervasive Developmental Problems subscales). Norms based on a nationally representative US sample are available for the CBCL/1½–5 and C-TRF separately by sex. A *T*-score of 64 or higher on the Internalizing and Externalizing broadband scales and a *T*-score of 70 or higher on the narrowband (e.g., Anxious/Depressed) and DSM-Oriented subscales (e.g., Anxiety Problems) are viewed as being clinically significant [163].

The reliability estimates for the ASEBA preschool scales are similar to those obtained for the school-age forms. Alpha coefficients for the CBCL/1½–5 and C-TRF Internalizing, Anxious/Depressed, and Anxiety Problems subscales scores are above 0.70. Retest reliability (*r*) estimates (over an 8-day interval) for these subscales are above 0.50 [163]. Less information is available regarding the validity of the Internalizing, Anxious/Depressed, and DSM Anxiety Problems subscales of the ASEBA preschool scales although the available research supports the validity of the CBCL Internalizing subscale and the CBCL and C-TRF Anxious/Depressed subscale. For example, the CBCL/1½–5 Internalizing subscale has evidence of convergent validity with the Internalizing subscales of the Infant-Toddler Social Emotional Assessment [169] (*r*s: 0.48 and 0.62). The Internalizing and Anxious/Depressed subscales of the CBCL and C-TRF also discriminate between non-referred and referred children [163]. More research is needed to evaluate the validity of DSM Anxiety Problems subscale.

In summary, there are only a few instruments available for the assessment of pediatric anxiety in preschool children. The PAPA is the only interview schedule designed specifically to diagnose psychiatric disorders in preschool children. Reliability estimates obtained for some anxiety disorders have been poor to modest, and information on the validity of the anxiety diagnoses is needed. The PAS/PAS-R, CMFWQ, and ASEBA preschool scales possess sufficient and adequate evidence with respect to internal consistency and retest reliability. The PAS and CMFWQ also have evidence of convergent and divergent validity, but only the PAS has evidence for discriminant validity. More research also is needed on the validity of the Internalizing, Anxious/Depressed, and DSM Anxiety Problems subscales of the ASEBA preschool scales.

Objective Measures

Interview schedules and rating scales have been emphasized in this chapter because they are the most widely used and researched categorical and dimensional assessment approaches for pediatric anxiety. As noted, however, interviews and rating scales do not capture directly the two additional aspects of anxiety: avoidance of anxiety-provoking situations or objects and physiological reactions. Direct behavioral observations and psychophysiological measures more directly capture these aspects. These are each briefly discussed below.

Direct Observations

Direct observational tasks have been used to identify and quantify specific avoidant behaviors in anxious children [170–172]. They also have been used to assess subjective levels of anxiety, based on child and/or observer ratings, while the child is in the anxiety-provoking situations (e.g., reading aloud to a group) [173–175]. These tasks have served as outcome measures in several pediatric anxiety clinical trials, with varied findings [171–175].

The two most widely used types of direct observation tasks have been behavior avoidance tasks (BATs) and social evaluative tasks. In BATs, children are typically asked to approach a feared object or situation in a series of graded steps (varying between 8 and 27) [171, 172]. Trained observers then record the number of steps taken by the child as he/she approached the feared stimulus. Children also are asked to rate their level of fear or anxiety during the BAT. In social evaluative observation tasks, children (usually those with SOP) are typically asked to role play with a peer, read aloud a story in front of a small group, or talk about themselves to a small group. Children, and often trained observers, provide ratings of anxiety. Children's performance of the task has also been rated in some studies [173–175].

Reliability of direct observation tasks has been evaluated. Studies that have used social evaluative tasks, for example, in samples of children with SOP, have reported large interrater reliability estimates

for the observers' ratings of the child's anxiety levels (*r*s: 0.82 and 0.87), as well as the child's performance during the tasks ($r = 0.89$) [173–175]. Studies that have used BATs in samples of children with specific phobias reported large retest reliability estimates for number of steps achieved ($r = 0.97$ over 1 week; $r = 0.92$ over 1 h) and for children's anxiety levels during the BAT ($r = 0.87$ over 1 h) [170, 171]. Currently, there is no information regarding the validity of direct observations for assessment of pediatric anxiety. For example, no studies evaluate whether direct observations can discriminate children with anxiety disorders from children without anxiety disorders, as well as among the different anxiety disorders.

Presence of observers may potentially influence how children behave [176]. It is therefore important to have some time to allow children to habituate to the observers' presence [176]. Another limitation of direct observations is the absence of a standardized approach for conducting such observations, as well as their coding. As a consequence, it is difficult to generalize findings across studies [177]. Despite these limitations, direct observation tasks are useful for directly capturing the extent of children's avoidance of anxiety-provoking stimuli as well as children's level of anxiety while performing the tasks.

Physiological Measures

Although physiological measures provide the most direct and unbiased way to capture fear or anxiety responses, such measures are used less frequently in the assessment of pediatric anxiety relative to the other assessment measures discussed in this chapter [178]. In general, physiological assessment of anxiety focuses on two systems: the sympathetic adrenal medullary (SAM) system and hypothalamic pituitary adrenal (HPA) axis [179].

The SAM system relies on indices of heart rate (HR) and blood pressure (BP) and, to a lesser extent, galvanic skin response (GSR). There is scant research on the psychometric properties and clinical utility of these measures in samples of anxious children. Few studies have examined the reliability of physiological measures using retest intervals of varying lengths (e.g., 2 weeks, 60 s). Beidel et al. [180], for example, reported 2-week retest reliability estimates that were moderate to large for BP (*r*s: 0.29–0.64) and weak to moderate for HR (*r*s: 0.15–0.48), both measured before and during two 10-min behavior tasks (vocabulary test, read-aloud task) in children with SOP and non-anxious children. Also of interest in the Beidel et al. study [180] was the stability of BP and HR over time. Findings showed that 6-month stability estimates were weak to large for BP (*r*s: 0.04–0.63) and weak to moderate for HR (*r*s: 0.19–0.22).

Weems et al. [181] examined retest reliability of HR and GSR over a 60 s interval in a community sample of children (6–17 years old) exposed to a video of a mildly phobic stimulus (i.e., large dog running toward the camera). HR and GSR were measured at several time points: after children viewed a blank screen for 10 s, after viewing an initial video (i.e., a pastoral scene for habituation) prior to the video of the phobic stimulus, and after viewing the video of the phobic stimulus. Large retest reliability estimates were reported for HR and GSR (*r*s: 0.71 and 0.97, respectively) between the initial blank screen and pre-video period.

In terms of discriminant validity, Beidel [182] found HR discriminated between children with test anxiety from children with no anxiety during two behavior tasks (vocabulary test and read-aloud task). BP however did not discriminate between these two groups of children. Using a community sample of adolescents (13–17 years), Anderson and Hope [183] found that neither HR nor BP discriminated between adolescents with SOP from adolescents without a diagnosis during two 10-min anxiety-provoking behavior tasks (i.e., speech task and conversation with an unfamiliar person). Additionally, in the Weems et al. [181] study mentioned above, HR discriminated children with high levels of anxiety from those with low levels of anxiety during and after exposure to the mildly phobic stimulus. GSR, however, did not discriminate between these groups of children. In addition, change in HR, but not in GSR, before and after watching the video was more strongly associated with anxiety

than depressive symptoms according to child report. Given the failure to find BP and GSR could discriminate between children with anxiety and children without anxiety, further research is needed on these measures before they are used for such purposes. HR has somewhat better evidence for discriminant validity, though findings are inconsistent. More research is needed here too.

Only one pediatric anxiety trial has examined the sensitivity of physiological measures to treatment change. Specifically, Ost et al. [172] examined a one-session treatment for various phobias and measured the BP and HR at the highest step they attained on a BAT at pre- and posttreatment. BP was found to be significantly lower at posttreatment than at pretreatment for children assigned to active treatment conditions versus a waitlist. HR, however, did not show sensitivity to treatment change.

Research studies conducted on physiological indices of the HPA system in pediatric anxiety are even scarcer than studies conducted on indices of the SAM system. HPA activity is usually assessed via cortisol levels in the blood, urine, or saliva or measurement of adrenocorticotropic hormone [179]. Most of the research on HPA activity has been conducted in samples of children with depression or disruptive disorders [184, 185]. In samples of anxious children, the few studies conducted have found increased basal cortisol activity among children with PTSD compared to non-anxious children [186] and among clinic-referred children with SOP [187, 188]. Here too, more research is needed to determine psychometric properties and clinical utility.

Summary

This section summarized briefly the information available using direct observations and physiological measures with anxious children. Compared to interview schedules and rating scales, objective measures are not as widely used or studied. Direct observational tasks have been used primarily to quantify avoidant behaviors, obtain subjective ratings of anxiety during the task, and evaluate treatment outcome. There is some information on the reliability of direct observations for assessing pediatric anxiety, but information on validity is lacking. Furthermore, reactivity of children during observation tasks may influence the external validity of the findings. There also are currently no standardized tasks and coding procedures, thus making it difficult to generalize across studies [177].

Physiological measurements aid in directly capturing physiological reactions of anxiety in children, but they have been insufficiently studied in the pediatric anxiety assessment area. Few studies have examined the reliability of physiological measures and have used retest intervals of varying lengths in the anxiety area, making it difficult to draw conclusions about the reliability of such measures for this problem area. Further, studies have not found support for discriminant validity of BP and GSR. Although there is some support for the discriminant validity of HR, findings are inconsistent. As noted, further research is needed on physiological measurement in pediatric anxiety before they can be recommended for clinical purposes.

Clinical Considerations

In pediatric anxiety treatment research, it is common practice to administer a full assessment battery to the patients and their parents, which includes an interview schedule, several rating scales, and in some cases direct observation tasks and physiological measures at pre- and posttreatment and during follow-up periods. However, this is not often the case in clinical practice, where such a comprehensive assessment is rarely feasible. In choosing which assessment instruments would be most practical for use in clinical settings, factors such as cost, time, and training must be considered.

Most interview schedules used to diagnose pediatric anxiety disorders need to be purchased (with the exception of the K-SADS which is freely available). Interview schedules are also lengthy, taking

anywhere between 90 and 120 min to administer per informant. However, clinicians have the flexibility of using the interview schedules as templates that can guide their questioning rather than a script that must be precisely followed [189]. By using the interview schedules this way, the interviewer has available a full range of empirically validated DSM-based questions to which he or she can refer.

Rating scales such as the RCADS, SCAS, and SCARED are freely available, while the MASC, RCMAS, STAIC, CBCL, and BASC-2 need to be purchased. Administration time for rating scales is minimal, taking between 5 and 20 min to complete. Training required for most rating scales also is minimal. Direct observations and physiological assessment of anxiety are costly, lengthy, and require extensive training and extra staff members available for administration, thus making them less feasible for use in clinical practice settings.

Future Research Directions

There remains a need for further research that cuts across categorical and dimensional perspectives. First, as previously mentioned, the advent of the DSM 5 will likely have implications for existing categorical and dimensional measures of pediatric anxiety disorders that may require revision and further psychometric assessment.

Second, another revision to the DSM that will likely have implications for the assessment of pediatric anxiety is the inclusion of dimensional severity ratings to the diagnostic categories of the upcoming DSM 5. Dimensional severity ratings would allow clinicians to rate both the presence and severity of symptoms (e.g., "very severe," "severe," "moderate," or "mild") [190]. Inclusion of dimensional severity ratings may address some of the limitations of a categorical approach. These include the DSM's inability to capture individual differences in severity of a given disorder and inability to provide information about severity of subthreshold symptoms [191, 192]. Research on whether including dimensional severity ratings successfully addresses these disadvantages will be needed.

Third, the instruments summarized in this chapter were originally developed in English and tested with predominantly Caucasian children. It is unclear whether these instruments are applicable for assessing anxiety disorders in children from diverse backgrounds. Some of the categorical and dimensional instruments summarized in this chapter do show promise for such use, at least in terms of similar reliability and validity estimates (e.g., Ólason et al. [72] and Mellon and Moutavelis [105]). More research is needed, however, especially on the issue of measurement equivalence—whether these instruments assess anxiety in the same way across diverse groups of children [193]. See Pina et al. [194] as an example of a measurement equivalence study, which showed the RCMAS yields equivalent information across European American and Latino children diagnosed with anxiety disorders.

In closing, as this chapter has illustrated, researchers and clinicians have available a number of sound measures, based on categorical and dimensional perspectives to assess pediatric anxiety. We hope the chapter will help guide decisions about "which measure to use for which purpose" and at the same time allow for continued advancements in our understanding of pediatric anxiety disorders from both categorical and dimensional perspectives.

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Cognitive–Behavioral Treatment for Pediatric Anxiety Disorders

Kendra L. Read, Connor M. Puleo, Chiaying Wei, Colleen M. Cummings, and Philip C. Kendall

Abstract Anxiety disorders are among the most prevalent and debilitating psychological disorders among children and adolescents. Cognitive–behavioral treatments (CBTs) for anxiety disorders are linked to a tripartite model of anxiety and address cognition (anticipated threat), behavior (avoidance), and emotions (agitated arousal). Empirical evidence supports the use of cognitive–behavioral interventions as efficacious treatment for many anxiety disorders in youth, including generalized anxiety disorder (GAD), separation anxiety disorder (SAD), social phobia (SP), obsessive–compulsive disorder (OCD), and post-traumatic stress disorder (PTSD). Along with descriptions of CBT, a number of recommendations are made for future work.

Keywords Anxiety • Treatment • Children • Adolescents • Cognitive–behavioral treatment

Anxiety disorders are among the most common psychological disorders affecting children and adolescents [1], with prevalence rates reported between 10 % and 20 % [2–4]. If left untreated, pediatric anxiety disorders can lead to impairment in socioemotional functioning across the lifespan, including high rates of other mental health disorders, such as substance use [5, 6]. Substantial consequences in academic, vocational, and interpersonal performance are also prevalent [4, 7, 8]. As such, anxiety disorders represent an important target in the development of evidence-based interventions for children and adolescents. According to The Association for Behavioral and Cognitive Therapies and the Society for Clinical Child and Adolescent Psychology [9], cognitive–behavioral interventions are the most highly recommended treatments for anxiety disorders in youth, described as either "well-established" or "probably efficacious" based on current research.

This chapter describes the theoretical basis and main components of cognitive–behavioral treatment (CBT) for anxiety disorders broadly and then reviews empirically supported treatments (ESTs) for specific disorders, including generalized anxiety disorder (GAD), separation anxiety disorder (SAD), social phobia (SP), obsessive–compulsive disorder (OCD), and post-traumatic stress disorder (PTSD). It will also review recent efforts to address issues of effectiveness in community settings and novel treatment approaches (e.g., computer-based delivery).

K.L. Read (✉) • C.M. Puleo • C. Wei • C.M. Cummings • P.C. Kendall
Department of Psychology, Temple University, Philadelphia, PA, USA
e-mail: kendra.read@temple.edu

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A Tripartite Model of Anxiety

Anxiety-focused cognitive–behavioral interventions are based on a tripartite model of anxiety, which proposes that anxiety results from the interaction of thoughts, emotions/physiological responses, and behaviors [10]. Elevated emotional responses and accompanying physiological arousal experienced by anxious children are linked to both cognitive distortion (e.g., exaggerated estimates of threat) and behavioral avoidance that keeps the anxious child from encountering, facing, and eventually mastering feared situations [11]. CBT for anxiety disorders helps children (1) identify and challenge anxious cognitions, (2) cope with and regulate anxious feelings and physiological responses to anxiety, and (3) unlearn patterns of behavioral avoidance in the face of anxiety-provoking situations or stimuli.

CBT Components

Although treatments for specific disorders may differ, most contain the following components: (1) psychoeducation, (2) relaxation/somatic management, (3) cognitive restructuring, (4) problem solving, (5) exposure tasks, and (6) relapse prevention. Treatment components are often delivered in this order, but much flexibility is needed to tailor the treatment to the child's needs and particular anxiety disorder. Overall, these components of CBT for child anxiety, described in detail below, are recommended to be delivered in a fun, flexible, and collaborative format that allows the child to be an integral player in the treatment of his/her anxiety.

Psychoeducation

Psychoeducation has been shown to be an important component of treatment and preventive interventions [12]. Essentially, the therapist provides information about anxiety and the CBT model to the youth and his/her family. This information helps the child identify triggers of anxiety in his/her body and the environment, addresses expectations about treatment, and provides a sense of knowledge about the course of therapy for the coming weeks. The therapist describes anxiety as an adaptive response that, for children with anxiety disorders, can become out of proportion in its reaction to the environment. For some children, it may be useful to use a metaphor, like an overly sensitive safety alarm that goes off when no danger is present. With OCD, therapists may refer to obsessions as "brain hiccups," for which one might attribute incorrect techniques to alleviate the hiccups (i.e., compulsions). The therapist dispels the common belief that therapy will eliminate anxiety and instead discusses how therapy will help the child to learn needed strategies to cope with anxiety. The therapist normalizes the experience of anxiety for the child, sometimes by sharing how s/he has coped with an anxiety-provoking experience.

Orienting the child and his/her parents to therapy includes discussion of anxiety symptoms and their manifestation. Providing this information to the child can help him/her recognize the early signs of anxiety in his/her body and how to differentiate these signs from somatic problems. Research suggests that anxious children may show deficits in recognizing the emotional states of self and others [13], and psychoeducation addresses these deficits by providing youth with a vocabulary to understand emotions in general and anxiety specifically. Further, by establishing connections between thoughts and actions and feelings, the therapist may discuss multiple avenues for regulating unwanted anxiety through treatment, for example, by altering self-talk (cognition) and experience (behavior).

Overall, the psychoeducation component offers the child with useful information, builds a collaborative relationship between therapist and child, and provides hope and confidence that the overwhelming anxiety s/he currently feels can ultimately be managed.

Relaxation/Somatic Management

Relaxation strategies, such as progressive muscle relaxation and deep breathing, though potentially effective when used alone [14, 15], may be combined with cognitive coping strategies in CBT programs for anxiety to help children identify and regulate the physiological arousal that often accompanies anxious or negative emotionality [16–18]. Thus, the goal of these strategies is to provide methods of gaining control over unwanted anxious (physiological) arousal. During progressive muscle relaxation, children learn to flex and relax specific muscle groups in succession to promote relaxation and increase awareness of physiological tension as an indicator of anxiety. Deep breathing involves taking deep diaphragmatic breaths, in contrast to quick and short breaths, which are likely reminiscent of anxious arousal responses.

The therapist uses a developmentally appropriate approach to introduce the rationale behind relaxation, as it might not always be evident to children [19], and to teach the skills. When introducing these strategies to children, the therapist may use a salient metaphor (e.g., squeezing lemons, blowing up a balloon in one's belly) to illustrate the procedures. The child is encouraged to choose which relaxation strategy they want to use. For younger children, the therapist may participate in the relaxation procedures along with the client. For older children and adolescents, the therapist may face away from the teenager to allow them to relax without feeling self-conscious. Therapists can use prerecorded scripts or recordings of the relaxation techniques to allow the therapist to participate and to facilitate use of strategies at home. It is important to note that not all CBT treatments emphasize a need to address relaxation (i.e., CBT-ERP for OCD, see below), illustrating the differential application of these components for particular disorders.

Cognitive Restructuring

Reduction in negative self-talk is a significant mediator of change in treatment outcome studies for child anxiety [20]. Thus, the cognitive restructuring component of treatment is an important one. One goal of this component is to introduce "self-talk" (thoughts) as a way to address the cognitive component of pediatric anxiety. The therapist introduces the premise that changing patterns of automatic self-talk can, in turn, provide a pathway to alter emotions and behavior. Conceptually, self-talk can be introduced to children as communication with oneself that can be either "helpful" or "interfering," depending on its effects on emotions and behavior. In anxious youth, this self-talk often takes the form of a cognitive distortion about the presence and likelihood of environmental threat (e.g., "If I give a speech, everyone will laugh at me" or "I will get sick if I do not wash my hands repeatedly"). Understanding self-talk allows the child to recognize patterns of negative thoughts, called "thinking traps" (e.g., all-or-nothing thinking, faulty attributions, catastrophic outcomes), and to challenge and restructure these thoughts. For example, a child with SAD may feel anxious about separating from his/her mother because of the thought that the parent will be in a car accident and die when driving alone (catastrophic thinking). The therapist helps the child challenge thoughts based on accuracy or value and encourages adaptive, helpful self-talk in response, thereby reducing the effects of the cognitive distortions on current anxiety. These strategies include reflection, decatastrophizing, examining evidence, and reframing [21, 22]. An example of "examining evidence" is when the therapist asks the

child matter-of-factly to calculate the number of times his/her mother has driven in a car in her life, along with the number of accidents sustained to demonstrate the low likelihood that an accident will occur. As an example of decatastrophizing, the therapist might encourage the child to consider what would happen if a car accident occurred (e.g., "Do you know for sure that your mom would get hurt?" "Do you think anyone would get help?"). The therapist never promises that the feared outcome will not happen, but encourages the child to consider a more realistic probability of such an event.

Discussing such abstract topics with children can be difficult. However, introducing the concept of "thought bubbles" with ideas that pop up in an individual's head can facilitate the discussion. When experiencing an unwanted emotion in a particular situation, the place for "helpful" or coping thoughts can be illustrated. Children practice identifying thought bubbles in cartoons and other people, progressively working to identify their own thought bubbles and the specific thoughts that surround their anxious arousal, as well as more helpful "coping" thoughts that they can implement when feeling anxious.

Problem Solving

The development and application of adaptive problem-solving skills is another feature of CBT for anxious youth that addresses the behavioral aspect of the tripartite model. Instead of perceiving anxiety as an insurmountable obstacle, children are taught to view it as a problem that can be solved. First, children identify "the problem" to be solved. Initially, this can be difficult if they feel overwhelmed by distress or have little experience moving past the unwanted arousal. By identifying the problem, it becomes concrete and potentially manageable, increasing the opportunity for the child to experience successful coping. The next step involves "brainstorming" many solutions, including outrageous or implausible ideas, which helps to facilitate creativity and flexibility. Considering all possibilities encourages the child to move past the search for the perfect solution. Each solution and its potential consequences are considered before it is put into action. The consequences of each attempt are discussed, and all efforts to cope are applauded. The therapist encourages the child to be ready to try an alternate solution in case the first does not achieve the desired result. The therapist might start with examples of problems to solve that are not anxiety inducing (i.e., looking for a lost sock) in order to allow the child to learn the principles of problem solving without becoming overwhelmed by or wary of the task [23]. Problem solving during anxious situations is later used during exposure tasks.

Exposure Tasks

Facilitating the practice of newly learned coping strategies in the face of real anxiety is considered a critical catalyst for change as part of the behavioral aspect of CBT [24–28]. Typically, children engage in "behavioral challenges," also called exposure tasks, in a graded, hierarchical order that erodes their patterns of avoidance. The therapist works with the child to collaboratively build a graded hierarchy based on the child's and parent's ratings of anxiety-provoking situations; the therapist does not decide exposure tasks unilaterally. Exposure hierarchies may list behavioral "challenges" from many anxiety problem areas, or it may include items specific to only one anxiety disorder (e.g., social phobia: saying "hi" to a stranger, ordering food at a restaurant, initiating conversation with a new peer), depending on the child's presenting problem and existing comorbidities. The therapist then works with the child and parents to determine the specific details for the upcoming challenges. During exposure tasks, anxious children practice engaging in adaptive coping, learning to distinguish real from perceived threat, and experiencing an increase in their sense of self-efficacy in the face of threat. Different

guidelines for exposure tasks detail specific methods for gauging the design and length of exposures [26–28]. However, with any exposure task, the therapist considers the severity of the disorder and the progress that the child has shown in deciding what task is appropriate so that the child is well prepared [23, 29, 30]. Exposures can either be imaginal or in vivo. Imaginal exposures include conjuring up the image or idea of the feared environment or stimulus, perhaps through role-playing the feared stimulus, or writing or listening to a narrative of the anxiety-inducing environment. Imaginal exposures are useful for worry about abstract events (e.g., death for GAD) or can be considered lower-tiered exposures on a fear hierarchy [27]. Imaginal exposures are the primary exposure source in PTSD treatment, given the ethical concerns in reexposing the youth to a traumatic situation. In vivo exposures require the child to confront the feared situation in person, which can occur in or out of the therapy office.

Throughout the exposure, the child's level of distress is measured on a scale of subjective units of distress (SUDS) [31], with 0 representing a state of total relaxation and a rating of 8, 10, or 100 (depending on the rating scale used) representing maximum anxiety, arousal, and distress. The therapist collaborates with the child to anchor each rating in definitions that are salient for the child. Generally, children are encouraged to endure the exposure task until their SUDS rating has decreased sufficiently and the feared stimulus no longer elicits a strong reaction from the child, but this exact standard differs somewhat based on the exposure procedure used [27, 28]. During the exposure, the therapist helps the child to tolerate the distress, reinforcing the benefits of facing one's fears rather than avoiding them [27]. Observing a child experience distress may be difficult for a novice therapist, but research indicates that these exposure tasks do not negatively affect the therapeutic alliance [32]. Following the completion of the exposure task, the therapist (or parent, in the case of exposure tasks done out of session) praises the child's efforts to cope with anxiety rather than focusing on the outcome of the exposure. Post-event processing of the exposure with the child allows him/her to discuss his/her feelings, thoughts, and appraisals of how well he/she managed his/her anxiety, as well as any obstacles to coping throughout the process.

To promote self-efficacy, exposures are often repeated to allow the child to build a history of adaptive coping such that s/he is able to more quickly and efficiently generate positive coping thoughts and reduce anxiety in challenging situations. Exposure tasks may be practiced in multiple settings to encourage generalization [26], which is especially important when the feared stimulus cannot be accessed in session (e.g., fear of flying [27]). CBT for each anxiety disorder differs in the exact approach of exposure depending on the theoretical understanding of the disorder and the nature of the child's anxiety. For example, exposures for SAD might include graduated challenges in which the parent or child leaves the therapy session or clinic for varying periods of time. For a child with social phobia, exposures might involve gradual interactions with others, including making eye contact, playing a game, reading aloud to a group, or ordering for oneself at a restaurant. With public speaking concerns, treatment might make use of video feedback following speeches, a procedure that has been associated with decreases in anxiety for subsequent speech exposures [33]. Treatment of OCD uses a technique called exposure and response prevention (ERP), which focuses on prevention of a ritualized response while managing obsessive thoughts. More detailed accounts of these procedures will be addressed later in the chapter, but these examples illustrate the ways in which exposure is adapted to address the specific nature of the anxiety disorder in question.

Interestingly, research indicates that although exposure tasks are important, the match between principal anxiety diagnosis (e.g., social phobia) and exposure content (e.g., conducting a survey with strangers) is not necessarily related to treatment outcome for children with GAD, SAD, or SP [34, 35]. Thus, exposing an anxious child to salient anxiety-provoking situations may be more important than targeting his/her exact fear. Engagement in graduated exposures helps to build the child's self-efficacy in the face of anxiety-inducing situations, which generalizes beyond the situations targeted as part of the child's exposure hierarchy. However, these findings may not generalize to the treatment of OCD and PTSD, given the specific and qualitatively distinct nature of these anxiety disorders.

Relapse Prevention

CBT for pediatric anxiety can vary in length, but termination occurs when children are able to effectively cope with and engage in anxiety-provoking situations in their lives. The child is encouraged to engage in an "exposure lifestyle" [36] where they routinely approach anxiety rather than follow the avoidance patterns of their old routines. The need to practice coping, involving all three aspects of the model (thoughts, emotions, and behavior), can be likened to the need to exercise muscles to increase and maintain their strength. Parents can help maintain gains by encouraging their child's bravery and praising any attempts to approach anxiety using appropriate coping strategies.

Terminating treatment can itself be an anxiety-provoking situation, and the therapist addresses this concern directly. Before ending treatment, the therapist reviews the goals of treatment and methods to prevent relapse. In doing so, a distinction is drawn between a "lapse" and a "relapse." A lapse is a minor setback that can be expected. In contrast, a relapse suggests more of a return of the larger problem of anxiety and the dissolution of the coping strategies that were fostered in treatment. But even a relapse is not a "collapse." A relapse may suggest that the child is no longer practicing the cognitive and behavioral strategies introduced in treatment and may require booster sessions to refresh coping strategies and regain control over anxiety.

Clinical Considerations

While most treatments incorporate these six general CBT components, therapist characteristics, as well as the delivery format (e.g., individual vs. group) or setting (e.g., school), are important considerations in the treatment for anxious youth.

Therapist Characteristics

An important duty of the therapist early in treatment is to facilitate the development of an alliance and rapport with the anxious child. Having a trusting relationship is very helpful when the therapist later asks the child to face his/her fears via exposure tasks. A strong alliance between child and therapist has been associated with improved treatment outcome in randomized controlled trials of CBT for pediatric anxiety [37]. In CBT, the therapist's role is likened to that of a coach [11, 38] who teaches the child new skills and encourages adaptive coping [29]. In this therapist-as-coach model, emphasis is placed on the child's efforts to utilize newly learned skills when anxious, not the elimination of anxiety. The model of a therapist as a coping coach further normalizes the experience of anxiety and fosters the alliance with the child [23]. The therapist-coach model introduces the collaborative nature of treatment by soliciting input from the child at every stage of the intervention.

Some have criticized the use of manualized treatments under the misconception that their application is too rigid to address individual problems. It is important to consider that the implementation of any empirically supported CBTs must be done flexibly to adapt to the particular child, while maintaining fidelity to the original treatment [39]. Therapists are encouraged to be collaborative and creative in treatment with their clients. For example, the therapist might take into account a particular child's difficulty remembering coping thoughts by making a fun coping thought keychain to remind them of helpful self-talk throughout the day. Thus, manualized CBTs are not rigid recipes to be followed in a strict manner, but rather detailed descriptions of core elements to be applied in a fun, flexible manner tailored to the needs of the client.

Delivery Format

Research supports the use of alternate modalities for CBT for pediatric anxiety, including group, school-based, and family formats [40–44]. Involvement of family members, caregivers, and school personnel may differ as a function of the child's presenting difficulties. Even in "individual therapy," parents or guardians are often consulted and engaged throughout treatment to help provide structure and support to the child. In some cases, treatment focuses on transferring control from the therapist to the parent by educating parents about adaptive responses to anxiety, praising efforts at bravery, and emphasizing consistent responses when parenting an anxious child [45].

Additionally, research supports the use of school-based prevention and intervention approaches for anxiety disorders in youth. These programs have been developed to target GAD, SP, and SAD [46] and PTSD [47]. In-school approaches represent an important delivery venue that may serve to close the gap between the development of evidence-based treatments and their dissemination in the community, while increasing the awareness of socioemotional functioning of these children in schools [48–50]. School-based preventative and treatment programs may be delivered in both individual and group formats [40]. Generally, empirical evaluations of these programs find that children participating in cognitive–behavioral prevention [51] and treatment [52, 53] programs delivered in the school environment reliably experience greater reduction in anxiety symptomatology than those in control conditions [48]. However, successful dissemination of school-based anxiety prevention and treatment relies on transportability of these treatments [39, 54–56], which represents a continuing challenge in the field.

The structure and format of CBT for pediatric anxiety may vary based on the nature of the child's anxiety disorder, the age of the child, and cognitive limitations of the child. Standard administration of CBT is often recommended for children ages 7 and older [29], although CBT may be used for younger children with appropriate adaptation. Anxiety CBT for younger children often mirrors that for older youth but necessitates the use of more developmentally appropriate language and techniques and places much greater emphasis on the involvement of the child's parents or guardians [57–59]. By the traditional CBT approach, parents may be trained, either alone or in groups [60–63], to identify anxiety in their children, differentially reinforce brave, coping behavior, and to cope with their own anxiety [58]. Adaptations may be made to address younger children's difficulty with abstract thinking. Research shows that younger children are able to engage in meta-cognitive tasks when they are made more concrete through the use of labels, pictures, or props (e.g., identifying "red" vs. "green" thoughts [63]) [59]. Similar adaptations may be made for children with mild cognitive limitations, although the use of many CBT programs is generally not recommended for children with an IQ below 80. Parent skills training approaches, primarily developed for externalizing disorders (i.e., parent–child interaction therapy [PCIT]), have been successfully adapted for use with anxiety disorders in younger youth (i.e., 2–5 years) [64–68]. In these approaches, parents are trained how to address their children's anxious thoughts and behaviors while fostering brave or confident behavior [59]. Minor adaptations may be made for adolescents [69] but generally involve the use of less "childish" language and techniques. For example, adolescents may be encouraged to keep a journal rather than use a treatment workbook.

CBTs for Specific Anxiety Disorders

The following sections discuss the variants of CBT for social phobia, GAD, SAD, OCD, and PTSD. CBT for each disorder involves many of the same components discussed above, but particular aspects are emphasized depending on the nature of the anxiety disorder in question. Evidence for efficacy and effectiveness of each intervention are reviewed, as well as various delivery formats and emerging novel treatments for each disorder from a cognitive–behavioral framework (e.g., computer-based

treatment, accelerated delivery). A comprehensive discussion of all cognitive–behavioral interventions for each anxiety disorder is beyond the scope of this chapter. See disorder-specific chapters for a more detailed discussion of specific treatments.

Social Phobia, Generalized Anxiety Disorder, and Separation Anxiety Disorder

Theoretically, SP, GAD, and SAD are understood as sharing an underlying anxiety construct [70–73]. These disorders frequently co-occur [74], and accordingly, they are often treated with similar interventions aimed at helping youth to develop coping self-talk and to learn to face their fears [75, 76]. One of the most frequently used and representative examples of CBT for GAD, SAD, and SP has been *Coping Cat* [40, 41, 77], a manual-based program developed at the Child and Adolescent Anxiety Disorders Clinic (CAADC) at Temple University. The *Coping Cat* program is a 16-week treatment, divided between teaching anxious youth various skills to manage their fears (first eight sessions) and then exposing them, in a graded fashion, to these fears (last eight sessions). Unlike some versions of CBT that move more quickly to exposures and minimize cognitive restructuring or relaxation (e.g., ERP for OCD [78]), the *Coping Cat* program devotes initial sessions to several CBT components (e.g., general knowledge about anxiety, affect recognition, problem solving, self-talk, and self-encouragement and reward for effort). The general CBT principles (e.g., psychoeducation, exposure) are applied flexibly [69] and can be adapted for the child's specific presenting problem.

As the most Empirically-Supported Treatment (EST) of anxiety for youth, the efficacy of *Coping Cat* has been demonstrated in numerous Randomized Clinical Trials (RCTs) conducted by several, independent research teams [77]. As such CBT, and *Coping Cat* specifically, is considered a "probably efficacious" treatment for childhood SP, GAD, and SAD according to guidelines set by Chambless and Hollon [79] and the American Psychological Association (APA) Task Force [80]. These RCTs have shown moderate to large effects when comparing *Coping Cat* to no treatment, a placebo, or an alternative treatment for youth with SP, GAD, and SAD [11, 40, 81, 82]. Consistent with a cognitive–behavioral framework, research supports that favorable treatment outcomes are mediated by reductions in negative, anxious cognitions [83, 84]. Moreover, *Coping Cat*-based CBT appears to offer similar benefits to pharmacological treatments for anxiety [77]. In the Child Anxiety Multimodal Study (CAMS), a recent, multisite, RCT, 488 youth (ages 7–17 years) with SP, SAD, and GAD were treated with either 14 sessions of CBT based on Coping Cat, sertraline, or their combination. CBT and sertraline improved anxiety in 59.7 % and 54.9 % of youth, respectively, with combined treatment resulting in a significantly superior response rate of 80.7 % [77].

CBT has been associated with favorable long-term outcomes [85]. Children with GAD, SAD, or SP treated with the *Coping Cat* CBT program have been found to maintain their gains at 1-year and longer follow-ups, ranging from 3.5 years [86] to as many as 7.4 years after treatment completion [86, 87]. Further, successful treatment of these disorders has been associated with reduced substance use problems in late adolescence and early adulthood [5, 6].

Effects of Comorbidity

CBT for SAD, SP, and GAD are equally effective in boys and girls as well as in children of varied ethnicities, though youth from single-parent homes and ethnic minorities may be more likely to terminate treatment prematurely [88–90]. Given that the majority of youth will have at least one additional comorbid anxiety or other psychiatric diagnosis [74, 91], it is worth noting that the efficacy of *Coping Cat* as well as several other CBT programs has been established in youth with multiple comorbidities (e.g., additional anxiety, attention, conduct, or mood disorders) as long as SAD, GAD, or SP

was considered the principal concern [77, 88]. However, for these children, successful gains in anxiety CBT may not always generalize to emotions other than those targeted in the primary intervention [92]. The impact of comorbid mood symptoms along with demographic characteristics on treatment outcome is not clear. Some studies suggest that age, greater internalizing severity, and depressive symptoms are inversely related to individual CBT improvement [93–95], while others have shown CBT to be effective in children with varying levels of severity [77] and comorbid anxiety and depressive disorders [77, 88]. Although children with developmental disorders and intellectual impairments have typically been excluded from controlled research studies, case studies have shown that tailoring CBT for children with special needs can lead to successful outcomes [91]. Further, some CBT programs for anxiety disorders in youth, such as the building confidence [96] and "Cool Kids" interventions [97], have been successfully adapted for use in high-functioning children with autism spectrum disorders [98, 99].

Alternative Delivery Formats

CBT for SP, GAD, and SAD, typically provided in one-to-one therapeutic interaction, can be delivered in a variety of formats, including group- and family-oriented interventions, weekly or biweekly sessions, or novel, electronic formats, designed to increase the portability of CBT to school, homes, and community clinics as opposed to specialty research settings [41, 100]. When delivered in a family format, the 16 sessions of the *Coping Cat* are adapted to include parents in each session (as opposed to conducting two parent-only sessions in the individual treatment) [40]. Parents are taught the CBT principles along with their child and are trained to become a "CBT coach" for their child between sessions. Other family CBTs for SP, GAD, and SAD, akin to *Coping Cat*-based Family CBT (FCBT [41]), have "family anxiety-management" sessions [101] or emphasize parent-specific skills (communication training) [102]. Whereas both individual and group modalities of CBT for GAD, SP, and SAD may be considered efficacious treatments according to Chambless and Hollon's criteria [79], further studies of family CBT, a possibly efficacious treatment, are needed to reach this standard [40]. Family CBTs have been indicated for subgroups of children, such as youth with anxious parents [103, 104] or youth with moderate autism spectrum disorder symptoms, whose ability to engage in treatment and practice CBT skills outside of session may be facilitated by parental involvement [105]. However, the relevant benefits of individual versus family modalities for anxious youth, overall, are unclear [41, 103]. In one RCT ($n = 161$) that focused on the relative efficacy of individual versus family treatment, youth with anxiety disorders were equally likely to benefit from individual (57 % improved) and family (55 % improved) modalities of CBT, though the improvement of youth assigned to a family education and support condition (i.e., a non-CBT treatment) was significantly less (35 % improved) [41].

As a more efficient and potentially more affordable treatment option, group formats of CBT have also been developed, often in combination with family CBT programs [106–108], and found to offer similar benefits to individual CBT. In a 1-year follow-up study of youth treated with individual versus group versions of the *Coping Cat*, Flannery-Schroeder and colleagues [100] found no significant differences in treatment outcome between groups (81 % vs. 77 % of treated youth no longer met criteria for an anxiety disorder). Similar to studies on family versus individual CBT, the benefits of family involvement in group CBT for GAD, SAD, and SP appear beneficial in some [108], but not all studies [107].

There is some empirical support for several novel delivery formats for CBT including stepped care and electronic or computer-based interventions. A non-RCT of CBT for 133 children (ages 8–12) with anxiety disorders provided preliminary support for the use of standardized, but also tailored treatment interventions [109]. Whereas 45 % of the sample improved and discontinued after ten sessions, 37 more (28%) improved with an additional five or ten sessions (i.e., stepped care). Much recent research has also focused on the development and evaluation of more cost-effective and transportable electronic

CBT approaches [110]. Interactive, computer-assisted versions of the *Coping Cat* as well as various other child CBT programs have been developed and received empirical support [111, 112]. Further, a recent RCT comparing clinic-based and electronic CBTs found that online delivery of CBT with minimal therapist support was as efficacious as a clinic-based CBT in reducing child anxiety, supporting the viability and potential promise of this novel approach for the future delivery and the dissemination of CBT for pediatric anxiety [113].

Effectiveness

Studies of the effectiveness of CBT (i.e., CBT's performance across more diverse communities and settings as opposed to controlled research samples) are emerging. In an RCT comparing CBT to usual care in a community clinic, CBT significantly reduced anxiety in 66.7 % of youth, an outcome that was comparable to usual care, which demonstrated improvements in 73.7 % of youth [114]. The authors suggest that the effects of CBT were not optimal because the therapists did not uniformly implement exposure tasks, which are often considered the most important catalysts for change in CBT. Additionally, youth receiving care-as-usual were also receiving multiple additional services, so it is unclear if decreases in anxiety could be attributable to the therapy they received. A study conducted in a community clinic setting in China found that youth treated with CBT showed significant reductions in anxiety compared to those on the wait list at posttreatment, 3-month and 6-month follow-ups, supporting the applicability of this treatment in non-Western cultural settings [83]. Together, these findings suggest the need for further, larger studies of the effectiveness of CBT for SAD, GAD, and SP to support the dissemination of these treatments on a large scale [114], with a special emphasis on the fidelity of the treatments when implemented in community clinics.

Obsessive–Compulsive Disorder

According to the Practice Parameters for the Assessment and Treatment of Children and Adolescents with OCD [115], CBT with exposure and response prevention (ERP) has demonstrated significant effects in reducing symptoms for youth with OCD, both alone or when combined with pharmacotherapy [116, 117], and is recommended as a first-line treatment for youth with OCD [116, 118, 119]. CBT for OCD targets characteristic obsessions and compulsions through exposure and cognitive restructuring methods similar to those used for other anxiety disorders in youth. However, CBT for OCD specifically emphasizes exposure tasks and response prevention [78]. ERP therapy for OCD involves gradually exposing patients to anxiety-provoking stimuli while they refrain from performing rituals or engaging in avoidance behavior. Similar to other anxiety disorders, cognitive restructuring strategies guide the youth to reduce anxiety during the exposure. For example, youth may be guided to refute obsessive thoughts underlying compulsions (e.g., "my hands are covered in germs"), which may serve to reduce anxiety when they are prevented from engaging in compulsions (e.g., washing hands). Thus, the use of cognitive coping strategies may facilitate the process of ERP and enhance compliance [120].

Among the CBT approaches for youth with OCD [121], the March and Mulle manual [120] is an empirically supported example of an ERP protocol. This treatment contains 14 weekly sessions across 12 weeks and includes the following components: (1) clinical evaluation and assessment, (2) psychoeducation, (3) cognitive restructuring, (4) severity ratings of symptoms and establishment of a fear hierarchy, (5) gradual ERP based on the symptom hierarchy, (6) homework, (7) parent sessions, and (8) relapse prevention. In addition to the March and Mulle individual protocol [120], CBT/ERP for youth with OCD has been delivered in various formats (e.g., individual, group, family-focused) and with different session frequencies (e.g., weekly, daily) [122–126].

Evidence from clinical trials supports the efficacy of CBT/ERP for youth with OCD [117, 119, 123, 127]. A recent meta-analysis [128] reviewed four RCTs comparing CBT to control conditions and found a significant effect size supporting the efficacy of CBT/ERP for youth with OCD. Additionally, the efficacy of CBT/ERP for pediatric OCD was recently tested in a large multisite randomized controlled trial (The Pediatric OCD Treatment Study [POTS I]) [129]. Youth with OCD ($N = 112$; aged 7–17) were randomized into four groups: individual CBT, medication (sertraline), CBT and medication combined, and pill placebo. Eighty-seven percent of the youth completed the 12-week treatment, and intent-to-treat analyses revealed that all treatment conditions yielded significantly superior outcomes at posttreatment as compared to the placebo condition. Specifically, combined treatment was superior to either CBT or medication alone, with no significant differences found between CBT- and medication-alone conditions. When measuring treatment outcome in terms of the remission rate (evidenced by score of Children's Yale–Brown Obsessive–Compulsive Scale [CY-BOCS] < or = 10 at posttreatment) [130], the combined (54 % remission rate) and CBT (39 %) conditions significantly outperformed medication (21 %) and did not significantly differ from one another [129]. This result confirms CBT as a first-line treatment for youth with OCD. Secondary analyses suggested comorbidity, poor insight, greater symptom severity or functional impairment, and higher family accommodation as impediments to optimal success from CBT for youth with OCD [131]. These predictors are consistent with findings from other studies [132, 133].

Alternative Delivery Formats

Empirical evidence supports the use of ERP protocols across various delivery formats. Barrett and colleagues [122] added a family component [42] to March and Mulle's [120] treatment and compared individual and group CBT with this addition to a wait list control. Whereas both individual and group treatments obtained superior outcomes compared to controls, there were no significant differences between individual and group CBT at posttreatment and follow-up [122, 123]. Manualized intensive treatment (5 sessions per week) has also demonstrated efficacy in treating youth with OCD [42, 118, 125]. Remarkably, there was no difference between weekly and intensive schedules in terms of treatment outcome [134], which implies that intensive treatment schedules allow the possibility of significant gain in a much shorter period of time than in weekly treatment, provided the family is able to comply to a more demanding treatment schedule. Treatment for pediatric OCD has also been tested in a technology-based modality. Findings from a pilot study examining a telephone-based CBT for youth supported the effectiveness, acceptability, and feasibility of such delivery format for pediatric OCD [135]. Overall, diversified delivery formats can be used to successfully treat pediatric OCD while fitting the particular needs of the family or youth [42, 119].

Effectiveness

Recent work has focused on evaluating the effectiveness of current pediatric OCD treatments in community settings. Specifically, two studies [125, 126] implemented manualized CBT-ERP treatment in community outpatient clinics achieving response rates over 60 %. Research also supports the effectiveness of group-based CBT-ERP in the community setting [128]. Additionally, to develop and test a more easily disseminated protocol, the Pediatric OCD Study team has been conducting a second study (POTS II) [136] to compare two treatment protocols: a "single doctor" model (with both CBT and medication management delivered by a child psychiatrist) and a "dual doctor" model (with CBT delivered by a psychologist and medication management a child psychiatrist). Although the study contains elements of an efficacy study, the primary aim is to investigate the effectiveness of both models. The results of this study will be revealed in the near future.

Post-traumatic Stress Disorder

CBT for PTSD typically involves exposure tasks, cognitive restructuring, and anxiety-management skills. In these treatments, exposure tasks, either imaginal or in vivo, consist of confrontation with fearful memories of the trauma [137, 138]. Exposures are said to be effective by (1) reducing conditioned fear responses associated with trauma cues and (2) challenging cognitive distortions surrounding perceived danger and threat [139]. Exposure-based CBT has been found to be effective for youth with PTSD [140–143]. However, Nixon et al. [144] determined that CBT (with exposure) did not significantly outperform cognitive therapy (CT) among 33 children with PTSD following a single-incident trauma (65 % CBT vs. 56 % of CT no longer met criteria for PTSD posttreatment). The authors acknowledged that CT, while lacking in formal exposure tasks, may include some element of exposure (e.g., discussion of the negative effects of avoidance and necessary retelling of the trauma). Treatment may require consultation with schools and others involved in the child's life and should take into account psychosocial stressors, risk factors, severity of PTSD symptoms, current cognitive and developmental functioning, family and parenting factors, and comorbidities [145]. In their review, Cohen and Mannarino [146] cited established treatments for PTSD, including trauma-focused cognitive–behavioral therapy (TF-CBT) [147], cognitive–behavioral therapy for PTSD (CBT-PTSD) [148], and CBT for trauma in schools (CBITS) [44].

TF-CBT consists of 12–15 sessions, which include both the child and the parents [149]. Intended for children ages 3–18 with a history of diverse traumas, TF-CBT's components include a psychoeducation/parenting component, relaxation, affect modulation, cognitive processing, trauma narrative, in vivo exposure and mastery of trauma reminders, conjoint child–parent sessions, and enhancing safety and future development [150, 151]. The efficacy of TF-CBT has been supported in RCTs for school-age children [152, 153] and, more recently, for very young children (ages 3–6) [154]. For example, in a study of 229 youth (aged 8–14) who had been sexually abused, TF-CBT was superior to child-focused therapy on most measures, although 21 % of children treated with TF-CBT still met diagnostic criteria for PTSD posttreatment [152]. TF-CBT has been adapted for underserved populations, including Hispanic and African American youth and their families [155], children impacted by the terrorist attacks [156], children with traumatic grief [157, 158], and children exposed to intimate partner violence [159].

An alternative model was developed by Smith and colleagues [148], who created an individual treatment (CBT-PTSD) for children who meet criteria for PTSD following single-event traumas. Treatment is based on the Ehlers and Clark [160] model, which postulates that PTSD is maintained through faulty memories of the trauma, cognitive misappraisals, and dysfunctional coping strategies. As this model has been applied to children [161], it also takes into account parental reactions [162]. CBT-PTSD, a manual-based treatment, consists of ten individual sessions and parent–child sessions as needed. Treatment components comprise psychoeducation, activity scheduling, writing and drawing trauma narratives, cognitive restructuring, visiting the trauma site, stimulus discrimination, targeting nightmares, and behavioral experiments. In an initial RCT consisting of 24 children with PTSD, those receiving CBT-PTSD showed significantly greater improvement in PTSD symptoms, depression, and anxiety compared to wait list [148]. Additionally, 92 % of CBT-PTSD participants no longer met criteria for PTSD at posttreatment, and gains were maintained at 6-month follow-up. Changes in maladaptive cognitions mediated improvements as a result of CBT treatment [20], which provides support for the cognitive model of PTSD [148].

Alternative Delivery Formats

A school-based group approach, the CBITS program [44], is a ten-session CBT for implementation in schools to address symptoms of PTSD, anxiety, and depression resulting from exposure to violence.

Treatment covers relaxation, cognitive restructuring, exposure to stress or trauma memory, and social problem solving. An initial RCT compared 61 sixth-grade students assigned to CBITS and 65 assigned to wait list. Three months post-intervention, students in the CBITS group showed significantly greater decreases in PTSD symptoms, depression, and psychosocial impairment compared to the wait list controls [163]. Further, an adaptation of CBITS, the Mental Health for Immigrants Program (MHIP), has initial support among Latino immigrant youth exposed to community violence [164].

Effectiveness

Growing support exists regarding the efficacy of CBT interventions for children with PTSD [145]. Nonetheless, future research regarding the dissemination and implementation of evidence-based treatments for youth with PTSD into the community, particularly among ethnic minority groups, is necessary [155]. Several studies have been conducted; others are ongoing [165]. The Child and Adolescent Trauma Treatments and Services (CATS) Consortium [47] conducted a large-scale implementation study of trauma treatments for youth affected by the World Trade Center terrorist attack in New York City. The investigators compared TF-CBT for children and trauma and grief component therapy for adolescents (includes common components with TF-CBT [166]) with moderate to severe trauma symptoms. Youth with mild trauma symptoms received a brief CBT skills intervention [167]. At a 6-month follow-up assessment, the moderate–severe group experienced an improvement in clinical symptoms to the mild range, while the mild group also reported lower scores. The authors noted that both therapies were feasibly implemented in a variety of settings, including outpatient, community, and school-based clinics [47]. In another field trial, New Orleans children with PTSD post-Hurricane Katrina were randomized to receive either CBITS in school or TF-CBT in community clinics. Although both led to significant improvements in PTSD symptoms, school-based treatment was found to be much more accessible to families [168].

Summary

Overall, CBT has been found to be an efficacious treatment for anxiety disorders in children and adolescents and is often recommended as the first line of treatment [9]. Despite the well-documented evidence regarding CBT's success in treating anxiety disorders in youth, future work is required to investigate the specificities of anxiety CBTs for different populations of youth, including greater consideration of developmental levels and cultural groups, continued exploration of novel augmentations for nonresponders, as well as further investigation of dissemination and implementation in the community.

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Psychopharmacology of Pediatric Anxiety Disorders

Justin W. Mohatt, Alex Eve Keller, and John T. Walkup

Abstract There are a number of pharmacological approaches used in treating pediatric anxiety disorders. Selective serotonin reuptake inhibitors (SSRIs) are first line treatment, but there are many other treatment options for nonresponders including serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), benzodiazepines (BZDs), buspirone, and other investigational and augmenting agents. This chapter will examine the evidence base for the pharmacological treatment of pediatric obsessive–compulsive disorder (OCD), non-OCD anxiety disorders, and posttraumatic stress disorder (PTSD). Additionally, augmentation strategies and general clinical considerations are presented to aid in formulating an approach to both simple and complex patients.

Keywords Pediatric • OCD • Anxiety disorders • SSRI • Psychopharmacology • Evidence base

Introduction

There is a substantial and growing literature supporting the use of selective serotonin reuptake inhibitor (SSRI) antidepressants for treatment of pediatric anxiety disorders. A number of SSRIs have received United States Food and Drug Administration (FDA) approval for use in children and adolescents for obsessive–compulsive disorder (OCD) and major depressive disorder (MDD) (see Table 1). Although no SSRI is FDA approved for use in anxiety disorders other than OCD, there is very good evidence supporting their use in separation anxiety disorder (SAD), generalized anxiety disorder (GAD), and social phobia (SoP) [1]. Even though SSRIs are the treatment of choice, a number of other medications can be used to treat pediatric anxiety disorders, including serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), benzodiazepines (BZDs), and other agents (i.e., buspirone). Despite demonstrated efficacy of antidepressant medications for childhood anxiety disorders, a substantial portion of children and adolescents do not respond. There is a small literature describing next steps for the pharmacological treatment of partial and nonresponders to SSRIs.

Use of a medication to treat a disorder for which there is no FDA approval is considered "off label" use. It is important to note that while FDA approval implies evidence of safety and efficacy, the lack

J.W. Mohatt (✉) • J.T. Walkup
Child Division, Department of Psychiatry, Weill Cornell Medical College, New York, NY, USA
e-mail: jum9071@med.cornell.edu

A.E. Keller
Department of Child and Adolescent Psychiatry, Weill Cornell Medical College, New York, NY, USA

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Table 1 Selective serotonin reuptake inhibitor (SSRIs)

Medication	Pediatric indications	Starting dose	Max dose	Primary metabolism and active metabolism (AM)	CYP450 system effects	Half life parent/active metabolites
Fluoxetine	OCD (7–17 years)	10 mg/day	60 mg/day	2C19, 2D6	2D6 inhibitor	Parent: 4–6 days
	MDD (8–18 years)			AM: norfluoxetine	3A4 inhibitor	AM: 4–16 days
Sertraline	OCD (6–17 years)	25 mg/day (6–12 years)	200 mg/day	2C9, 2D6, 3A4	3A4 inhibitor	26 h
		50 mg/day (13–17 years)			2D6 weak inhibitor	
Paroxetine	None	10 mg/day	60 mg/day	2D6	3A4 inhibitor	21 h
Fluvoxamine	OCD (18 years)	25 mg/day at night	200 mg/day div	1A2, 2D6	3A4 inhibitor	15.6 h
					1A2 inhibitor	
Citalopram	None	10 mg/day	60 mg/day	2C19, 3A4	2D6 weak inhibitor	35 h
Escitalopram	MDD (12–17 years)	10 mg/day	20 mg/day	2C19, 2D6, 3A4	2D6 weak inhibitor	27–32 h

of FDA approval does not mean that a medication does not have substantial evidence of efficacy or safety. Prescribers who practice "evidence-based medicine" for children with anxiety disorders will inevitably prescribe "off label" as the FDA labeling process does not reflect the complete evidence base. Even if there is good evidence of medication efficacy in the scientific literature, if neither the manufacturer nor the FDA pursues labeling, the medication will not receive an indication. Therefore, practicing "evidence-based medicine" in pediatric psychiatry often means following the scientific literature rather than only using FDA-approved medications.

In this chapter, we will review the evidence base for the use of medications in OCD, non-OCD anxiety disorders, and post-traumatic stress disorder (PTSD) in children and adolescents and will discuss the small literature of pharmacological augmentation strategies. This structure, which separates OCD and PTSD from other anxiety disorders as well as each other, is consistent with the organization of current large studies and with the most recent changes in nosology.

Pharmacologic Agents

As an introduction to the psychopharmacology of pediatric anxiety disorders, this chapter first provides a brief overview of neurotransmitters and fundamentals of pharmacokinetics focusing primarily on drug metabolism. This is followed by a review of the major medication categories including SSRIs, SNRIs, TCAs, BZDs, mirtazapine, and buspirone. Primary indications, pharmacological effects, and adverse effects are discussed for each medication or category of medications. Information on starting doses and dose ranges are included in the accompanying tables along with reiteration of important metabolic effects.

Neurotransmitters

Neurotransmitters are the chemicals that nerve cells use to communicate with one another. They are stored in bundles in nerve cells and are released into the space between nerve cells (the synapse) when

stimulated to do so. The nerve cell from which they are released is referred to as the presynaptic neuron. When the neurotransmitter is released into the synapse, it interacts with receptors on the second nerve cell (postsynaptic neuron). Neurotransmitters are then removed from the synapse in one of two ways. They are either degraded within the synapse or removed from the synapse by reuptake pumps in the presynaptic neuron.

The major neurotransmitters discussed in psychiatry are serotonin, dopamine, norepinephrine, acetylcholine, gamma-aminobutyric acid (GABA), and glutamate. Psychotropic medications modulate the activity of these neurotransmitters in a variety of ways. Some agents work by mimicking the effects of a neurotransmitter. These are called agonists. BZDs act as agonists by mimicking the effects of GABA at its receptors. Other agents work by inhibiting the effects of neurotransmitters. These are called antagonists. Older antipsychotic medications act as dopamine antagonists by blocking its effect at dopamine receptors. Many of the medications used to treat anxiety act by blocking the reuptake of neurotransmitters from the synapse. For example, SSRIs selectively block the reuptake of serotonin from the synapse.

Pharmacokinetics

Pharmacokinetics is the underlying factors that determine how a given dose of medication leads to a particular concentration of the drug in the body. The four processes that determine a drugs concentration are absorption, distribution, metabolism, and excretion. In general terms, absorption and distribution determine the rate at which medication effects are felt by patients. Metabolism and excretion affect the rate at which these effects stop.

A basic understanding of drug metabolism is critical for understanding the appropriate use and dosing of medications in anxiety disorders. After medications are absorbed in the gastrointestinal tract, they undergo metabolism in the liver, referred to as "first-pass" metabolism, before entering the larger circulation on the body. The proportion of medication that remains in "parent" form after first-pass metabolism is called the bioavailability. While the "parent" drug is usually the effective compound, some medications also have active metabolites (i.e., fluoxetine and clomipramine). As a patient continues to take doses of a medication, the blood levels of the medication steadily rise until they reach a point at which the rate of absorption equals the rate of removal, which is referred to as a "steady-state" level. The rate at which a medication reaches steady-state is affected by how quickly a medication is metabolized or eliminated. For medications with rapid metabolism and excretion, steady-state is reached more quickly than for medications that are slowly metabolized or excreted by the body. The time it takes to reduce the blood concentration of a single dose of medication by half is called the "half-life." Half-life can be used to predict the time to steady-state, usually approximately five half-lives. This can be useful in determining the frequency of medication dosing. Medications with shorter half-lives may need to be dosed more frequently than ones with longer half-lives. Some medications require monitoring of therapeutic levels and knowledge of when steady-state will be reached helps guide when to check the level to get accurate results.

Metabolism of most psychotropic medications within the liver is performed by an extensive system of enzymes called the P450 system. A full explanation of the P450 system is beyond the scope of this chapter, and readers interested in learning more are referred to primary psychopharmacology textbooks. For the purposes of this chapter, it is important to be familiar with the primary P450 enzymes involved in the metabolism of medications used to treat anxiety and to understand the mechanisms by which medications can alter the P450 metabolism of other medications and sometimes themselves.

The most common P450 enzymes involved in metabolism of psychotropic medications are 2D6, 2C19, 3A4, and 1A2. If a medication is metabolized by a given P450 enzyme, it is referred to as a

"substrate" of that enzyme. In addition to being metabolized by the enzymes, medications can affect the rate at which the enzymes metabolize drugs. Medications that slow the metabolism by an enzyme are called inhibitors, and medications that increase the rate of metabolism by an enzyme are called inducers. If a medication inhibits a P450 enzyme, this can lead to elevations in blood concentrations of any medication that is a substrate of the enzyme. For example, fluoxetine is both a substrate of 2D6 and an inhibitor of 2D6 metabolism. If a medication such as risperidone, which is also a 2D6 substrate is added to the fluoxetine, levels of risperidone will be higher than otherwise expected for a given dose. In addition, because fluoxetine is itself a 2D6 substrate, increases in its dose can lead to much higher levels of the drug than expected if it was not inhibiting its own metabolism. Most psychotropic medications have linear pharmacokinetics, meaning that doubling of the dose of medication will lead to a doubling of concentration of medication in the body. However, some medications like fluoxetine that inhibit or induce their own metabolism have what is called nonlinear pharmacokinetics.

Children and adolescents have more efficient livers and kidneys than adults. This means that they have more efficient metabolism and elimination than adults as a general rule. Children can often tolerate adult doses of medication because of their faster metabolism and elimination. At the same time, children are not just small adults and they are often more sensitive to side effects than adults. Because each medication is different in its effects, side effects, and pharmacokinetics, it is impossible to make general statements about dosing of medications. It is important that prescribers are familiar with each agent and review the specific information for each when prescribing for children and adolescents. Familiarity with the dosing protocols in clinical trials can provide a rough guideline for dosing and titration in order to avoid under-dosing or excessively prolonged or rapid titration.

Selective Serotonin Reuptake Inhibitors

The SSRIs are first line agents for childhood anxiety disorders due to consistent and substantial evidence of safety and efficacy in a number of high quality clinical trials. The SSRIs available in the United States include regular and sometimes extended release preparations of the following: fluoxetine (Prozac, Prozac Weekly), paroxetine (Paxil, Paxil CR), fluvoxamine (Luvox, Luvox CR), regular release sertraline (Zoloft), citalopram (Celexa), and escitalopram (Lexapro). At this time, there is FDA approval for fluoxetine for OCD (age >7) and MDD (age >12), sertraline for OCD (age >6), fluvoxamine for OCD (age >8), and escitalopram for MDD (age >12). There are no medications with FDA approval for non-OCD anxiety disorders. However, there is considerable evidence supporting their use in the non-OCD anxiety disorders. Table 1 provides a summary of the SSRIs including information on starting doses, maximum doses, and metabolism.

Pharmacological Effects

The primary mechanism of action of the SSRIs is the selective inhibition of serotonin reuptake from the synaptic cleft with very little or no effect on dopamine or norepinephrine uptake. The SSRIs differ however in their activity for other receptors, pharmacokinetics, metabolic pathways, and risk for drug–drug interaction. Hence, some patients may respond to or tolerate one SSRI better than another. Long half-life SSRIs are preferable for those who miss an occasional dose as they have minimal withdrawal effects. However, the longer half-life of the drug may result in a greater duration of side effects for patients after discontinuation. For example, fluoxetine has a long half-life. If a patient develops adverse effects on fluoxetine and it is discontinued, the adverse effects will persist longer than they would for a medication like paroxetine with a shorter half-life. On the other hand, shorter half-life SSRIs like paroxetine may not be the best choice for less adherent patients; these medications have a greater risk for withdrawal effects but also clear quickly with discontinuation. Additionally, most

SSRIs have linear accumulation (linear pharmacokinetics), whereas others (fluoxetine and paroxetine) have nonlinear and less predictable accumulation. The desired clinical effects of SSRIs are due to alteration of receptor sensitivities, not the immediate increase in serotonin levels seen with SSRI administration. As a result clinical effects are only observed after several weeks on the medication.

Some SSRIs have more prominent drug–drug interactions (e.g. fluoxetine, paroxetine, fluvoxamine). SSRIs with minimal drug–drug interactions (e.g., sertraline, citalopram, and escitalopram) may be better first choices if the doctor anticipates combined pharmacotherapy. The knowledge of how the SSRIs differ will likely inform drug choice as much or more than results of efficacy studies and help improve outcome and minimize side effects.

Adverse Effects

The SSRIs have relatively benign safety and side effect profiles, especially when compared to their predecessors, the TCAs and monoamine oxidase inhibitors (MAOIs). Compared to the TCAs, the SSRIs are less sedating and cause less weight gain because of low anti-histamine effects. SSRIs have less anti-cholinergic effects, causing less dry mouth, constipation, and urinary retention than TCAs and MAOIs, and they have very few adrenergic effects and therefore have low risk of orthostatic hypotension. The SSRIs have no effect on Na^+ channels. As a result, they do not carry the same serious cardiac risks in overdose as the TCAs. Finally, they do not burden the patient with the dietary restrictions as the MAOIs.

Side effects generally occur early in the course of treatment and are likely due to the rapid and dramatic increases in serotonin concentration in the brain and periphery. Headache, nausea, diarrhea, constipation, and loss of appetite are common early side effects but usually mild, transient, and very responsive to adjustments in the dosage. Few side effects present late in the course of treatment.

Among the most common and problematic adverse events in clinical trials is central nervous system activation, a phenomenon called behavioral activation, which can vary in severity from mild internal restlessness to insomnia, significant impulsivity, and hyperactivity. Activation occurs early in treatment and with dose adjustments. Preadolescent patients appear more likely to experience behavioral activation than adolescents [2]. Rates of activation by SSRIs have ranged from approximately 11 % to as high as 50 % [2–5]. Activation is often easily managed by lowering the dose of medication, though significant reductions may result in loss of the desired clinical effect. In children who cannot tolerate the activation side effects of SSRIs, a trial of the non-activating antidepressants (e.g., clomipramine, duloxetine, mirtazapine, imipramine, or nortriptyline) may be useful.

Like other antidepressants, the SSRIs also have been associated with mania. Data from large randomized controlled trials (RCTs) indicate that the rates are very low (<2 %) especially compared to behavioral activation, which does not present with the euphoria, grandiosity, and mood changes of mania. Mania can occur at any point in treatment whereas behavioral activation presents early in treatment or with dose titration [6–9]. Of note, rates of antidepressant induced mania are substantially higher in retrospective case studies (5.4–55 %) likely reflecting less stringent screening for risk factors (e.g., familial history of bipolar disorder) in general clinical populations than RCTs [6]. While a family history of mania, especially a parent with bipolar disorder, is not a contraindication to SSRI use, clinicians must proceed with caution and be watchful for any emergent symptoms of a mania in this population.

Sexual dysfunction is another side effect of SSRIs. This includes reduction in or loss of libido for both males and females. Additionally, for male patients, it can include an inability to get or maintain an erection, delayed ejaculation, or inability to ejaculate. In female patients, it can lead to delayed orgasm or anorgasmia [10]. Adolescents should be monitored for sexual side effects, which they may not discuss spontaneously and which may lead to reduced medication adherence. It is important to lay the base for these discussions by including education about sexual side effects in the informed consent

process with adolescents. Going forward, direct questioning about sexual side effects in a nonthreatening manner using clear medical terminology will be most effective.

Sexual effects can be dose dependent. Therefore, reducing the dose is one option for managing them. Other options include switching to an antidepressant with less sexual side effects (i.e., mirtzapine, nefazodone), adding an agent to promote libido (i.e., buproprion), or adding an agent to improve erectile function (i.e. sildenafil or tadalafil) [11, 12]. Choice of agent should be guided by the underlying psychiatric disorder being treated and the underlying pathology of the dysfunction (loss of libido vs. erectile dysfunction vs. anorgasmia vs. overall dysfunction).

A syndrome of apathy, manifested by lack of motivation in the absence of sedation or depression, can occur with the SSRIs. This is dose dependent, may not appear until later in titration, and does not tend to improve with time. Reducing the dose may help. If dose reduction is ineffective, then switching to a different class of antidepressant may be necessary.

Abrupt discontinuation after long-term use of SSRIs has been associated with discontinuation effects including unusual sensory experiences and a flu-like syndrome. As noted previously, discontinuation effects appear to be more common in SSRIs with a short half-life as compared to those with a longer half-life. Slow and graduation discontinuation is generally recommended for the SSRIs both to avoid withdrawal effects and to reduce the chance of rapid return of anxiety or depressive symptoms. The speed of reduction can be guided in part by pharmacokinetics. Medications like paroxetine with short half-lives require a slower dose reduction to avoid or reduce discontinuation effects, while medication like fluoxetine can often be discontinued quickly without notable discontinuation effects. It is impossible to make general statements about how quickly to lower a given medication because individuals are widely variable in their sensitivity and tolerance of these effects.

Serotonin syndrome is a potentially fatal complication of treatment with any medication that increases serotonin levels including the SSRIs. It is usually due to the combined effects of two or more drugs that both elevate serotonin levels. Symptoms of serotonin syndrome include agitation, hyperreflexia, myoclonus, tremor, ataxia, agitation, diarrhea, nausea, vomiting, fever, heavy sweating, shivering, and mental status changes such as confusion and hallucinations. Serotonin syndrome is a medical emergency and should be treated as such. Once it is recognized, the offending medications must be stopped and the patient should be admitted to the hospital for monitoring and supportive care. Appropriate care can include medications to reduce agitation, muscle stiffness and myoclonus, cyproheptadine to block serotonin production, and IV fluids for hydration. If appropriately recognized and treated, patients usually recover quickly and well.

All antidepressants, including the SSRIs, carry an FDA Black Box warning label indicating that they may increase the risk of suicide in patients 24 years and younger. The FDA added labeling about increased suicide risk in October 2004 following an analysis of pooled data from prior antidepressant trials that found 4 % of subjects on antidepressants reported increased suicidal thoughts or behaviors compared to 2 % of patients on placebo. There were no actual suicides among the approximately 4,400 children and adolescents in these studies. Subjects in the studies carried diagnoses of MDD, OCD, and other anxiety disorders. In 2007, the label was expanded to include adults 24 years or younger. For further details about the FDA review, please refer to the FDA website (www.fda.gov). Information about the black box warning written specifically for parents can be found at www.parentsmedguide.org along with other information about antidepressant use in children.

Since the original announcement in 2004, there has been significant controversy and concern about how to address the black box warning in clinical practice. While there does appear to be a small increased risk of suicidal thoughts and behaviors, there are also great risks associated with untreated mental illness. Suicide remains the third leading cause of death in youth [13]. Since the black box warning was implemented, the rate of antidepressant prescribing in children and adolescents has declined and at the same time the adolescent suicide rate has gone up for the first time in over 10 years [14]. In clinical practice, patients must be given appropriate information about these risks, and the potential risks versus benefits must be weighed carefully when deciding how to treat. When starting

Table 2 Selective norepinephrine reuptake inhibitors (SNRIs) and miscellaneous medications

Name	Pediatric indication	Starting dose	Max dose	Primary metabolism and active metabolites (AM)	CYP450 system effects	Half life parent/ active metabolites
Duloxetine (Cymbalta)	None	30 mg/day	120 mg/day	1A2, 2D6	2D6 moderate inhibitor 1A2 weak inhibitor	12 h
Venlafaxine (Effexor)	None	37.5 mg/day	375 mg/day	2D6	2D6 weak inhibitor	Parent: 5 h
				AM: O-desmethyl-venlafaxine	3A4 inhibitor	AM: 11 h
Venlafazine Er (Effexor XR)	None	37.5 mg/day	225 mg/day	2D6	2D6 weak inhibitor	Parent: 5 h
				AM: O-desmethyl-venlafaxine	3A4 Inhibitor	AM: 11 h
Dewvenlafaxine (Pristiq)	None	50 mg/day	50 mg/day	Liver: minor 3A4 UGT	2D6 very weak inhibitor	11 h
Miscellaneous medications						
Mirtazapine (Remeron)	None	15 mg/day	45 mg/day	1A2, 2D6, 3A4	None	20–40 h
Buspirone (Buspar)	Anxiety	15 mg/day bid	60 mg/day bid	3A4	None	2–3 h

an antidepressant in someone under 25 years of age, additional monitoring is suggested with close follow-up as clinically indicated on an individualized basis. Some recommendations have called for weekly appointments for the first 4 weeks, then every 2 weeks for the following 4 weeks. This is not always possible due to scheduling issues, insurance coverage, and other logistical factors. Phone check-ins can be used to partially address this and close coordination with other care providers who see the patient more often can be helpful in monitoring during the early stages of treatment.

Serotonin Norepinephrine Reuptake Inhibitors

The SNRIs include venlafaxine (Effexor and Effexor XR), desvenlafaxine (Pristiq), and duloxetine (Cymbalta). The SNRIs do not have FDA approval for any indication in children or adolescents. However, some prescribers may choose to use SNRIs for children who have failed or not tolerated SSRIs or when looking for a broader spectrum of receptor activity. Published clinical trials of SNRIs for pediatric anxiety are few and support the efficacy of venlafaxine for social anxiety disorder [15] and show mixed evidence for efficacy for GAD [16]. There are no studies of duloxetine or desvenlafaxine in children, and therefore this medication will not be discussed in this chapter. Table 2 presents the SNRIs, mirtazapine, and buspirone, along with their indications, starting and maximum dosing, and details of their metabolism. Similar to the SSRIs, the SNRIs and mirtazapine take several weeks to show clinical effects.

Pharmacological Effects

The primary pharmacological effect of the SNRIs is to prevent the reuptake of norepinephrine and serotonin from the synaptic cleft, with less potent dopamine reuptake inhibition. Lower doses of venlafaxine act primarily as an SSRI with norepinephrine reuptake inhibition occurring with higher

doses. At the highest doses, dopamine reuptake inhibition occurs. The half-life of venlafaxine is about 5 h, and it is metabolized by the CYP-450 2D6 but does not appear to inhibit this or other CYP-450 pathways to a clinically significant extent. Drug interactions are few with most reports focusing on cumulative serotonin toxicity with combined use of venlafaxine with other serotonergic medications [17].

Adverse Effects

Common adverse effects of venlafaxine include nausea, headache, insomnia (activation), dry mouth, and sedation. Blood pressure monitoring is also suggested as elevations in blood pressure related to the added norepinephrine reuptake inhibition at higher doses can occur. It is not uncommon for people to experience discontinuation effects with the short acting form of venlafaxine. These can include dizziness, nausea, stomach cramps, sweating, tingling in the extremities, and various unusual sensory phenomena such as burning, itching, pins and needles, and electric shock-like sensations.

The SNRIs can cause similar side effects as the SSRIs, including sexual side effects. Management of these is the same as outlined for the SSRIs. Serotonin syndrome is a possible adverse effect when venlafaxine is combined with other medications that raise serotonin levels. Details of serotonin syndrome and its management can be found in the SSRI section. The SNRIs carry the same warning label about suicidality as the SSRIs and similar care should be taken when prescribing and monitoring them.

Tricyclic Antidepressants

Although the TCAs have been available much longer than the SSRIs, they are not considered first line treatments for pediatric anxiety disorders due to their inconsistent performance in the few available efficacy studies as well as their less favorable adverse effects profiles. Clomipramine is the exception. Clomipramine has demonstrated efficacy for OCD and has an FDA indication in children, ages 10 and older. Imipramine has an indication for nocturnal enuresis and has demonstrated mixed evidence of efficacy in childhood anxiety disorders. The strong norephinephrine reuptake activity of some TCAs (e.g., desipramine) has led to their use in the treatment of ADHD [18, 19]. Case reports of sudden death on desipramine in the early in 1990s led to decrease use of TCAs [20]. Table 3 presents the TCAs, their indications, starting and maximum dosing, and details of their metabolism.

Pharmacological Effects

The TCAs primarily inhibit the reuptake of norepinephrine, acetylcholine, and serotonin from the synaptic cleft and less strongly inhibit reuptake of dopamine. In addition, all the TCAs block histaminic (H1), muscarinic, cholinergic, and alpha-1 adrenergic receptors, which accounts for many of their nuisance side effects. TCAs vary in how strongly they inhibit one neurotransmitter as compared to the others. Clomipramine, for example, is a stronger serotonin reuptake inhibitor than the other TCAs. This may explain its unique effectiveness in OCD. In contrast, desipramine is a potent norepinephrine reuptake inhibitor, which may explain its efficacy in ADHD and lack of efficacy in OCD. One advantage of the TCAs over the SSRIs is their relative lack of significant inhibitory effect on the P450 system [21]. However, they are extensively metabolized through the P450 system and thus blood level and half-life can be elevated by concurrent use of TCAs with some SSRIs. Like the SSRIs and SNRIs, it may take several weeks to see improvement on TCAs.

Table 3 Tricyclic antidepressants

Name	Pediatric indication	Starting dose	Max dose	Primary metabolism and any active metabolites (AM)	CYP450 system effects	Half life parent/active metabolites
Clomipramine (Anafranil)	OCD (>10 years)	25 mg/day	3 mg/day for the first 2 weeks, up to 200 mg/day	1A2, 2D6, 2C19, 3A4	2D6 inhibitor	Parent: 32 h
				AM: desmethylclomipramine		AM: 69 h
Amitriptyline (Elavil)	MDD (>9 years)	9–12 years: 1 mg/kg/day	9–12 years: 5 mg/kg/day, up to 200 mg/day	1A2, 2D6, 3A4	1A2 inhibitor	Parent: 10–26 h
		>12 years: 10 mg tid	>125 years: 200 mg/day	AM: nortriptyline	2C19 inhibitor 2D6 inhibitor	AM: 18–44 h
Desipramine (Norpramin)	None	25 mg/day	300 mg/day	2C19, 2D6	2D6 weak inhibitor	12–27 h
Nortriptyline (Pamelor)	MDD (>6 years)	1–3 mg/kg/day tid–qid dosing	150 mg/day	2D6	2D6 weak inhibitor	Parent 18–44 h
				AM: 10-hydroxynortiptyline		AM: 8–10 h
Imipramine (Tofranil)	MDD (>6 years)	6–12 years: 1.5 mg/kg/day tid	6–12 years: 5 mg/kg/day	1A2, 2C19, 2D6, 3A4	2D6 weak inhibitor	Parent: 11–25 h
		>12 years: 30–40 mg/day qd–tid	>12 years: 100 mg/day	AM: desipramine		AM: 12–27 h

Adverse Effects

Anti-histamine effects include weight gain and sedation. Anti-muscarinic effects include dry mouth, blurry vision, constipation, and urinary retention. Anti-alpha-1 adrenergic effects include orthostatic hypotension and dizziness. The TCAs vary in how strongly they block each of these, leading to different relative side effect profiles. For example, nortriptyline has the least alpha-1 adrenergic effects and causes the least orthostatic hypotension, and desipramine tends to cause less anti-muscarinic effects than the other TCAs.

The TCAs also block sodium channels in the heart and brain. This accounts for the risk of cardiac arrhythmias, cardiac arrest, and seizures in overdose. The cause of sudden death in children is not known, but it is presumed that individuals vulnerable to cardiac arrhythmia when exposed to QTc prolonging agents such as desipramine may develop malignant arrhythmias [20]. How best to screen for the presumed cardiac vulnerability is controversial as EKGs and echocardiograms may not identify any vulnerability. At this time, it is recommended that a baseline EKG and thorough cardiac history of the child and family (focusing on vulnerability for arrhythmia, sudden death not due to coronary artery disease, and nonvasovagal syncope) should be obtained before initiating a TCA in children. Further testing may be necessary based on the results of the history and EKG results. Follow-up EKGs should be obtained as clinically indicated for a given patient.

The TCAs carry the FDA black box warning regarding increased risk of suicidality in children, teens, and adults under 25 years of age. As with the other antidepressants, this should be monitored closely, especially when initiating treatment and when adjusting the dose.

Benzodiazepines

The BZDs, while indicated for treatment of adult anxiety and used by clinicians to treat children and adolescents, do not have an FDA indication for pediatric use with the exception of pre-anesthesia. In addition, there are limited data to support their use in youth. Despite the lack of an evidence base, they are used clinically in the context of panic attacks and for acute situational anxiety such as before medical procedures, performances, and before school in children with severe school anxiety.

Pharmacological Effects

The primary action of BZDs is to bind to GABA receptors, potentiating the effect of GABA at these receptors, thereby increasing GABA's inhibitory effects in the brain. In contrast to the antidepressants, whose effects develop over time and persist due to changes in receptor sensitivity, the BZDs are only useful for the time that they are being used. Hence differences in the duration of action inform the choice of agent in specific anxiety disorders. Shorter half-life BZDs, such as alprazolam, may be more helpful in acute anxiety attacks. Longer half-life agents such as clonazepam would be a better choice for persistent lowering of overall anxiety (see Table 4).

Adverse Effects

BZDs have prominent central nervous system depressant effects leading to reduced anxiety but also sedation and occasionally disinhibition, which can include hyperactivity, impulsivity, and agitation. Care must be taken when prescribing the BZDs to adolescents or patients known to abuse alcohol or

Table 4 Benzodiazepines and equivalent doses (dose ranges for pediatric anxiety reflect off-label use)

Name	Pediatric indication	Dose range	1 mg lorazepam equivalents[a]	Half life
Alprazolam (Xanax)	None	*Adult panic*: 0.5–3 mg pot id 3–6 mg ER po qd *Adult anxiety*: 0.25 mg po tid, Max 4mg/day total	0.5 mg	12 h
Clonazepam (Klonopin)	Seizures	<10 yo or 30 kg: up to 0.1–0.2 mg kg/day >10 yo or 30 kg: up to 20 mg/day	0.25 mg	>24 h
Diazepam (Valium)	Muscle spasm, tetanus, status epilepticus	*For anxiety*: 6 mos–12 yo: 0.12–0.8 mg/kg/day div po q6–8 h >12 yo: 2–10 mg po bid–qid	5 mg	>72 h
Lorazepam[b] (Ativan)	Status epilepticus, nausea, sedation	*For anxiety*: 0.05 mg/kg q4–6 h, max: 2 mg/dose	1 mg	15 h
Temazepam (Restoril)	None	7.5 mg qhs for insomnia in adults	7.5 mg	11 h

[a]The amount for a given BZD that is equivalent to 1 mg of lorazepam—for example 0.25 mg of clonazepam = 1 mg lorazepam
[b]Lorazepam has no liver metabolism

drugs as BZDs can be lethal when combined with alcohol or other depressants. In addition, patients develop tolerance to the effects of BZDs and have potential for dependence and abuse.

Buspirone

Buspirone is approved to treat anxiety in adults but not in children. There is evidence of effectiveness for generalized anxiety in adults, but the one trial of buspirone in pediatric GAD is negative and unpublished [22]. Given the superior efficacy of SSRIs, buspirone should not be considered a first line agent for pediatric anxiety disorders. Given buspirone's serotonergic activity, prescribers may use it as an adjunct in individuals with a partial response to SSRIs, although there are no data to support this use in children. The indications, dosing, and details of buspirone metabolism are included in Table 2.

Pharmacological Effects

Buspirone is a 5HT1A receptor partial agonist with both presynaptic and postsynaptic actions. Buspirone has a delayed onset of action similar to antidepressants. Buspirone is metabolized by the CYP450 3A4 system. As a result, it has drug–drug interactions similar to the BZDs.

Adverse Effects

Buspirone's advantages over the BZDs are lack of risk for dependency and abuse, lack of withdrawal effects, low overall side effect profile, and lack of interactions with CNS depressants. The most common side effects include headache, nausea, and dizziness.

Mirtazapine

Mirtazapine (Remeron) is approved to treat depression in adults but does not have an indication to treat anxiety disorders in either adults or children. It should not be considered as first line treatment for anxiety in children but could be considered if standard treatments fail. Because it is available as a rapidly dissolving tablet, it can be considered in patients who have trouble swallowing pills and because of its sedating side effects it can be considered for use in patients with sleep disturbance. There is a single 8-week open-label trial of mirtazapine for treatment of social anxiety in 18 children age 8–17, in which 56 % of subjects responded but 4/18 discontinued due to irritability and fatigue [23]. The indications, dosing, and details of mirtazapine metabolism are included in Table 2.

Pharmacological Effects

Mirtazapine acts as an antagonist for alpha-2 adrenergic receptors and for serotonin 5-HT2 receptors. Mirtazapine, like the other antidepressants, has a delayed onset of action. Mirtazapine is extensively metabolized in the liver by CYP450 1A2, 2D6, and 3A4, and its levels could be affected by coadministration of other medications that either induce or inhibit these enzymes. Mirtazapine itself does not act as either an inducer or inhibitor of CYP450 enzymes.

Adverse Effects

The most common adverse effects of mirtazapine include somnolence, dizziness, increased appetite, weight gain, constipation, dry mouth, and nausea. Mirtazapine carries the FDA black box warning regarding increased risk of suicidality in children, teens, and adults less than 25 years of age. As with the other antidepressants, this should be monitored closely, especially when initiating treatment and when adjusting the dose.

Evidence Base for Specific Disorders

The current evidence base for pharmacological treatments will be reviewed for specific pediatric anxiety disorders. In the case of OCD, where this is a larger evidence base, this includes evidence for primary pharmacological treatments and augmenting and experimental agents. For the non-OCD anxiety disorders, including PTSD, the focus is on primary pharmacological treatments.

Obsessive–Compulsive Disorder

Primary Pharmacological Treatments

There are numerous RCTs, open-label trials, and comparison trials supporting the use of serotonin reuptake medications as first line pharmacological treatment (with or without CBT) in mild to moderate OCD and certainly as first line in the most severe cases.

The Pediatric OCD Treatment Study (POTS) is a moderately large ($n = 112$) multicenter, randomized, placebo-controlled trial comparing sertraline up to 200 mg daily, cognitive behavioral therapy (CBT), CBT with sertraline, and placebo in children and adolescents 7–17 years old. All three active

treatment arms showed statistically significant improvement compared to placebo, and combined treatment with sertraline and CBT (ES 1.4) was superior to both CBT alone (ES 0.97) and sertraline alone (ES 0.67) [24]. While sertraline was generally well tolerated, the most common adverse effects were insomnia, agitation, nausea, and tremor. Based on the results of the POTS I trial, it is recommended that treatment for pediatric OCD consist of a combination of CBT and medication when possible.

Following up on the results of the POTS I trial, a second trial was conducted to examine the addition of CBT to an SSRI in patients with a partial response to the SSRI treatment alone. POTS II is a 12-week RCT of 124 outpatient children and adolescents comparing SSRI alone, SSRI plus CBT, and SSRI plus brief CBT instruction as part of medication management appointments. The SSRI plus CBT intervention was superior to the other two arms of the study on all outcome measures. Among subjects receiving SSRI alone, 30 % were considered responders compared to 34 % in the brief CBT group and 68.6 % in the CBT group. Number needed to treat for the medication alone group was 25 compared to 3 for the two other groups [25]. The findings of POTS II further support the combination of CBT and medication management in the treatment of OCD when it is possible.

An earlier industry-sponsored RCT also demonstrated efficacy of sertraline up to 200 mg/day over 12 weeks among 6–17 year olds ($n=187$) with OCD [26]. During the 1-year open-label extension phase of the study, 85 % of initial responders maintained their gains, and 43 % of initial nonresponders became responders by the end of the study [27].

Other SSRIs including fluoxetine [28, 29], paroxetine [30], and fluvoxamine [31] have RCTs supporting their efficacy for treatment of OCD.

A number of controlled trials support the effectiveness of clomipramine, a TCA, in OCD, as compared to placebo and desipramine [32–34]. Most significant among these was a multicenter, double-blind, RCT of 60 children and adolescents (age 10–17) treated with up to 200 mg daily of clomipramine over 10-weeks. Subjects in the treatment group showed a 37 % reduction in CYBOCS scores compared to 8 % in the placebo group ($p<0.05$). While clomipramine was generally well tolerated, the most common side effects were dry mouth, somnolence, and dizziness. No clinically significant EKG changes were found, but mild pulse elevations, drops in systolic blood pressure, and weight gain were present [32].

In clinical practice, a variety of agents have been tried in combination with clomipramine for treatment-resistant OCD patients. Of these, the combination of fluvoxamine and clomipramine is notable. Fluvoxamine uniquely inhibits the conversion of clomipramine to desmethylclomipramine, thereby increasing blood levels of the serotonergically active parent compound in the blood and reducing the level of the almost exclusively noradrenergic effects of desmethylclomipramine. Such augmentation strategies require great care with close monitoring of clomipramine/desmethylclomipramine blood levels and periodic EKGs. Other SSRIs such as fluoxetine and paroxetine (and sertraline to a lesser extent) when used in combination with clomipramine may actually increase the level of the noradrenergically active desmethylclomipramine and may not be as useful in reducing OCD symptoms. Other medications have little or no effect on clomipramine metabolism (e.g., citalopram and escitalopram).

Patients with OCD and comorbid tic disorders, ADHD, and ODD may not respond as well to SSRI treatment [35–37]. Other medications and behavioral treatments for these comorbid disorders may be needed for optimal outcome. Patients with comorbid tic disorders may show more improvement with the addition of an antipsychotic [38].

Augmenting and Alternative Agents

Despite the evidence supporting use of SSRIs and clomipramine for OCD, a substantial portion of patients with OCD will not respond to monotherapy, will have an incomplete response, or not tolerate antidepressant medications [32, 37, 39]. As a result, a variety of agents have been suggested and/or tried as possible augmentation strategies. The augmentation strategies focus either on potentiation of

serotonin reuptake by using a second medication with serotonergic agonist activity (e.g., a second serotonin reuptake inhibitor, lithium, or inositol) or by modulating the activity of other neurotransmitters such as dopamine (e.g., antipsychotics) or glutamate [e.g., riluzole and *N*-acetylcysteine (NAC)]. More recently, there have been efforts based on our understanding of fear learning to improve the outcome of CBT using D-cycloserine. With the exception of the addition of antipsychotics, the body of evidence supporting the efficacy of any augmentation strategy in youth (or adults) is very small or nonexistent; there are no controlled trials for augmentation strategies in the pediatric population.

At least nine double-blind placebo-controlled trials of antipsychotic augmentation of SSRIs exist in the adult OCD literature, all of which demonstrated significant effect [40]. There is some evidence that antipsychotic augmentation may be beneficial in pediatric OCD. One case series of risperidone augmentation of an SSRI showed that all four patients demonstrated improvement in OCD symptoms [41]. In an open-label trial of risperidone augmentation of an SSRI, 4/17 patients had a moderate (>25 %) improvement in Y-BOCS scores and another 10/17 had slight (10–25 %) improvement; only one patient's score dropped from clinical to subclinical OCD during the 12 week trial [42]. A single-case series looked at aripiprazole augmentation of SSRI for 39 adolescents with medication-resistant OCD. Of the 39 participants, 29 (59 %) showed significant improvement in symptoms. Responders were less functionally impaired at baseline but no different from nonresponders in overall clinical severity. No participants dropped out due to adverse effects, and the most commonly reported adverse effects were mild transitory agitation, mild sedation, and sleep disorders [43].

Inositol, a precursor in the phosphatidylinositol cycle, has been evaluated in small treatment trials of OCD and for augmentation of SSRIs. A single double-blind crossover RCT of 13 adults using a two-way repeated measures analysis of variance demonstrated no improvement versus placebo over the course of 6 weeks at a dose of 18 g/day [44]. There have been no studies to date looking at inositol in pediatric OCD, and other studies of inositol augmentation in adults did not show significant improvement [45, 46].

Given the postulated role of glutaminergic dysfunction in the pathophysiology of OCD, riluzole, a glutaminergic antagonist, was evaluated and demonstrated benefit in a single small ($n=6$) open-label trial for treatment of pediatric OCD, with four out of six subjects responding by week 12 at doses up to 120 mg daily. No adverse effects led to discontinuation during the study, and all subjects chose to remain on the riluzole after study completion [47]. There is also a single published positive case report using fluvoxamine augmented by NAC for an adult subject with treatment-resistant OCD [48]. There are no published reports supporting NAC use in pediatric OCD. Other studies of both medications are underway and are appealing as possible options given the positive initial experiences and low adverse event profile of NAC.

D-cycloserine is an *N*-methyl-D-aspartate (NMDA) receptor partial agonist that has been found to facilitate fear extinction in animal models of anxiety [49, 50]. D-cycloserine has been evaluated in adults as an augmenting agent to enhance fear extinction in behavioral therapy for anxiety disorders. Specifically, it has been studied in adult SoP [51, 52], panic disorder [53], and OCD [54, 55] with positive results for SoP and panic disorder. The adult OCD studies did not find statistically significant differences. A single small ($n=32$) double-blind placebo-controlled study compared CBT augmentation with D-cycloserine versus CBT plus placebo for treatment of pediatric OCD. Subjects received DCS 1-h before exposure sessions. The study found no statistical difference between groups on primary or secondary outcome measures. There were no reported adverse effects [56].

Non-OCD Anxiety Disorders

The non-OCD anxiety disorders are a heterogeneous group consisting of SAD, GAD, SoP, panic disorder, selective mutism, and specific phobia. SAD, GAD, and SoP have overlapping symptomatology

(e.g., school avoidance behavior), are commonly comorbid, and have a positive treatment response to CBT and antidepressant medications. As a result, many clinical trials group together children and adolescents with GAD, SAD, and/or SoP and evaluate treatment effects on overall anxiety severity. The data for panic disorder, specific phobia, school refusal, and selective mutism are limited; therefore, this section will primarily focus on the treatment of GAD, SAD, and SoP with briefer mention of the research on panic disorder, selective mutism, school refusal, and specific phobias.

There are numerous acute, double-blind, placebo-controlled RCTs assessing medication treatment of non-OCD anxiety disorders: some provide definitive evidence of efficacy whereas others are small and evidence is equivocal. With increasing awareness that anxiety comorbidity is the rule rather than the exception in children presenting to child and adolescent psychiatry clinics [8, 57–60], the largest and most definitive pharmacological studies have assessed medication in children with SAD, GAD, and/or SoP. Studies of subjects with a combination of SAD, GAD, and/or SoP, which generally are larger and more rigorous, are discussed first followed by a section on diagnosis specific studies.

Studies Combining the Three Disorders

The largest and most rigorous study of multiple anxiety disorders to date is the Child Adolescent Anxiety Multimodal Study (CAMS), which evaluated sertraline up to 200 mg/day, placebo (double-blind), CBT, or sertraline plus CBT (not blinded) in 488 children age 7–17 years presenting with GAD, SAD, and/or SoP over 12 weeks. In addition, participants were allowed to enroll with comorbid ADHD, PTSD, ODD, conduct disorder, and dysthymia. On all primary outcomes, CBT plus sertraline was superior to CBT alone and sertraline alone ($p<0.001$), which were equally effective, and all three treatments were superior to placebo ($p<0.001$). The effect size was 0.86 for combination therapy, 0.45 for sertraline, and 0.31 for CBT. The number needed to treat was 1.7 for combination therapy, 3.2 for sertraline, and 2.8 for CBT. Sertraline was generally well tolerated and there was no statistical difference in rates of adverse events in the sertraline group versus placebo group. There was no evidence of harm-related adverse events, and drop-out rates were similar between sertraline (17.3 %) and placebo (19.7 %) groups. There were no suicide attempts by any subjects [8].

The Research Unit on Pediatric Psychopharmacology Anxiety Study Group multisite, double-blind placebo-controlled trial studied 128 children age 6–17 years with diagnoses of GAD, SAD, and/or SoP over 8 weeks who were randomized to fluvoxamine (up to 300 mg daily) or placebo [59]. Participants could have comorbid ODD and dysthymia but not ADHD, PTSD, conduct disorder, or MDD. Participants in the fluvoxamine group showed statistically greater response (CGI-I <4) rates (76 %) compared to placebo (29 %, $p<0.01$). Adverse events were generally mild with abdominal discomfort and increased activity level being more common on fluvoxamine than placebo. Additionally, treatment gains were maintained for 94 % of subjects during the 6-month open-label follow-up [61].

Similar to the RUPP study, fluoxetine, up to 20 mg daily, was compared to placebo over 12-weeks in 74 children age 7–17 years. Participants were diagnosed with GAD, SAD, and/or SoP. Allowed comorbidities included ADHD, PTSD, ODD, conduct disorder, and dysthymia. The fluoxetine group showed significantly greater response rates (61 %) as compared to placebo (35 %) on a variety of primary outcomes. By week 9 of the study, there was statistically significant difference between study groups. Fluoxetine was generally well tolerated with abdominal pain being more common (44 %) compared to placebo (22 %). Behavioral disinhibition was more common in the fluoxetine group (n = 7) compared to placebo ($n=4$), but this was not significant. Treatment gains were maintained in a 1-year open-label follow-up [62].

Social Phobia

A RCT ($n=80$) of children age 7–17 with SoP compared fluoxetine alone, psycho-education alone, and Social Effectiveness Training for Children (SET-C) combined with fluoxetine up to 40 mg daily over 12 weeks. Children receiving fluoxetine plus SET-C showed the greatest response rate (72.7 %); fluoxetine alone showed greater response rate (30.1 %) than children in the psychoeducation group (6.3 %) [63].

A large ($n=322$) 16-week multisite, double-blind placebo-controlled RCT of paroxetine (up to 50 mg daily) in children and adolescents ages 8–17 years with SoP demonstrated greater response rates in the paroxetine group (77.6 %) as compared to children in the placebo group (38.3 %). As in the other studies of SSRIs, the medication was generally well tolerated with mild to moderate side effects including insomnia, vomiting, and reduced appetite [64].

A few trials of SNRIs and other antidepressants have been published. Venlafaxine XR (up to 225 mg daily) was compared to placebo in SoP among 293 children (8–17 years) over 16 weeks. Response rates of participants on venlafaxine (56 %) were greater than those in the placebo group (37 %). While most adverse events were mild to moderate (most commonly nausea, anorexia, weight loss, pharyngitis, mydriasis); it is notable that three participants in the venlafaxine group developed new suicidal ideation compared to none in the placebo group [15]. There is one small ($n=18$) 8-week open-label trial of mirtazapine in children with SoP, which found improvement in 56 % (10/18) of subjects. However, four of the subjects discontinued due to adverse effects including fatigue and irritability. There was also significant weight gain on the medication [23]. No other studies exist to date regarding mirtazapine's use in children with anxiety. Mirtazapine may be considered for use in children with anxiety after a trial of other medications with more evidence supporting their effectiveness. It may also be considered in patients with prominent sleep disturbance or weight loss.

Generalized Anxiety Disorder

Two double-blind RCTs evaluated venlafaxine XR doses up to 225 mg daily to treat GAD in children age 6–17 over 8 weeks [16]. Pooled data ($n=320$) identified greater response rates on venlafaxine (68 %) as compared to placebo (47 %). Venlafaxine was generally well tolerated. Most common adverse events included asthenia, pain, anorexia, and somnolence. A small double-blind trial ($n=22$) demonstrated the efficacy of a fixed dose of sertraline 50 mg daily in subjects age 5–17 years over 9 weeks [65]. An industry-sponsored trial of buspirone for children and adolescents with GAD did not demonstrate greater response in the active as compared to placebo group. The study was not published but described briefly in the buspirone product information [22].

Selective Mutism

Selective mutism is closely tied with social anxiety [66], has an early age of onset (i.e., preschool and school age children), and is rare [67]. The efficacy of antidepressants for older children with SoP informs the pharmacological approach to this young and often substantially impaired group of children. To date, open trials and two controlled trials demonstrate promise for the SSRIs. A small ($n=21$) 9-week open trial of fluoxetine up to 60 mg/day in selective mutism demonstrated improvement in symptoms among 76 % of subjects. Improvement was inversely correlated with age [68]. A small ($n=5$) 16-week double-blind RCT (single-case research trial) of sertraline with selective mutism showed a nonsignificant improvement in the active treatment group, but two of the five subjects no longer met criteria for selective mutism after 10 weeks on sertraline (100 mg/day), and a

third subject was asymptomatic 20 weeks after the study [69]. A second slightly larger 2-week RCT ($n=15$) of children also showed improvement for the fluoxetine group, but the small sample size precluded statistical significance and the short duration of the study may have precluded further treatment effects [70].

School Refusal

The first study to address school refusal was a small ($n=35$) 6-week trial of imipramine (up to 200 mg daily) and behavioral treatment in children with school phobia. A greater number of children on imipramine (81 %) had improved school attendance as compared to placebo (47 %). All of the children on imipramine reported feeling much better after 6 weeks compared to 21 % of the children on placebo ($p<0.005$) [71]. A subsequent attempt to replicate this study did not find imipramine effective [72]. Another study compared CBT plus imipramine to CBT plus placebo in 24 depressed adolescents with school refusal. The combination of CBT plus imipramine was superior to CBT plus placebo ($p<0.001$) over 8 weeks [73]. A single double-blind placebo-controlled trial compared clomipramine (up to 75 mg/day) to placebo over 12 weeks in 51 youth with school refusal and found no difference between groups [74]. A double-blind placebo-controlled 8-week trial of 24 school refusing children and adolescent compared imipramine (up to 275 mg/day), alprazolam (up to 4 mg/day), and placebo. No differences were found between groups.

Specific Phobia

The first line treatment for specific phobia is cognitive behavioral therapy; the evidence base for pharmacotherapy is small. One double-blind RCT ($n=11$) found paroxetine to be effective at doses up to 20 mg/day [75]. A small open-label trial of fluoxetine showed benefits in specific phobia. The participants had multiple comorbid anxiety disorders, and none of the specific phobia subjects had only a diagnosis of specific phobia. However, global severity scores were obtained for each disorder and five of six subjects with specific phobia showed significant improvement on fluoxetine [76].

Panic Disorder

Panic disorder is uncommon in children as it has a late adolescent–young adult age of onset [77]. There are no RCTs of pharmacological treatment of panic disorder in children. A single small ($n=3$) open case series of citalopram 20 mg daily in children with panic disorder symptoms and school refusal found benefit [78]. A small retrospective chart review ($n=18$) found significant improvement in panic disorder symptoms for children and adolescents treated with up to 40 mg daily of paroxetine [79].

Post-traumatic Stress Disorder

There are few controlled trials of medications in pediatric PTSD and all have shown no benefit to SSRI treatment. A small ($n=24$) 12-week double-bind, randomized, placebo-controlled trial comparing

trauma-focused CBT (tf-CBT) with sertraline up to 200 mg daily to tf-CBT plus placebo in subjects found no difference between groups. Both groups showed significant improvement in PTSD symptoms [80]. Another larger ($n=131$) 10-week multisite placebo-controlled trial of sertraline up to 200 mg daily in children and adolescents with PTSD also found no difference between active treatment and placebo groups [81]. The most recent controlled trial was a brief (1-week) trial comparing fluoxetine (5–20 mg daily), imipramine (1 mg/kg), and placebo in children with acute stress disorder following burns, which showed no difference between groups [82].

However, a number of smaller uncontrolled studies have suggested possible benefits of antidepressant medication in PTSD. Citalopram up to 40 mg daily demonstrated improvement in 67 % of participants in a small 8-week open-label trial ($n=24$) of children [83]. Imipramine up to 100 mg was studied in one small ($n=12$), prospective, randomized trial for acute stress disorder in pediatric burn patients and was found to be helpful in ten subjects [84].

Medications other than antidepressants have been studied in pediatric PTSD. The first such group is adrenergically active medications including alpha-agonists, beta-blockers, and alpha-1 antagonists. The alpha-agonists, clonidine and guanfacine, have limited data supporting their use in children and adolescents with PTSD. There are no double-blind placebo-controlled trials of the alpha-agonists in pediatric PTSD. However, a small ($n=7$) uncontrolled trial of the clonidine patch 0.1–0.2 mg/day in pediatric PTSD found some benefit [85], and there is a single-case report of guanfacine reducing nightmares in a 7-year-old girl with PTSD [86]. The beta-blocker propranolol (up to 2.5 mg/kg/day) was found to reduce PTSD symptoms in a small 5-week open trial in 11 youth with PTSD as measured by the mean reduction in PTSD inventory scores ($p<0.0005$). Propranolol was generally well tolerated but mild drops in blood pressure and pulse rate limited the maximum dose in two subjects [87]. There are no controlled trials of beta-blockers for treating pediatric PTSD. The alpha-1 antagonist, prazosin, has been studied in adults with PTSD and found to be effective for nighttime symptoms including nightmares [88–90]. There are three case reports of successful treatment with prazosin treatment of these same symptoms in adolescents with PTSD [91–93] but no controlled trials.

The second group of possible medications for treatment of PTSD is the atypical antipsychotics. The only medications in this group with data on their use in pediatric PTSD are risperidone and quetiapine. There are no studies supporting the use of olanzapine, aripiprazole, ziprasidone, or other newer agents. Risperidone (mean effective dose 1.37 mg/day) was studied in a small case series of 18 boys with severe PTSD. There was a positive response in 15 of 18 subjects over the course of 16 weeks [94]. There is a single small ($n=6$) 6-week open trial of quetiapine up to 200 mg daily in adolescents with PTSD, which found reductions in PTSD symptoms as well as anxiety, depression, and anger.

The final group of medications considered in the treatment of pediatric PTSD is the anti-epileptic mood stabilizers. There are only two published trials of these, one for carbamazepine and one for divalproex. A case series ($n=28$) documented improved PTSD symptoms with carbamazepine 300–1,200 mg/day. All subjects showed improvement, and 22 of 28 were asymptomatic at therapeutic blood levels (10–11.5 mcg/mL) [95]. A single 7-week double-bind randomized trial of 12 male subjects with PTSD and conduct disorder compared divalproex at either a high (500–1,500 mg/day, $n=6$) or low dose (up to 250 mg/day, $n=6$) and found significant improvement in the high-dose group compared to the low-dose group [96].

Despite the lack of controlled data, the current practice parameter from the Academy of Child and Adolescent Psychiatry does state that clinicians may consider SSRIs and other medications in the treatment of pediatric PTSD but with caution based on the lack of supporting studies. Generally speaking, evidence-based psychotherapies for PTSD should be the first line treatment. Medication should be considered earlier in the treatment course when a child presents with comorbid disorders for which there is strong data supporting the role of medications [97].

Clinical Considerations

Pharmacologically treating a child with an anxiety disorder has numerous components that must be addressed by clinicians in a logical and stepwise manner. These include the pre-initiation evaluation, the processed of initiating medication, dosing strategies, and next steps if there is lack of response to treatment. Once there is a treatment response, focus shifts to maintenance treatment and ultimately to consideration of medication discontinuation.

Prior to Initiating Medication

Practice guidelines from the American Academy of Child and Adolescent Psychiatry provide an outline of important steps in the evaluation and treatment of children and adolescents with anxiety disorders and for the use of psychotropic medication in children and adolescents, some of which are reviewed here [97–100]. First and foremost, a comprehensive diagnostic assessment should be performed and should include information from the child, parents, and when possible from other important people in the child's life such as their teacher or therapist. A review of prior records should be performed to assess prior interventions and their effectiveness. Standardized assessment forms and interviews can be used when available to the clinician. A complete medical history must be taken to rule out the possibility of medical problems causing psychiatric symptoms, to assess the baseline health of the child before considering medication, and to assess whether further medical testing needs to be done before medication can be prescribed to the child. An example would be obtaining an EKG prior to initiating a TCA. While a physical exam is not essential, it can provide a baseline for future comparison. Baseline laboratory testing, while not required, may allow for comparison later should issues arise during treatment. If considering medication, such as the atypical antipsychotics, which are associated with metabolic changes or other laboratory abnormalities, it is wise to always check labs before initiating treatment. Finally, in addition to providing information on medication options, it is important to keep in mind the evidence base supporting non-pharmacologic approaches and to offer these to patients when appropriate and available. The AACAP has practice guidelines for OCD, anxiety disorders, and PTSD, and the use of psychotropic medications in children is available on-line at www.aacap.org for further detailed review.

Initiating Medication

When planning the pharmacological approach to an anxious patient, discuss the purpose and goals of each treatment phase and the value of psychological treatments. During the *acute* phase of pharmacological treatment, the goal is to demonstrate very good response with minimal, if any, side effects. *Maintenance* treatment focuses on maintaining response and enhancing functional capacity with complete symptom remission. After remission and recovery, consideration can be given to a *discontinuation* trial, which will require close monitoring to avoid any unobserved return of symptoms. Discussing the phases of treatment will address common parent concerns about dosing (an effective dose and duration is needed), expectation for outcome (children do very well with SSRI treatment), and how long to treat before considering discontinuation (children do not necessarily have to be on medication "forever"). Discussing the phases of treatment also prepares the patient and family for what to expect and assures that they are prepared for the treatment trial.

When considering what medication to begin numerous factors may be taken into account including the evidence base, effectiveness and tolerability of prior trials, patient or family concerns or

preferences regarding specific potential side effects, family history of response to medication, baseline health status, and medical history. In addition, it is important to pay attention to the family's attitude about medication and directly address any concerns or negative feelings they have about medication. If this step is skipped, it may lead to treatment nonadherence.

Once a medication is chosen, a patient and their parents must be provided with adequate information to complete informed consent. This should include psycho-education about the child's disorder including symptoms, treatments, and prognosis. The name of the medication, alternative options, starting and target doses, possible side effects, and expected benefits should all be discussed with the family. It is also important to inform families how long it takes for medications to take effect. The starting place with respect to medication in most pediatric anxiety disorders is an SSRI as outlined in the earlier sections of this chapter. SSRIs are recommended as first line medications for both OCD and non-OCD anxiety disorders by AACAP [98, 100]. There are no guidelines regarding which specific agents to start. Clinicians need to make this choice based on the evidence base in combination with all the other factors listed above.

Dosing

There are no specific guidelines for how to dose children with anxiety disorders, but it is generally recommended that prescribers begin with low doses and adjust as clinically indicated based on the patient's response and any emergent side effects. When available it can be useful to follow the dosing protocols found in clinical trials to avoid inadvertent under-dosing, waiting too long to assess effectiveness, and considering alternative strategies. Benefit from an SSRI should be seen within 3–6 weeks, but maximum effect for a given dose may take 12 weeks or longer. A patient may continue to make gains even after this time frame so clinicians must be cautious about reducing doses too soon.

OCD may take longer to respond to a trial of an SSRI than other anxiety disorders or depression. Once a patient is on the maximum tolerated dose, improvement may continue for up to 6–12 months. Educating parents about the therapeutic time course and reassuring them throughout the acute phase of treatment is critical to assuring long-term adherence and the best outcomes.

Next Steps in Partial or Nonresponse

First and foremost, a partial or nonresponse should prompt the clinician to reevaluate the initial diagnostic impression for accuracy. In addition, adequacy of dosing and duration of treatment should be considered. Medication adherence should be assessed with the patient and family, and attention must be paid to psychosocial factors that may be impacting the patient's symptoms or adherence to treatment.

If a patient fails an initial SSRI trial and the diagnosis is again found to be accurate, consider trying a second SSRI. Evidence suggests that children may respond to a second SSRI trial. Following completion of the RUPP Anxiety Study, participants could participate in a 6-month open-label extension. Subjects who were fluvoxamine nonresponders in the original study were offered treatment with fluoxetine. Of the 14 who switched to fluoxetine, 10 (71 %) significantly improved over the course of the follow-up study [62]. Addition of CBT should be considered if the patient is not already receiving evidence-based psychotherapy as studies (discussed in detail in previous sections) such as CAMS, POTS I, and POTS II have shown added benefit with combination of SSRI and CBT for OCD and non-OCD anxiety disorders [8, 25, 26].

Augmentation strategies, which were discussed earlier in the section on OCD, can be considered with persistent nonresponders, though the evidence base supporting these strategies is very small and limited to OCD. Other reasons to consider adding a second medication are to treat any comorbid disorders, to treat side effects of a medication (i.e., benztropine for extrapyramidal symptoms on antipsychotics), and when there is evidence that a particular combination of medications may be effective for certain clinical presentations. An example of the last is the use of antipsychotics with SSRIs when patients have both OCD and tics [39].

Maintenance Treatment

During the maintenance phase of treatment, patients should continue to show improvement in symptoms and overall stability. Visits to monitor medications may be reduced in frequency as clinically indicated based on the number of life stressors for a given child and family, adherence to medication and treatment, perceived reliability of the family, and adequacy of response to treatment. Coordination with allied professionals such as the patient's psychotherapist, pediatrician, and school during this time can provide valuable interim feedback on how the patient is doing and may prompt a more timely return to more frequent monitoring if an increase in symptoms is seen between regularly scheduled visits.

Discontinuation of Medication

Deciding when to attempt a taper or discontinuation of medication has many components to it. Overall life stressors must be taken into account along with duration of recovery, any side effects, or if the medication has stopped working for the patient. For instance, it would likely not be a good idea to attempt discontinuing medication just prior to a major stressful event in child's life such as returning to school for a school phobic child or leaving for summer camp for a child with separation anxiety.

There are limited data suggesting the optimal duration of treatment in the absence of major life stressors. Data from clinical trials suggest that SSRI treatment for 1-year is both safe and effective in anxiety disorders [101]. Given this, if a patient responds well to the acute phase of treatment, it is appropriate to keep them on the medication for at least 12 months before considering closely monitored discontinuation of the medication. It may be a good idea to wait as long as 18 months after remission in OCD to begin discontinuation [102].

Any attempt to discontinue medication must be done carefully both to monitor for return of symptoms and to avoid withdrawal symptoms. The pace at which one can lower an SSRI without prompting withdrawal symptoms is very individual. Clinicians must go slowly and monitor closely. At the same time, it is important to monitor for any return of symptoms. If the symptoms return in a milder form, the patient may choose to remain on the lower dose or off of medication and work on their symptoms in CBT. However, with any return of symptoms, strong consideration must be given to restarting or increasing the medication back to maintenance levels. Educating the patient and family about this process ahead of time is critical to assuring both a smooth discontinuation and prompt return to treatment should symptoms recur during the taper. Once a patient is off of medication it is a good idea to follow up with the patient for a period of time to monitor for recurrence of symptoms and facilitate return to treatment, be that medication, therapy, or both. There are no specific guidelines as to how long one should monitor a patient after stopping medication; this is left to the clinical judgment of the prescriber.

Conclusion

SSRIs are the treatment of choice for OCD and the non-OCD anxiety disorders including SAD, GAD, and SoP. While other medications including the TCAs and BZDs are used to treat anxiety in children, the evidence base supporting their use is not as robust as it is for SSRIs. Although the outcome of TCA studies is mixed, the findings for BZDs in pediatric anxiety disorders are uniformly negative [103–105].

In contrast to the evidence base for OCD and the non-OCD anxiety disorders, there is a paucity of data to inform clinicians on best approaches for youth with PTSD, panic disorder, and selective mutism. With the exception of clomipramine for OCD treatment, TCAs and SNRIs cannot be recommended as first line treatment of pediatric anxiety. SSRI failure due to incomplete response or side effects should lead to a comprehensive reevaluation, increase in the intensity of psychosocial treatments, and careful consideration of SNRIs and TCAs alone or in combination with SSRIs.

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Part IV
Special Topics

Anxiety in Children with Chronic Medical Illness

Patrick M. Kelly and Emily J. Frosch

Abstract Anxiety symptoms are common in chronically medically ill children and can have unique issues which make their management complex. Anxiety can precede the medical illness, be a consequence of the illness, or the two conditions may coexist with no clear chain of causality. As illustrative examples, certain medical conditions particularly notable for their relationship to anxiety are discussed in greater detail. These include asthma, headache, inflammatory bowel disease, other forms of gastrointestinal illness like irritable bowel syndrome, and cancer. For each of these conditions we discuss the impact of preexisting anxiety as well as how (psychologically and biologically) these illnesses can lead to anxiety. Psychotropic medication, psychotherapy, psychoeducation, family therapy, group therapy, and improved psychosocial supports are all options for management and have varying roles depending upon the particular medical and psychological concerns of a given patient. Addressing this anxiety is critical, as evidence has shown that increased levels of anxiety in the child and in their family can lower health-related quality of life, interfere with effective family functioning, and at times even biologically worsen the course of the illness itself.

Keywords Pediatric anxiety • Mental health concerns in chronically ill children • Psychotropic medication in medical illness

Introduction

The United States National Center for Health Statistics [1] defines a chronic illness as any illness of "long duration" (persisting for >12 months, with impairment in daily functioning for >3 month/year or hospitalization for >1 month/year). Chronic pediatric illnesses are on the rise. The point prevalence of these conditions in children between the ages of two and eight years old increased from 12.8 % in 1988 to 26.6 % in 2006 [2]. The reasons for this increase in prevalence are multifactorial and include increased incidence (e.g., obesity), increased length of survival (e.g., cystic fibrosis), and decreased infant/early-life mortality from previously fatal conditions (e.g., AIDS) [2, 3].

P.M. Kelly (✉)
Division of Child and Adolescent Psychiatry, Department of Psychiatry and Behavioral Sciences,
The Johns Hopkins Hospital, Baltimore, MD, USA
e-mail:pkelly14@jhmi.edu

E.J. Frosch
Division of Child and Adolescent Psychiatry, Department of Psychiatry and Behavioral Science,
The Johns Hopkins University School of Medicine, Baltimore, MD, USA

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This chapter highlights the complexities of identifying and managing anxiety in youth with chronic medical illness. General issues about the interaction between anxiety and chronic illness are discussed, followed by a discussion of common manifestations and treatment of anxiety in select medical disorders.

Developmental Considerations

Milestones Important to Understanding the Illness Experience

A child's developmental level impacts his understanding of his illness, symptoms, and consequences, which in turn affects anxiety levels. Pain is a common symptom of most chronic illnesses, and studies have demonstrated age-related changes in abilities to rate pain accurately. Hicks et al. [4] found, through the use of the Faces Pain Scale-Revised (FPS-R), that children begin to accurately rate their pain sometime between the ages of 3 and 7, with a mean of 4.4 years of age. By "accurately," the authors meant that the self-report of painful experiences were congruent with the potential causes of pain, the parents' perception of pain, and the physiological (heart rate, blood pressure, etc.) and behavioral (withdrawing from stimuli, etc.) manifestations of the reported pain. In a study of pediatric surgery patients, Von Bayer et al. [5] found that most children overreported their pain before surgery but accurately reported their pain subsequent to surgery. The authors theorize that some of this overreporting could be due to anticipatory anxiety, and it is only after the children have experienced true pain that they become familiar enough with the sensations to rate it accurately. As such, children who have experienced repeated pain throughout their life may be more precise, though no studies have been performed to evaluate this supposition.

Understanding of the consequences of illness, including death, varies considerably with age, which is likely to alter the impact of a chronic illness diagnosis on anxiety. Before the age of about 8 years old, children do not understand that death is permanent [6]. This is likely to protect the young child from experiencing the same level of anxiety as his/her parents who are well aware of possible mortality when faced with their child's diagnosis. Consequently, discussions about mortality held with younger children with chronic illness may be far more difficult for the parents than for the patient.

The Impact of Illness on Development

Chronic illness brings with it not only episodic or persistent symptoms but also potentially recurrent medical treatments. As a result, children may be isolated from some of the more normative experiences of childhood and their development may subsequently follow a different trajectory [3, 7]. For example, during adolescence, normal milestones such as having a romantic relationship, playing sports, and going to social gatherings can all be delayed or missed due to chronic conditions. These perturbations in the developmental tasks can lead to a sense of disconnect from peers and decreased self-efficacy. One questionnaire used to evaluate these milestones is the Course of Life questionnaire [8], given to young adults to evaluate their successful achievement of certain developmental tasks necessary to exit adolescence. The five domains addressed (and an example of a question addressing each) include the following: development of autonomy (going on vacation without parents), social development with peers (belonging to a social group in high school), psychosexual development (first time falling in love), antisocial behavior or acting out (being sent out of the classroom or punished in school), and substance use/gambling (age of first drink). In a study of patients with chronic renal failure in childhood, Grootenhuis et al. [9] found that young adults who achieved milestones such as

autonomy, social development with peers, acting out behavior, psychosexual development, and substance use did so at a later age. The greatest delay was in psychosexual development. These delays corresponded to lower quality of life (QOL) and a lower overall sense of health, particularly "mental health" scores. This study replicated the results of an earlier, similar study by Stam et al. [10] specifically evaluating survivors of childhood cancer. Further, since adolescence is typically defined as a period of separation and individuation, dependence on external assistance from families or health-care providers might interfere with the natural course of separation and identity development.

Comorbidity of Anxiety and Chronic Illness

The prevalence of anxiety disorders in medically ill children is 3–4 times higher than in the general population, suggesting that anywhere from 7 % to 40 % of medically ill children are suffering from impairing anxiety at any given time [11–13]. Anxiety disorders have been proven to worsen symptom management, treatment adherence, medical outcome, and the ability of the child/adolescent to cope with illness [14–16]. At times, the line between anxiety symptoms and illness symptoms becomes blurred. For example, children with DSM-IV anxiety disorders and no complicating medical illness often complain of somatic symptoms. The most common of these is restlessness (74 %), followed by stomach aches (70 %), palpitations (48 %), muscle tension (45 %), sweating (45 %), and tremulousness/shaking (43 %) [17]. Thus, for many pediatric providers, teasing apart these conditions can be a challenge that may be even more difficult in children with chronic illnesses which may cause a myriad of somatic symptoms. When discussing the interaction of anxiety and chronic medical illness, there are multiple possible ways in which these two factors may combine, none of which are mutually exclusive. The task of the physician is to conduct a complete assessment of the child and his family in order to determine which pattern seems the most likely. This assessment will subsequently guide the child's treatment.

The first contextual framework in which anxiety and medical illness can interact includes cases in which a preexisting anxiety disorder influences care of a medical illness. For example, young patients with separation anxiety disorder have a difficult time undergoing procedures or hospitalizations in which they are surrounded by strangers in the absence of their parents. As a result, the prospect of a hospitalization may be more frightening than the illness itself for these children [18]. Generalized anxiety can be a burden for medically ill children, as they may constantly fear the next hospitalization/procedure and reassurance from their providers is unlikely to help. The child with obsessions about germs may develop extreme fears while in the hospital. Specific phobias typically revolve around procedures in ill children (oxygen masks or needle sticks). Socially phobic children may shy away from forming relationships or interacting with peers or care providers, potentially leading them to feel isolated and misunderstood. To enact effective treatment, it is essential for practitioners to obtain a complete history of the child's symptoms and feelings of anxiety in order to determine whether they preceded illness onset. In assessing for preexisting anxiety, the clinician can begin with a family history, as a biological relative with an anxiety disorder may predispose the patient to the same. Premorbid functioning, including early indicators of separation or social anxiety, can also reveal an underlying proclivity to an anxiety disorder.

The second context includes the child's psychological responses to a physical disorder including the response to the medical diagnosis itself. For many children and families, this initial period is met with a natural time of accommodation and adjustment that, with appropriate psychosocial support, will come to its own natural resolution. For some, however, the adjustment is never successfully navigated, resulting in psychological worries that can interfere with appropriate functioning in all life domains [19]. When this occurs, it is unlikely that the patient will have a spontaneous resolution without mental health intervention. Even a brief stay in an intensive care unit can psychologically

disturb children and their families; Stowman et al. [20] found that 25 % of these patients had symptoms consistent with posttraumatic stress disorder after discharge. It is the responsibility of the physician to discuss the psychological impact of the diagnosis and treatment with the child and family members to determine whether any anxiety or mood symptoms are typical and may be expected to resolve or are persistent and may require specific intervention. This is most clearly evaluated via the longitudinal relationship between a provider and patient. One sign of concern is anxiety which seems to be generalizing beyond the medical condition. Patients and families who are newly hypervigilant, socially constricted, or overly concerned about aspects of life unrelated to illness (e.g., a mother who has never previously been anxious develops sudden stage fright at the prospect of giving a presentation) may all represent anxiety becoming more entrenched and deserving of dedicated treatment. This said, the initial distressed reaction may give little information as to the prognosis for a later anxious condition, so continued observation on the part of the clinician is critical.

The third category contains anxiety disorders that are a direct physiological consequence of the medical illness. Various underlying medical processes can contribute to the presentation of anxiety in a medically ill child. For example, increased blood carbon dioxide concentration, through conditions such as asthma or cystic fibrosis, leads to increased symptoms of anxiety and can simulate a panic attack [21]. Many systems can be involved in the generation of anxiety, including endocrine (hyperthyroidism, pheochromocytoma), cardiac (paroxysmal tachycardia, cardiac failure), or neurologic (complex seizures, delirium) [22]. Table 1 contains a lengthy, though incomplete, list of conditions that can directly produce anxiety symptoms. At times, the treatments for medical illnesses can themselves be direct causes of anxiety. For example, for asthma sufferers, both an asthma attack and its treatment (albuterol) can lead to somatic sensations of anxiety [23]. Albuterol mimics the biological effects of adrenaline, leading to increased heart rate and the "fight-or-flight" response. In patients with gastrointestinal (GI) distress and cancer, some antiemetics, particularly procloperazine [24] or metaclopromide [25], can lead to akathisia, which resembles the physiological discomfort of anxiety and can make the patient appear, and feel, anxious. For certain illnesses that are accompanied by exacerbations of symptoms, the physician can obtain regular ratings of anxiety from the child in order to determine whether increases occur concurrently with increases in physical symptoms, either by direct clinical interview or through standardized assessments. See Chap. 12 for questionnaires that assess pediatric anxiety and that could be used for this type of monitoring.

Though not distinctly a fourth category per se, there is another important factor to consider in childhood medical illness: the anxiety of the patient's parents or caregivers. Though frequently overlooked, this can often impact the successful treatment of the patient. Parents of children with multiple types of illnesses, including such conditions as sickle cell disease [26], cancer [27], and chronic pain [28], report more "chronic sadness" and anxiety than their peers. Caregiver anxiety has been shown to be an independent predictor of worsened patient functioning, increased number and frequency of symptoms [29], increased biological markers of illness [30], and increased acute care utilization [31]. Furthermore, some evidence seems to indicate that women are more prone to distress when faced with illness in their child than men, regardless of their parental role in the family [32]. Walker et al. [33] developed and evaluated the Illness Behavior Encouragement Scale (IBES), a child questionnaire asking how their parents respond when they report that they feel sick. In this study, parental affect was associated with worsening functional performance and increased number of symptoms in their children. Thus, evaluating parental worries and helping to alleviate them can lead to improved outcomes for the child, as can brief screening for parental anxiety disorders including a family history.

When looking at a patient's symptoms through this framework, it becomes easier for the clinician to determine how the patient's anxiety and medical problems interact. A family history of anxiety, early anxiety symptoms, or characteristics of particular syndromes [like obsessive-compulsive disorder (OCD)] point to a preexisting or independent anxiety disorder. Anxious symptoms which peaked after a particular diagnosis was given may indicate a psychological response to an illness, whereas anxiety which seems conscribed to ill episodes or treatments may indicate a more biological response.

Table 1 Medical conditions which can cause anxiety

Neurological
Encephalopathy
Mass lesion
Postconcussive syndrome
Poststroke
Seizure
Vertigo
Endocrinologic disorders
Carcinoid syndrome
Diabetes mellitus
Hyperadrenalism
Hyperthyroidism
Hypothyroidism
Hypoglycemia
Pheochromocytoma
Metabolic
Hypercalcemia
Hypocalcemia
Hypomagnesemia
Hyperkalemia
Cardiac
Arrythmias
Congestive heart failure
Hypovolemia
Valvular disease
Pulmonary
Asthma
Hypercapnea
Hypoxia
Hyperventilation
Pneumothorax
Pneumonia
Pulmonary edema
Pulmonary embolism
Miscellaneous
Anaphylaxis
Hyperthermia
Pancreatic tumor
Porphyria
Systemic lupus erythematosus

Adapted from Cartwright-Hatton et al. [11]; used with permission

Familial difficulties may be determined by either the content or the process of taking a complete history, and many clinicians who describe "frustrating" interviews are actually recognizing and experiencing an aspect of the patient's daily life which can have a tremendous impact on her psychosocial functioning and ability to adapt to her illness condition.

In addition to a clinical assessment, there are standardized instruments which may help a clinician better understand the medical and psychological health of their patient. One of the more general tool sets, the Child Health Questionnaire (CHQ) [34, 35], is actually a family of self-report measures. These tools are designed to be an analogue of the RAND-36 tool for adults and evaluate the child's overall physical well-being and the psychosocial impact of illness on his life. There is a parent version

for parents of children 5 and older and a child self-report designed for children 10 and older. The shortest version can be completed in 5–10 min, while the longest version takes a half hour or more. The Pediatric Quality of Life Inventory (PedsQL) [36] is another brief tool which has both parent and child reports and even includes additional, disease-specific modules (for asthma and cancer, among others). It should be noted that both the CHQ and the PedsQL must be purchased from the publishers.

In addition to general QOL measures, there are several illness-specific measures, including three for asthma, six for cancer, and three for inflammatory bowel disease (IBD), among others (25 in all). Davies et al. [37] completed a review and comparison of these various instruments, so providers treating children with particular conditions are advised to review her work to choose the best tool for their practice based on patient age, time that can be devoted to completing a tool, parent vs. child instruments, questionnaires vs. structured interviews, etc. Unfortunately, despite having illness-specific measures, at the time of this writing there are no anxiety-specific measures targeted to the medically ill child [19]. However, the Patient-Reported Measurement Information System (PROMIS) project has at the time of this writing begun standardizing a retrospective assessment scale for anxious and depressive symptoms during a medical hospitalization [38].

Specific Medical Conditions

Though anxiety and medical illness can be comorbid in many situations, there are certain illnesses for which anxiety is a special concern. This may be because the illness is more likely to cause anxiety in all persons, because the biological mechanisms of the illness or treatment may be particularly anxiogenic, or simply because their prevalence makes them more likely to be seen by providers. We have selected the following illnesses to discuss in more detail: asthma, headaches, IBD, functional gastrointestinal disorders (FGID), and cancer. For each condition, the authors will provide a brief description of symptoms as well as treatment, discuss the application of the above mentioned interaction themes between anxiety and the condition, and discuss any treatments that specifically target anxiety. At the time of this writing, an ongoing clinical trial is investigating the utility of a cognitive-behavioral intervention strategy for patients with various types of chronic illnesses and their families to preserve good psychosocial function and stave off anxiety [39]. This preventative model could provide significant advances in the field of psychosocial treatment of patients with chronic illness; however, most of the treatments discussed in this chapter will be illness-specific and targeted towards patients already exhibiting anxiety symptoms.

Asthma

Billy was a regular in the pediatric emergency room. He was a small-for-his-age 9-year-old boy who knew many of the nurses by name. His presenting complaint was usually the same—he had forgotten to take his preventative inhaled steroid medications, leading to an asthma attack. His initial (rather mild) wheezing would cause him to panic, making breathing even more difficult. During these attacks, he would worry about going to the hospital or being intubated. Even if he was able to take his rescue albuterol, he was frequently too overwhelmed to hold the medication in his lungs for any period of time. Sometimes, the medicine seemed to make him even worse, as he would become red and covered with sweat, eyes wide in fear. He and his mother were very close, and whenever she saw him suffering, she became anxious herself which impeded her ability to help him manage his symptoms. Each admission was a painful process—upon learning that he would have to be away from his family, Billy would wail and cry, only worsening his breathing problems. Despite the pediatricians' best efforts to emphasize

behavioral and medical interventions, they simply could not seem to get his debilitating asthma under control. As a result, Billy frequently missed school. His mother had been told that he was failing the 3rd grade and couldn't miss any more school, something that kept running through her mind as she rode in the ambulance with her child back to the emergency room.

When Billy and his mother returned to his regular doctor, he recommended that they seek help from a therapist who could teach Billy ways to slow down and control his breathing that could ultimately keep him out of the hospital. Though Billy's mother was skeptical, she took the doctor's advice. The therapist taught Billy some relaxation exercises involving tensing and relaxing his muscles and deep breathing. The therapist even made a tape of these exercises that Billy and his mother could listen to together at home. Not only did this help Billy to manage his symptoms but his mother had begun using some of these tricks herself and was finding it easier to manage her own anxiety.

The National Center for Health Statistics reports that approximately 14 % of children in the United States have been diagnosed with asthma, though the number continues to grow [40]. Male children typically have a higher prevalence (17 %) than female (11 %) [40]. There is a large skew towards minorities and persons who live in urban areas. Black non-Hispanic children have a higher rate (22 %) than Hispanic children (17 %) or white non-Hispanic children (12 %) [40]. Furthermore, black children with asthma have more poorly controlled symptoms resulting in more self-reported attacks and show a higher rate of emergency department use than white children [40]. In 2005, asthmatic children had 12.8 million physician office visits and 1.8 million emergency room visits. Mortality from asthma is increasing, though the absolute numbers remain low. In 1980, the rate of mortality from asthma was 1.7 per 1,000,000 children, which increased to 2.6 per 1,000,000 children in 2004 [40].

Asthma is a chronic inflammatory condition of the lungs. It is typically characterized by episodic attacks during which the pulmonary airways constrict and prevent the flow of oxygen to the body. The most common way to measure this is by using a peak expiratory flow (PEF) meter, which assesses how quickly a person can move air into and out of her lungs. During an attack, the PEF decreases. Symptomatically during this time, the child often feels a tightening sensation in her chest and throat that can mimic panic. Asthma, like many illnesses, presents with varying degrees of severity. For some, asthma is easily controlled with the correct medications. For others, asthma attacks can occur at any time and for seemingly no reason. Medical management of asthma has two goals—to stop the current attack and to prevent future attacks. Interrupting the current attack depends primarily upon bronchodilators, such as albuterol or ipratropium. Unfortunately, the effects of albuterol are quite similar to those of epinephrine, an endogenous chemical the body uses to signal the fear response. Preventing future attacks primarily relies on immunomodulatory and immunosuppressant medications such as corticosteroids. These can be inhaled or taken as a pill. Regular use of these medications is critical to staving off future attacks and can be particularly important to emphasize in adolescent patients as Sadof and Kaslovsky [41] found that they tend towards greater medication nonadherence, which is the number one risk factor for mortality in asthma [40].

Asthma and anxiety are highly correlated in children [42]. Among asthmatics, preexisting anxiety conditions have been shown to be an independent risk factor for more severe symptom course and more severe morbidity. Haby et al. [43] found that young adolescents with anxiety had significantly more asthma symptom days and a more difficult and prolonged treatment course than their anxiety-free counterparts. Though many believe this and similar findings to be solely due to anxiety interfering with care adherence, some authors [44, 45] theorize that a heightened state of anxiety generally exacerbates immunologic reactivity, making a person more likely to have an asthma attack.

The psychological reaction to the diagnosis of asthma can lead to an increased amount of worry, on the part of both the child and the family [46]. They may be hypervigilant about small changes in their breathing, wondering if it is the sign of an impending attack. Furthermore, should children have an asthma attack, hypoxia itself can trigger a panic-like response, as can the rescue medication (albuterol), creating a cycle from which the patient has difficulty escaping. Caregiver anxiety has been

linked with increased inflammatory markers in asthmatic children [30], increased frequency and number of hospitalizations [45], and lower overall patient QOL [47].

Although psychoeducational asthma management plans are recommended by the American Academy of Pediatrics, few families receive them from their providers [41]. Among 130 young families of young children with asthma, only 39 % reported receiving an asthma management plan from their health-care provider, 57 % reported being taught how to monitor peak flow, and 52 % reported being advised to change things at home or school to improve asthma management [43]. Family involvement is also important, as anxiety symptoms in parents have shown to predict a worse asthma course in their children [48]. Fiese et al. [49] present an excellent review of family responses to asthma. Families who are able to come together and form new routines around asthma care (including thoroughly cleaning the home environment and checking peak flows) feel more in control, become closer as a family unit, and have fewer asthma and anxiety symptoms.

Regardless of the interaction between asthma and anxiety, children with both are more impaired than with either condition alone. Richardson et al. [50] found that children with anxiety and asthma had significantly higher rates of medical care utilization and hospital costs than those without anxiety. Assessing for anxious symptoms in asthmatic children and their families has been helped by the creation of standardized self-reports, such as the Youth and Parent Asthma-Related Anxiety Scale (YAAS and PAAS, respectively). Both of these are available online [51] and can provide an excellent, rapid method to screen large numbers of patients in a busy outpatient practice.

Once discovered, treatment of anxiety in children with asthma does not differ greatly from treatment of anxiety in general [42]. Should a preexisting anxiety condition exist, treatment with SSRIs may lessen the symptom burden and thereby improve the medical illness. Treatment with cognitive behavior therapy has shown to reduce both psychological and medical symptoms in anxiety sufferers with asthma [52]. Chiang et al. [53] evaluated relaxation breathing techniques combined with progressive muscle relaxation (PMR). Providers directed children to sit comfortably in a quiet room for 5 min, tense a group of muscles, such as those in the right arm, hold the contraction for about 8 s, and relax the muscle group for about 30 s while breathing slowly. After a short rest, this sequence was repeated with another set of muscles (15 sets in total). Through repetition, patients learned to recognize the feelings associated with a tensed muscle and a completely relaxed muscle. This process and the sequence of PMR exercises were recorded onto a CD, and one-page instruction sheet was provided to parents, who were taught how to coach their child to practice relaxation at home. Patients were instructed to practice 30-min sessions, three times per week for 12 weeks until they achieved some proficiency and could perform the exercise without the CD. This simple, rapidly taught intervention required only 30 min to administer but reduced anxious symptoms and improved physiologic measures of asthma. At the end of 12 weeks, the experimental group had fewer asthma symptoms, used less asthma medication, had improved peak flow ratings, and reduced anxiety [53].

Headache

Katie had suffered from headaches since she was a young child. Her parents also suffered with migraines, and so, as she got older, she was starting to accept that pain would simply be a fact of life. She had been to numerous specialists, none of whom had yet found a medicine to prevent her headaches—the best she could get was temporary relief once they had started. Recently, she had been using these types of medications even more frequently. During a recent visit to a neurologist, he suggested that her headaches might be stress-related. He took a lot of time to explain that psychological stress can cause a biological headache. She wasn't imagining the pain, but rather it was directly caused by physiologic changes in her body when she became anxious. It was true, she supposed, that her headaches worsened during finals (which was particularly problematic since it caused her to miss

more school exactly when she needed to be there most). She began cognitive-behavioral therapy (CBT) with a psychologist, learning ways she could reduce her stress. Not only were her headaches fewer and less intense but overall she felt more confident.

Headaches are common in children. By age 15, nearly 75 % of children will report having had a significant headache [54]. Generalized headaches can be divided into migraines, tension-type headaches (TTH), and chronic daily headaches (CDH). Migraine has been reported in 3.9 % of children age 7–15 years, with increases from 1.7 % in 7 year olds to 5.3 % in 15 year olds [54]. On a monthly basis, almost half of all children experience some form of headache, with up to 15 % of children suffering from migraines [55].

A recent meta-analysis [56] of 33 papers investigating the burden of generalized headache in children and adolescents found the morbidity to be significant, most consistently in terms of missed school days (an average of 8.3 days per school year). Three papers [57–59] published by tertiary headache care centers estimated an average of 32 days of schooling were "totally or partially affected" by headache in a 3-month period (1 in 3 days). Many of these studies investigated total QOL, which was significantly lower for children with headache vs. those without, based on various standardized instruments. In one study of children asked to rate their current headaches, 17 % endorsed the statement "this is terrible, I wish I would die."

The American Academy of Neurology (AAN) [60] recommends that the evaluation and management of recurrent headache in children be assertive, addressing the headache directly in each pediatric visit, striving for complete remission as soon as possible, and minimizing the impact of any residual symptoms on functionality and family life. The first step of management is to stop current headaches with NSAID medications like ibuprofen, with triptans being prescribed only for resistant headaches [61]. Subsequently, the focus expands to preventing future headaches with a variety of treatments. Many of these medications have demonstrated efficacy in treatment studies of adult migraine but have been expanded to use in children with various forms of chronic or recurrent headaches. Examples include neurologic medications (antiepileptics, such as valproic acid and topiramate), psychiatric medications (antidepressants, such as amitriptyline), cardiac medications (antihypertensives, such as propranolol or amlodipine), and antihistaminic medications (such as cyproheptadine) [62].

Recurrent headaches in children are strongly correlated with anxiety. Kowal et al. [63] found that children with anxiety at baseline are more prone to develop headache pain later in life. Knook et al. [64] examined 134 children and found that headache was an independent clinical predictor of psychiatric morbidity. In children with recurrent headaches, the level of anxiety has been reported to increase from childhood to adolescence [65], and researchers have found that a history of childhood headaches increases the risk for anxiety disorders in early adulthood [66]. A particularly vulnerable subset of pediatric patients appears to be those who suffer from recurrent migraines. These patients have more anxious symptoms and more missed days of school than their peers with other recurrent headache varieties [67–70].

There may be an overriding biological association between anxiety and headache, particularly migraine, which predisposes the individual, independently, to both problems. One strong candidate is serotonin, which has been implicated in migraine [71] as well as anxiety. Studies have found that 5-*h*ydroxy*i*ndole*a*cetic *a*cid (5-HIAA) levels, a by-product of serotonin metabolism, are low in the cerebral spinal fluid of both patients with anxiety disorders and patients who suffer from migraines [72]. Additionally, an abrupt reduction in plasma serotonin has been associated with onset of migraine [73], and intravenous infusion of serotonin was found to abort migraines [74]. This is also reflected in the primary action of triptans, which reduce migraines by increasing cerebral serotonin.

It would seem, then, that treatment with antidepressant medications may be a way to alleviate both anxiety and migraine pain. In the pediatric literature, there is evidence for the use of low-dose amitriptyline [60, 75], though evidence for SSRI or SNRI medications has not yet been established. In the adult literature, there are some supportive studies suggesting that fluvoxamine (Luvox) [76], fluoxetine (Prozac) [77–82], and citalopram (Celexa) [83] may be as effective as amitriptyline,

though methodological problems (lack of a placebo control, small sample sizes, and underpowered studies, or minuscule dosing of comparative medications) reduce the clinical utility of these results. Among SNRI medications, a retrospective analysis [84] of 65 adult migraine patients receiving duloxetine (Cymbalta) found a significant reduction in migraine attacks, and the effect was most strongly seen in patients with comorbid anxiety. An open-label trial [85] of adult patients with migraine and depression yielded similarly promising results, though both studies were small. Venlafaxine (Effexor) has been evaluated in an open-label trial of 42 adult patients with migraine [86] and a retrospective analysis of 115 cases [87], both of which showed significant improvement in headache attacks and days with headache after 4–6 months. A prospective, double-blind placebo-controlled trial [88] showed fewer migraine attacks and lower use of analgesic medication in adult patients taking 150 mg of venlafaxine XR, and a prospective crossover trial [89] showed equivalent efficacy between venlafaxine and amitriptyline, with significantly greater side effects on amitriptyline. In summary, for pediatric patients, low doses of amitriptyline are effective in preventing migraine attacks and may help reduce anxiety symptoms. More targeted therapies (SSRI, SNRI) are currently used only to treat anxiety, though adult studies of SNRIs are promising for migraine prophylaxis as well.

Behavioral interventions are critical in the medical management of all forms of pediatric headache. Regardless of any anxiety component, the AAN [60] recommends "biobehavioral" therapy for prevention, which emphasizes adherence to treatment, psychoeducation, lifestyle changes to avoid triggers, and coping strategies. Two particular modalities have been shown effective and at times overlap—relaxation training and CBT. Relaxation training consists of teaching patients to voluntarily control muscle tension through techniques including mental visualization and muscle tensing. Specific protocols, such as PMR [90], are effective for children—a meta-analysis [91] examining all forms of relaxation training found that they reduced the frequency of headaches by 32 % and the intensity of headaches by 41 %. CBT seemed to be even more effective (though, admittedly, typically contains elements of relaxation training), with a 49 % reduction in headache activity over seven studies. Studies have also evaluated phone-based guided therapy [92], a CD-ROM computer system [93], and Internet protocols [94] based largely on cognitive behavior therapy. All of these were found to be effective in reducing both headache frequency and disability, even in the absence of measuring any effect it may have on anxiety. Other treatments including acupuncture, chiropractic adjustments, hypnosis, or TENS units are not supported by the AAN as viable treatment options for children [91].

Inflammatory Bowel Disease

Charley was admitted to the hospital for surgery. Unfortunately, despite all the medical management possible, at the young age of 14 he was about to have most of his colon removed. On one hand, this was an excellent development, as the surgery would likely fully cure the ulcerative colitis which had ravaged his life. However, surgery is never benign and was accompanied by endless worries. His mother had a diagnosed anxiety disorder for which she took antidepressants, and the patient himself had always been perfectionistic and routine-based, so everyone was concerned as to how he would handle this procedure. Initially, all went well—he was able to remain hopeful and focus on the positive aspects of being, eventually, pain- and symptom-free. But after the surgery was another matter entirely. His pain would not seem to respond to any amount of narcotics—he was on such a high dose at one point that it actually threatened his ability to breathe. The team contacted psychiatry to discuss whether his underlying anxiety may be contributing to this, whether he was misperceiving his actual pain level. After seeing him, the psychiatrist thought that not only was this true but nothing was being done to address the anxiety. Given the known relationship between the GI tract and the brain, and the presence of serotonin receptors in both, the patient was started on the same SSRI as his mother, with promising initial results, not only on his anxiety but also his pain.

Severe gastrointestinal illness like IBD, which includes ulcerative colitis (UC) and Crohn's disease (CD), can have a lifelong course and multiple psychiatric complications, including anxiety. About 1.4 million persons in America suffer from IBD. Incidence rates of CD are 3.1–14.6 per 100,000 patient-years and for UC are 2.2–14.3 cases per 100,000 person-years [95]. Twenty-five percent of all IBD cases are diagnosed prior to age 18, and 5 % are diagnosed before age 10 [96]. Cases which present in childhood and adolescence are generally more extensive and aggressive at the time of diagnosis and typically worsen during the first 5–7 years. These children also have a much higher rate of family history of IBD (30 %, compared with 18 % for those cases presenting after adolescence) [97].

At its core, IBD is an overactive immunologic reaction to the digestive tract. This reaction causes the tract to become inflamed, which can lead to various gastrointestinal effects [abdominal pain, constipation, diarrhea, hematochezia (blood in stool)]. Associated symptoms include weight loss, malnutrition, anemia, fatigue, fevers, mouth ulcers, and joint pain or swelling. Should the inflammation become chronic, it can lead to electrolyte abnormalities, ulcerations, fistulas, and dysfunction so extreme as to require surgical intervention (a partial or full colectomy). Despite these serious and diffuse symptoms, many patients are not immediately diagnosed with the condition. In a study of over 2,000 providers, Sawczenko et al. [98] found that the mean duration of symptomatology before diagnosis was 47 weeks (range 4 weeks to 7 years). In 10–20 % of cases, the abdominal pain was thought to be primarily psychiatric in nature, and patients were diagnosed with depression, anxiety, or anorexia nervosa with no suspicion for a physical underlying cause for their pain.

There are some differences in the symptomatology of ulcerative colitis and Crohn's disease. The hallmark of UC is bloody diarrhea [99], which typically results in an earlier diagnosis than CD because of this characteristic symptom. The disease nearly always begins at the rectum and spreads upwards, involving the entire colon in 10 % of patients (but slightly over half of those 10 % require a full colectomy) [100]. It never spreads beyond the colon, and colonic resection of the affected portion is generally curative of the illness (although comes with significant morbidity, such as postsurgical complications and potential use of a colostomy bag, and therefore is frequently avoided as long as possible) [100]. CD, on the other hand, does not usually have any sort of characteristic external symptom and so the diagnosis can be delayed [101]. In the pediatric population, the patient may initially present for an evaluation of malnutrition, short stature, delayed puberty, fatigue, or even a primary eating disorder (like anorexia) [102]. The illness can be present in any part of the digestive tract, from the mouth to the rectum. CD typically involves multiple areas at once separated by unaffected bowel, leading to the typical "skip lesion" pattern. Surgical interventions to manage this condition are common (half of all CD patients require surgery at some point; of those, half will require multiple surgeries) [103]. Unlike UC, surgery is not curative, as the disease can return to a different part of the GI tract. Peripheral conditions, such as gallstones and kidney stones, are also increased in CD [104].

The medical management paradigm in both CD and UC has shifted from symptom control to mucosal healing [105], which is likely to result in prevention of disease progression, fewer complications, and reduction in the need for surgery [106]. In children and adolescents with CD, nutritional therapy alone can sometimes be as effective as management with immunomodulatory medications [107]. The dietary protocols are difficult, however, as they require forbearing all "real" food in favor of sometimes unpalatable chemical formulas for a minimum of 8 weeks. As a result, lack of adherence is the number one reason for treatment failures [108]. In both CD and UC, medications called mesalamines can reduce mild to moderate inflammation and alleviate pain. According to the American College of Gastroenterology, in CD (and severe UC), the treatment of choice continues to be steroids [109]. Confined disease in CD and UC can sometimes be treated with local steroids, but systemic steroid use is common, even though these medicines cause their own significant side effects. Physical side effects can unfortunately be somewhat synergistic with IBD and can include short stature, weight gain, moon facies, and skin striae [110]. Even in low doses, steroids can directly produce anxiety as well as mood changes and other alterations in mental status [3, 111].

IBD can be a difficult experience for a young person and their family. In CD, the symptoms are frequently insidious and involve lifelong complications like short stature, which can make the child feel different [112]. In a survey of 80 children (ages 7–19), Nicholas et al. [113] found that the most concerning aspects of illness to children included negative body-image perceptions from the disease process (short stature, weight loss, physical weakness), side effects from treatment (weight gain, acne, a visible nasogastric tube), and embarrassment related to frequent use of public bathrooms and the risk of encopresis. A separate survey by Mamula et al. [114] found that, as opposed to adults, the most prominent concerns in children include delays in physical growth or pubertal maturation, shame associated with fecal incontinence, and steroid-induced weight gain. These negative effects seem to amplify as children age. College students who had been diagnosed with IBD as adolescents report a lower overall QOL than younger peers with the same disease and feel poorly prepared to transition to young adulthood [115]. A large summative meta-analysis by Ross et al. [116] of 12 studies (after a further 266 were rejected for methodological problems) concluded that the overall health-related QOL for children and adolescents with IBD is lower than their same aged peers, particularly in the areas of self-esteem and social competence.

Up to 28 % of newly diagnosed IBD children meet criteria for an anxiety disorder, with lifetime prevalence as high as 59–73 % [112, 117]. Though researchers have attempted to identify risk factors for psychosocial dysfunction in IBD, the results are currently somewhat contradictory so it remains necessary to screen all patients [118]. Anxiety can negatively impact the medical condition of IBD. Reigada et al. enrolled a cohort of adolescents with IBD and compared those with significant anxiety to those without. She found that adolescents with IBD and anxiety had significantly worse psychosocial functioning and higher health-care utilization than their medically ill, but non-anxious, peers [119]. A potential cause of this may be related to medical management of the illness, as higher levels of anxiety in adolescents are correlated with lower medication adherence [120].

In adults, there is a clear biological association between higher levels of stress and more frequent IBD flairs [121]. An animal model of IBD has demonstrated that inducing a depressive episode in mice leads directly to flairs [122]. As with headache, there appears to be a close biological relationship between IBD and anxiety, again through the commonality of the serotonin molecule. The neuronal connections in the intestine are highly complex with about 400–600 million enteric neurons, which is greater than the total of all sympathetic and parasympathetic ganglia combined and approximately equal to the number of neurons in the spinal cord [123]. Serotonin is both a critical signaling factor in the intestinal tract, regulating peristalsis and secretion, as well as a core neurotransmitter. In fact, 95 % of the body's total amount of serotonin is present in the GI tract [124]. As discussed above, serotonin is thought to be decreased in patients with anxiety disorders. Coates et al. [125] collected biopsies from the GI system of 22 patients with IBD and compared them with normal peers. In the affected patients, cells which secrete serotonin (enterochromaffin cells), mucosal serotonin concentration, and serotonin transporter concentration were all decreased. It appears that the chronic inflammatory state itself decreases serotonin. This is consistent with studies finding reduced serotonin and increased inflammatory markers in patients with anxiety and depression [126].

Family conflict and low family QOL have been positively correlated with pain, fatigue, and depression in children with IBD [127]. Parents of children with IBD reported significantly less social support, and mothers reported greater distress compared with parents of healthy children [128]. These interactions can become a downward spiral in which the child's illness and the family's distress feed into each other. Directly addressing parental anxiety may improve psychosocial distress, as positive affect in mothers of adolescents with IBD is inversely correlated with the adolescents' depression [127]. Treatment of the family could also improve illness trajectory. In study of 62 adolescents and their parents, Hommel et al. [129] found that the mean rate of adherence with daily medications was 38 % and was inversely correlated with family dysfunction.

Treatment for anxiety in children with IBD can take many forms. First and foremost, patient education about the illness is critical. In a survey of 237 patients and parents by Casellas et al. [130], only

half described having "adequate" information, though all listed health-related information as extremely important to their health-related QOL. A large, multisite, (700 patients) trial of adult patients by Kennedy et al. [131] investigated a protocol to teach patients to manage their own symptomatology. In fact, the intervention was specifically aimed at reducing health-care burden to providers, as it focused primarily on creating alternative resources for patients so they did not feel the need to see the provider as frequently. The patients were given a brief guidebook, "A Handy Guide to Managing Ulcerative Colitis," [132] and had a 2-hour consultation with a provider to obtain psychoeducation and address questions. Despite the brevity of this intervention, at a time point of one year later, patients reported fewer hospital and outpatient visits, improved QOL, and improved perceived "ability to cope with their condition."

Group psychoeducational interventions have also been examined [133]. In one intervention, Grootenhuis et al. taught adolescents to implement an alternative, concurrent response (e.g., active muscle relaxation) when facing a stressful, anxiety-evoking procedure (e.g., a venipuncture). The protocol also discussed how to be a more active participant in treatment, including role-plays of "approaching the physician," and how to rate and describe pain accurately. The intervention resulted in improved coping, greater feelings of competence, and overall improved health-related QOL.

A manualized protocol, Primary and Secondary Control Enhancement Therapy-Physical Illness (PASCET-PI), has been evaluated in IBD children [134, 135]. The protocol involves nine modules provided in a structured and hierarchical way. The first module concerns psychoeducation about the illness. Modules 2–5 focus on building skills such as visualization, relaxation, and distraction to help tolerate abdominal pain or distress. Modules 6 and 7 address negative and unhelpful thoughts about IBD and its effect on the young person's life. Module 8 helps the patient identify the most helpful of the above techniques and create a personalized plan, and module 9 practices and reinforces it, with a view towards anticipating and deflecting future problems. In a randomized controlled trial of 31 patients, there was a greater reduction in anxious and depressed symptoms, improved feeling of control, and improved functioning in the PASCET-PI group compared with a treatment-as-usual group [134].

Pharmacologic treatments targeting psychiatric symptoms are also effective in this population and are frequently prescribed directly by the primary care team. In one study, children with Crohn's disease were twice as likely as their disease-free counterparts to receive an SSRI and over four times as likely to receive a tricyclic antidepressant (TCA) [136]. In adults, about 30 % of IBD patients have taken antidepressant medications [137]. In a survey of 18 adult gastroenterologists, 78 % had prescribed antidepressants for their IBD patients for the purpose of treating pain, depression, anxiety, and insomnia [138]. Medications with evidence for efficacy in patients with IBD include bupropion, paroxetine, amitriptyline, and desipramine (though many are not considered first-line therapy in the pediatric population) [139]. In animal models, treatment with fluoxetine and desipramine reduced intestinal inflammation [140]. The reasons for this, the authors note, could be multiple. It may be due to the intricate (and as yet poorly understood) brain-gut connection, in that improving anxiety somehow alters the inflammatory cascade. Alternatively, it may be that increasing serotonin in the intestine helps to alter inflammatory patterns. Due to the novelty of these results, antidepressant therapy has not yet been evaluated in humans to assess efficacy in reducing inflammation, but they are promising. Only one antidepressant, mirtazapine, is specifically not recommended for IBD and other inflammatory conditions, as it increases the circulating levels of pro-inflammatory cytokines and may worsen the underlying illness [141].

Functional Gastrointestinal Disorders

Annie is a 6-year-old girl who had been having attacks of severe abdominal pain since age 4. At that time, her entire family suffered from a bout of viral gastroenteritis, but while the rest of the family

recovered, Annie continued to have intermittent symptoms. She has already missed enough school that she may get held back—an eventuality that her high-achieving parents have difficulty accepting. Her mother reports feeling frustrated and unsure of what else can be done to help her daughter. Despite multiple visits to the pediatrician and to two gastrointestinal specialists over the past 2 years, nothing could be found to explain Annie's pain. Her mother, in desperation, had been researching online and decided to try dietary restrictions. Annie was now lactose- and gluten-free, which initially seemed to make a difference, but was currently having little impact. Recently, the pediatrician recommended that Annie's mother consult with a behavioral specialist to help her daughter more effectively manage the pain. The mother scheduled an initial appointment, but, given their long road, her hopes were low.

First, the specialist started Annie on an antidepressant to address her anxiety symptoms and to improve her intestinal function. Then, he worked closely with her, following a treatment protocol for children with her condition that focused on teaching her how to manage her attacks. Her bouts of pain were now less frequent, and, maybe more importantly, she felt less scared and out of control when she did have one. She was back in school, and doing even better than she had before the pain started, seeming more confident and more competent.

As opposed to IBD, FGID, otherwise known as recurrent abdominal pain (RAP) in children, is characterized by pain or distress without structural or biochemical changes which could explain the etiology or symptomatology. The first person to study this disorder, John Apply, began his research in the 1950s and defined RAP as "3 or more episodes of abdominal pain of such severity as to interfere with the child's normal activity over a 3-month period without any clear etiology" [142]. In 1988, the Rome Foundation (http://www.romefoundation.org) was founded to further investigate these phenomena, and still exists as an independent nonprofit organization dedicated to the evaluation and treatment of FGID in children and adults. It has developed diagnostic criteria for various categories and created an extensive screening questionnaire for children and adolescents. There are a number of functional GI disorders, but for the purposes of this chapter, we remain focused primarily on childhood FGID involving abdominal pain. FGID is subdivided into irritable bowel syndrome (IBS), abdominal migraine, functional dyspepsia, functional abdominal pain (FAP), and FAP syndrome [143].

Abdominal pain in general is common, and functional GI disorders affect up to 19 % of children and adolescents [144]. Up to 95 % of children with RAP do not have any explanatory physical syndrome. There seem to be two main peaks of prevalence—the first occurs from approximately 4 to 6 years old, and the second peak occurs in early adolescence. This epidemiology was also seen in studies of Sri Lankan [145], Malaysian [146], and Chinese [147] pediatric patients, so the phenomena is not conscripted primarily to Western cultures. More females than males are affected, and there is a greater prevalence among children of more highly educated parents [148]. In a large study by Baber et al. [149], children with FAP were stratified according to Rome III diagnostic criteria. Forty-five percent met criteria for IBS, 23 % for abdominal migraine, 15 % for functional dyspepsia, 11 % for FAP, and 6 % for FAP syndrome. Approximately 2–4 % of pediatric office visits include complaints of abdominal pain, and Shannon et al. [150] found that 8 % of middle and high school students had reported seeing a physician for abdominal pain in the prior year.

Many children actually tend to underestimate the severity and/or number of pain episodes. In a study by Chogle et al. [151] 63 children with RAP were instructed to maintain a daily pain dairy of their abdominal pain for one month. At the end of that month, the diary was collected and the children were separately asked to summarize their course over the study period. Sixteen percent of the children were accurate, but the majority (53 %) underreported their number and severity of painful episodes. The authors conclude that the majority of children underreport their number of painful episodes when asked retrospectively, with adolescents underreporting more frequently than young children.

Many of the other conditions in this chapter have a distinct etiology that is important to know as it may influence treatment options. FGID conditions are unique in that the etiology is, by definition, unknown. One theory is that children develop RAP as a result of a traceable insult, such as a bout of

gastroenteritis [152]. Though the biological inflammatory markers seem to recede, the discomfort continues to assert itself. It is thought that this inflammation leads to heightened gut sensitivity in these youth, which can be recurrently activated. Parental suspicions about alternative etiologies, such as food allergies, lack of dietary fiber, and lactose intolerance, are common [153]. However, attempts to ameliorate symptoms with alternative diets (i.e., fiber supplementation or lactose-free diets) have not proven globally beneficial and are not recommended by the American College of Gastroenterology [154]. A small study of 22 children and adolescents enrolled for 10 sessions of yoga [155] showed decreased abdominal symptoms and improved QOL, but further research is needed into complementary and alternative therapies for this condition, and they are not yet recommended treatments.

Anxiety is closely linked with FGID. In adults, a large prospective study seems to show that the relationship is bidirectional (anxiety predisposes patients to develop RAP, but preexisting abdominal pain also predisposes to the later development of anxiety symptoms) [156]. In pediatric patients, the prevalence of anxious or depressive symptoms is far higher in 2–6 year olds with FGID (28.8 %) than in the general population (10 %) [157]. Prospectively, a study of 28 children with functional pain found that as these children entered adolescence and adulthood, they were significantly more likely than controls to endorse anxiety symptoms and disorders, hypochondriacal beliefs, greater perceived susceptibility to physical impairment, poorer social functioning, treatment with psychoactive medication, and generalized anxiety in first-degree relatives [158]. In a separate survey, most of the patients with recurrent pain described themselves as "sickly" [159]. Parents of children with this condition were almost twice as likely to have depressive or anxious symptoms, though in this study, causation was not addressed [157]. Ramchandani et al. [29] divided parents of children with FGID into two groups—those with a history of anxiety disorders and those without. Parents with anxiety disorders reported higher ratings of anxiety in their children, more severe abdominal pain, more school days missed due to pain, and less hopeful prognosis than their peers, regardless of the patient-reported severity of symptoms.

Biologically, there may be a firm link between anxiety and FGID. In adult studies, markers of elevated anxiety [increased serum cortisol, hypothalamic–pituitary–adrenal (HPA) axis dysregulation] are also found in many patients with RAP regardless of their self-reported levels of anxiety. A central brain structure involved in both processes is the amygdala. This region of the brain is known to be involved in emotional regulation and emotionally informed information processing [160]. It also controls the fear response. In laboratory experiments, fear causes colonic hypermotility in rats [161]. Additionally, the amygdala connects directly to the nerves collecting sensory information from the intestine, so some authors posit that, in a fearful situation, the amygdala may misinterpret neutral somatic sensations as painful [162]. This interaction represents only one part of the incredibly complex brain-gut axis, which is thought to represent the central connections between somatic sensations, colonic motility and secretions, and anxiety [163].

In medically treating FGID, first and foremost, physicians must rule out more dangerous medical conditions. However, they must balance this with the fiscal and physical well-being of the patient, as a study by the American Academy of Pediatrics [148] found that adolescents with recurrent pain have far more medical tests, procedures, and even abdominal surgery than their peers, all of which include costs and risks. Medications, such as antispasmodics and antacids, are not used without specific targeted indications. Famotidine, an antihistamine, may reduce pain in children with dyspepsia. Peppermint oil has one supportive study in reducing recurrent pain in children, but this has not been replicated [164]. Antinausea medications which interrupt serotonergic tone in the GI tract, such as alosetron, have some evidence for efficacy in adults [165] but have not been studied in children.

Some trials exist for psychotropic medications in FGID patients regardless of their self-reports of anxious symptoms. As in IBD (see above), there is some likelihood that patients who experience RAP may have irregularities in their ability to regulate serotonin in their intestine [152]. Selective serotonin reuptake inhibitors (SSRI) or other antidepressants may help regulate the serotonergic tone, which can limit fluctuations in this tone and reduce both constipation and diarrhea [166]. Increasing GI serotonin

decreases visceral afferent signaling, a phenomenon associated with painful perceptions in patients with FGID, and thereby may act as a peripheral analgesic [167]. In a trial by Campo et al. [168] involving 25 children and adolescents who had denied depressive or anxious symptoms, 84 % reported significant improvement in their somatic symptoms after a 12-week trial of citalopram.

Because of the activity of norepinephrine in the GI tract, it may be that agents targeting this chemical in addition to serotonin [both TCA and serotonin norepinephrine reuptake inhibitors (SNRI)] may be even more effective for this population. In adults, TCAs show good evidence for efficacy and are the most thoroughly studied agents [169]. In children, one small study showed improvement in abdominal symptoms [170], while another did not differ significantly from placebo [171]. A recent further evaluation not only showed TCAs to be effective but that patient response persisted for an average of 10 months, with some patients responding for nearly 4 years [172]. In adults, duloxetine (Cymbalta) has been studied in one trial and found to improve patient ratings of pain, severity of illness, QOL, loose stool, work and family disability, and anxiety [173]. There has been a single case report in the literature of a pediatric favorable response to duloxetine, though it has not been formally evaluated in children [174]. In sum, there exists evidence for treatment of functional GI diseases with SSRI medications regardless of the presence of anxious or depressed symptoms, though other agents (TCA and SNRI), despite seeming mechanistically more effective, have not yet been thoroughly investigated in children. Camilleri et al. [163] summarize some novel therapies which may prove effective as they are more rigorously studied, including serotonin (and other neurotransmitter) modulators, colonic secretion controllers, and anti-inflammatories.

Psychological treatment for anxiety in FGID can be difficult. The provider may be met with defensiveness, denial, or even hostility at the misperceived suggestion that patients' pain is "all in their head" or that they are fabricating this distress [175]. It is important to acknowledge that the pain itself is real and distressing, regardless of its etiology. It can be helpful to frame psychotherapy and psychotropic medications as helpful in coping with the anxiety that is intertwined with or the result of the real physical discomfort that they are experiencing, even though the causality of the pain may still be in question. Many of these children may be experiencing unintended, though reinforcing, consequences of their pain such as being able to miss school days or having fewer demands at home [176, 177], but this in no way implies that they are fabricating the pain artificially.

Psychotherapeutic treatment has traditionally revolved around self-regulating strategies to manage the anxiety accompanying recurrent pain, including guided imagery and basic relaxation training [178, 179]. These techniques have been shown to reduce the number and intensity of painful episodes in children. Cognitive behavior therapy has been evaluated for treatment of pain and anxiety and overall found to be effective [180, 181]. There is a manualized treatment, the treatment for anxiety and physical symptoms (TAPS) protocol [182], specifically targeted at children with comorbid anxiety and abdominal pain. Though provided by therapists, the goal of the protocol is to incorporate techniques into the patient's regular medical visits so that they can be utilized by mental health professionals in primary care settings. TAPS presumes that some of the symptoms of FGID are behavioral in nature—that is, they are acquired over time through subtle reinforcement provided by the environment. By recognizing this, and practicing new, more adaptive behavior, patients are better able to manage their condition. The TAPS program includes the following components: (1) information about stress and its relationship to FGID, (2) self-monitoring of antecedent and consequent events associated with painful flare ups, (3) problem-solving strategies around stressors that aggravate symptoms, (4) muscle relaxation exercises for lowering physiologic arousal and increasing a sense of mastery over symptoms, and (5) cognitive restructuring for modifying faulty cognitions that underlie physiologic and emotional reactivity to pain (i.e., believing that the pain is an indication of a malign and harmful internal process). When compared to a wait-list control, Warner et al. [183] found that 80 % of children responded favorably to the TAPS program as indicated by reduced somatic discomfort and reduced anxiety scales from both the patient and parents. These gains persisted through the end of the study, 3 months after intervention.

There are various theories as to why and how CBT can be effective for FGID symptoms, as to whether they address the symptoms of the condition itself, or rather they improve the patient's psychosocial well-being and thereby make the patient better able to tolerate the distress caused by their GI condition. Interestingly (and perhaps counter intuitively, as CBT was in fact created to address psychological distress), the former seems to be the correct theory. Lackner et al. [184] evaluated the records of 147 patients with FGID randomized to a 10-week regimen of CBT, psychoeducation, or a wait list. Two weeks after the intervention, CBT patients noted an improvement in gastrointestinal symptoms, QOL, and overall psychosocial distress above the other two groups. However, using structural equation modeling, the authors found that improvement in GI symptoms was the core factor upon which others depended. By that, the authors mean that the GI symptom improvement was not dependent on improvement in QOL or in overall psychological distress.

Given the preponderance of evidence for increased parental psychopathology in terms of anxiety, depression, and somatization, it is also important to engage the family in therapy. Studies of family-based CBT techniques are quite promising [185–191]. The foundational ideas behind these techniques are multiple. One idea is that parental psychopathology contributes to abnormal pain behavior. The other, somewhat more complicated theory posits that the pain crises of children serve a behavioral goal not only for the child but for the family as a whole. Duarte et al. [186] evaluated a family therapy technique utilizing this theory. In this treatment, the consequences, both positive and negative, of pain crises are explored. For example, if the child goes into a pain crisis and has to miss school, his mother may be able to miss work and spend more time with their child. Once any unknown reinforcers are brought to the forefront, families are better able to understand their role in the pain crisis and shift from accommodating the crisis to assisting their child through it. The treatment focus then moves to teaching specific skills to accomplish this goal, both cognitive (thought stopping, distraction) and behavioral (increased physical activity, PMR). These are taught both to the child and to the family, so that the family can aid in coaching the child through difficult times. The study showed that as few as four 50-min sessions were effective at reducing self-reports of pain and of familial distress. Furthermore, these sessions were led by general pediatricians, though the protocol was not manualized and therefore may be difficult for other physicians to adopt.

Oncology

Mr. and Mrs. Jones' teenage son, Matthew, had recently been diagnosed with cancer. One month prior, Matthew had been feeling more tired than usual and after some lab work was referred to a specialist who made the diagnosis. Despite spending an hour with the doctor, Mr. and Mrs. Jones realized that they couldn't remember much of what they were told. They later described feeling "in shock." Over the subsequent weeks, Matthew and his parents tried to navigate the intense treatment regimens that were prescribed while maintaining their hope that they would be successful. Matthew seemed to take much of this in stride, but his parents struggled. They were not sleeping or eating regular meals, and Mr. Jones was finding it nearly impossible to concentrate while at work. Matthew's oncologist recommended that they see a therapist who could help them to manage their stress regarding this new, terrifying situation. They initially felt selfish, taking time away from their son for their own treatment, but eventually realized that they had to take care of themselves if they were to take care of him. They began seeing a therapist in the hospital while Matthew received his chemotherapy to talk about how the diagnosis had changed their lives, and though it took a number of visits, they began to feel, in some ways, stronger as a family than they had ever been.

Cancer in young persons is still, fortunately, a low-prevalence condition based on absolute numbers. According to the American Cancer Society [192], about 15 children out of every 100,000 develop cancer annually, though the incidence has been increasing slightly (0.6 % per year). In general, the

prognosis for pediatric malignancies is better than in adults. The 5-year survival rate for all cancers in children is about 80 %. However, morbidity from cancer is quite high, in multiple domains. Up to 40 % of childhood cancer survivors develop neurocognitive problems, including problems of attention, memory, and information processing [193]. The biggest risk factors include central nervous system cancers and radiation treatment [194].

Cancer in children is a heterogeneous group of disorders. Epidemiology, prognosis, and treatment all vary significantly depending on the type of malignancy. However, there are similarities in how a cancer diagnosis can affect a child and a family. In general, cancer treatment is difficult to tolerate. It can include surgeries, radiation therapy, chemotherapy, or any combination of these. Chronic nausea, fatigue, pain, infection, and ulcers can all interfere in a child's normal development. Immunosuppression can isolate a child from his peers, not only psychologically but also physically. Cosmetic side effects, such as hair loss, can be difficult for children eager for peer acceptance. In fact, questions about hair loss are frequently the first asked by adolescents upon learning their diagnosis [195]. Long-term problems can include altered bone metabolism (leading to early-onset osteoporosis), cardiotoxicity/cardiomyopathy, hypothyroidism, growth hormone deficiency, learning deficiencies, hearing loss, and infertility [196, 197]. The use of treatment medications (corticosteroids, interferon, etc.) can affect a child physically and emotionally, potentially leading to anxiety, depression, or neurocognitive effects [198, 199]. All of the above can disrupt a child's normal developmental trajectory, so the oncologist must carefully balance the benefits of treatment with these severe side effects. Even after recovery, a history of cancer treatment is associated with poorer psychosocial outcomes [200].

The most commonly reported mental health symptoms of pediatric cancer survivors are those of posttraumatic stress, emerging in 13–16 % of survivors once they reach young adulthood [201, 202]. As many of these symptoms can persist or even develop beyond the acute phase of treatment, screening at each outpatient visit, a protocol evaluated and found to be practical by Kersun et al. [203] is essential. As common as PTSD symptoms seem to be in cancer survivors, parents are at even greater risk. Fifty-one percent of mothers and 40 % of fathers reported symptoms of acute stress disorder 1 week after diagnosis [204], and half of those continued to report symptoms consistent with PTSD 4 months after diagnosis [205]. These symptoms persist in many parents even after the completion of successful treatment [206]. For some parents, posttraumatic symptoms seem to develop most profoundly after treatment, with anxiety during treatment a strong predictive factor for mothers but not fathers [207]. Greening and Stoppelbein [208] found that in a cohort of 150 parents with children diagnosed with cancer, risk factors for developing anxiety and PTSD symptoms include avoidant coping (substance use) and negative self-blame, while protective factors included enhanced social support. Enhanced social support in the form of group therapy was also found to decrease anxiety in the siblings of oncology patients [209].

To an extent, management of anxiety is embedded within cancer treatment. In 2009, the American Academy of Pediatrics [196] officially recommended that all children diagnosed with cancer be treated at specialized cancer centers, which all have psychosocial support built into the treatment protocols. That said, some anxiety is refractory to this basic support and requires special attention. Fortunately, behavioral therapy has been proven to lessen anticipatory (but not post-chemotherapy) nausea and vomiting, reduce procedure-related anxiety, and potentially reduce self-reported pain levels [210]. The National Child Traumatic Stress Network created a Pediatric Medical Traumatic Stress Toolkit [211], primarily designed to aid the medical team in detecting and preventing PTSD in this population (and other medically ill children). The toolkit contains a rapid screening assessment of symptoms in children, including questions to ask the parents and the child. If any are positive, addressing concerns follows the D–E–F protocol: addressing *d*istress, *e*motional support, and the *f*amily. Also included are handouts for children and parents that discuss symptoms, normalize phenomena such as not wanting to talk about stressful events, nightmares, and even reexperiencing, and give external resources such as online support groups.

Studies have demonstrated that the mental well-being of the family has a direct effect on the well-being of the child. A meta-analysis of studies of adolescents with cancer by Decker et al. [212] found

that social support from their families (particularly their mothers) was the most highly correlated factor in improved health-related QOL. Robinson et al. [213] found that children whose parents are suffering from anxiety are more likely to be distressed during treatment. As such, helping parents manage their anxiety may be the single most helpful intervention a mental health clinician can provide for the patient. In an effort to identify at-risk families, Kazak et al. [214] investigated the feasibility and validity of the psychosocial assessment tool (PAT). This tool evaluates various domains of risk, including resource availability, family problems, and social supports. In their study of 52 families (47 treatment-as-usual controls), 72 % were not at risk, 24 % required further evaluation, and 4 % were obviously in need of intervention. In a separate study [215], identification of difficulties with the PAT was strongly correlated with higher rates of family treatment, indicating that once this need is identified, resources are available to meet it. In one form of family treatment, called the Surviving Cancer Competently Intervention Program-Newly Diagnosed (SCCIP-ND) [216, 217], the goal is to prevent symptoms in parents before they start. It has four main components: *joining* highlights the process by which the therapist and family work together to achieve therapeutic goals; *maintaining an interpersonal focus* gives permission for the family to take a break from focusing solely on the patient, emphasizing that a family member's own ability to cope will be the very best thing they can learn to help their child; *normalizing the family experience* reduces feelings of anxiety, anger, and isolation and frames each person's reaction to cancer as understandable responses under the circumstances; and *focusing on the family strengths* enhances a family's feeling competence despite the illness. The first session ideally takes place within 1 month of the cancer diagnosis. In this session, the therapist discusses the diagnosis and presents the A–B–C framework for understanding the current situation, focusing on *a*dversities (the diagnosis of cancer), the families' *b*eliefs about these adversities, and the relationships of these to their physical and emotional *c*onsequences. The family watches a 5-minute video clip of other families participating in a similar exercise as modeling (this will occur in each session). In the second session, the therapist introduces the idea of changing one's thoughts to produce different consequences. Families are coached to (1) accept the uncontrollable ("We could not have prevented this illness."), (2) change the controllable ("We can use skills to help our child cope with procedures."), (3) acknowledge and celebrate strengths ("We are a strong family and together we can get through anything."), and (4) focus on the positive ("We can support each other while acknowledging that we have different ways of coping with our child's illness."). The third session focuses on supporting family growth in the future, as the diagnosis of cancer takes a more normalized role. The therapist uses two metaphors, "the Family Survival Roadmap" and "Putting Cancer in its Place" [218], to help caregivers recognize their beliefs about the family's future. The Roadmap is a physical drawing of a map (with obstacles, bridges, etc.) which helps families see their current relationship and the upcoming future process of dealing with their child's cancer. Putting Cancer in its Place helps the family incorporate the diagnosis of cancer into the family life while diminishing its centrality. Kazak et al. [216] found this intervention to be easily tolerable and to reduce anxiety and stress in the family. Treating family anxiety with these protocols has also proven, in the long-term, to lower patient anxiety and PTSD symptoms [219].

Conclusions

Anxious conditions are highly prevalent in medically ill children and can precede the medical illness, be the consequence of the illness, or the two conditions may coexist with no clear chain of causality. Family must always be kept in mind, as caretaker anxiety is an important but under-recognized complicating factor in these cases. Certain medical conditions are known to be associated with higher rates of anxiety, and thus, specific treatment protocols have been developed. Some protocols are meant to be provided directly by the primary medical team, while others involve dedicated mental health professionals. Medication, psychotherapy, psychoeducation, family therapy, group therapy,

and improved psychosocial supports have all been evaluated in these cases with varying success. Anxiety in medically ill youth should always be evaluated and treated, as evidence has shown that increased levels of anxiety can lower health-related QOL, interfere with effective family functioning, and at times even biologically worsen the course of the illness itself.

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Anxiety in Children with Autism Spectrum Disorder

Heather Jennett, Roma A. Vasa, and Louis Hagopian

Abstract Autism spectrum disorders (ASDs) are a group of neurodevelopmental disorders characterized by impairments in social and communication skills as well as restricted interests and stereotyped behavior. Researchers generally agree that individuals with ASD are at high risk for anxiety disorders. However, due to overlapping symptoms between ASD and anxiety disorders, the assessment of anxiety in this population can be challenging. Further, the identification of appropriate and effective psychosocial and pharmacological treatments for children with ASD significantly lags behind these same efforts for typically developing children with anxiety disorders, leaving many questions about how to best address anxiety in this population once it has been diagnosed. This chapter aims to discuss the current knowledge related to the clinical presentation, prevalence, etiology, assessment, and treatment of anxiety in children and adolescents with ASD.

Keywords Autism spectrum disorders • Anxiety • Behavioral assessment • Behavioral treatment • Cognitive behavioral treatment • Pharmacological treatment

Case 1: Jessica is a 14-year-old girl with autism and severe intellectual disability. She has some single words and uses picture cards to communicate. Her parents report that, at the sight of a dog, she cries inconsolably, her body shakes, her eyes become wide, and she attempts to run away. At times, Jessica's fear has been so intense that she has run out into the street and has almost been hit by a car. Jessica's next-door neighbor has a dog, which makes it very challenging and time-consuming for her to leave for school in the morning. When her mother prompts her to pass the dog to get in the car, she hits and kicks her. Coupled with direct observation of Jessica's response to dogs, behavioral interviews conducted with her parents ruled out the possibility that the purpose of such aggressive behaviors was to avoid going to school or to get attention from her parents. Based on this assessment, Jessica was given a DSM-IV diagnosis of a specific phobia.

H. Jennett (✉)
Director of Clinical Services, Little Leaves Behavioral Services, Washington, DC, USA
e-mail: hjennett@littleleaves.org

R.A. Vasa
Division of Child and Adolescent Psychiatry, Education and Training, Kennedy Krieger Institute, Baltimore, MD, USA

L. Hagopian
Neurobehavioral Unit, Department of Behavioral Psychology, Kennedy Krieger Institute, Baltimore, MD, USA

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Case 2: Danny is a 10-year-old boy with a diagnosis of high functioning autism. He attends a public school where he is placed in a mainstream classroom with 25 other students, one primary teacher, and a teacher's aide. According to his teacher, he is frequently rejected by peers due to his immaturity as well as his intense preoccupations with dinosaurs. His parents report that he has no friends outside of school aside from his older brother. He often makes statements that "he is scared of his friends" and "no good at talking." When a teacher suggests that he approach his peers, he screams and runs away. Danny expresses fear of crowds and refuses to go anywhere without his parents and his "safety" object—his favorite teddy bear. Based on interviews with Danny, his parents, and his teacher, Danny was diagnosed with social phobia.

Overview of Chapter

Anxiety was described as a characteristic commonly seen in children with autistic disorder when it was first described by Leo Kanner in 1943 [1]. Despite this, research and clinical practice related to anxiety in this population is a relatively new undertaking, with an increase in studies over the past decade. This may be due, in part, to the multiple conceptual and clinical issues related to disentangling symptoms of anxiety from those of autism spectrum disorder (ASD) as well as the lack of clarity as to whether anxiety should be conceptualized as a core feature of ASD or a separate and distinct comorbid psychiatric disorder. This discordance amongst researchers and clinicians is likely due to the symptom overlap between the two conditions. For example, symptoms such as social avoidance and repetitive questioning are inherent features of both anxiety and ASD. When attempting to delineate between disorders, developmental problems commonly seen among children with ASD, such as deficits in verbal skills, cognitive abilities, and capacity to identify emotional states, limit the assessment of this relationship. While clinicians can differentiate these symptoms through careful qualitative assessments [2, 3], no standardized measure has been developed to successfully address this issue [4]. Further, research on the identification of appropriate and effective psychosocial and pharmacological treatments specific to anxiety in children with ASD is still in its infancy. Between the increased prevalence of ASD in general and the increased risk of anxiety disorders in this population, an understanding of how to assess and treat anxiety in children with ASD is critically needed.

This chapter aims to discuss the current knowledge related to the clinical presentation, prevalence, etiology, assessment, and treatment of anxiety in children with ASD. Based on the proposed diagnostic criteria for the diagnostic and statistical manual of mental disorders-V (DSM-V; see www.dsm5.org), the term ASD will be used to refer collectively to autistic disorder, Asperger's disorder, and pervasive developmental disorder not otherwise specified (PDD-NOS), unless otherwise indicated. The term HFA will refer to those children with high functioning autism (defined as IQ>70) or Asperger's disorder.

Description of ASDs

ASDs are a group of neurodevelopmental disorders characterized by impairments in social and communication skills as well as restricted interests and stereotyped behavior [5]. The phenotype of ASD is markedly heterogeneous with respect to cognitive level, language level, and the type and severity of associated medical and psychiatric comorbidities [6]. Approximately 50–75 % of children with ASD have comorbid intellectual disabilities [7–9]. Seizures, gastrointestinal issues, and sleep problems are also frequent [10]. Psychiatric concerns are common and include short attention span, hyperactivity, aggression, self-injurious behaviors, and mood and anxiety symptoms and disorders [11, 12].

Autism prevalence has soared during the past decade with recent estimates from the Center for Disease Control and Prevention (CDC) reporting that 1 in 88 children has an ASD, favoring males with a 5:1 gender ratio [13]. Hypothesized factors contributing to this rising prevalence include broader case definitions, improved diagnostic instruments, availability of services, and greater awareness of the disorder [14].

The definition of ASD has gone through multiple reconceptualizations over the past several decades. The current DSM-IV [1] classifies autistic disorder, Asperger's disorder, and PDD-NOS as part of a larger group of pervasive developmental disorders (PDDs). In order to be diagnosed with autistic disorder, impairments must be observed across three domains—communication deficits, social deficits, and the presence of repetitive and stereotyped behavior. Criteria for Asperger's disorder are similar to autistic disorder except that there is no delay in language development. The diagnosis of PDD-NOS is a catchall term used to describe children who fulfill some but not all criteria for autistic disorder or Asperger's disorder. In the proposed DSM-V nomenclature, separate and distinct diagnoses under the label PDD are collapsed into a single category—ASDs. Moreover, impairments are observed across two domains, social-communicative and repetitive behaviors, in order to receive a diagnosis of ASD (see Table 1 for further information about the diagnostic criteria across the two manuals). The proposed criteria are intended to help clinicians diagnose a single disorder based on a common set of symptoms rather than the presence or absence of a certain diagnosis (see www.dsm5.org). The single disorder can be further specified by other clinical features including severity, verbal abilities, and the presence of intellectual disability (ID). Research has found that the labels of autistic disorder, Asperger's disorder, and PDD-NOS are applied inconsistently across sites [15]. This shift to a dimensional classification system, rather than a categorical one, is aimed at improving accurate diagnosis and has been validated through field trials.

Overview of Anxiety in ASD

Research on anxiety in children with ASD is still in its infancy when compared to knowledge of anxiety disorders in typically developing children. Leo Kanner was the first to describe and define ASD in his paper entitled "Autistic Disturbances of Affective Contact" [1]. In this paper, he described 11 children who preferred to be alone, had difficulty with language and communication, engaged in repetitive behaviors, and seemed to be experiencing anxiety when encountering a variety of environmental events, such as loud noises, medical procedures, interruption of rituals, transitions, and novel situations. With regard to anxiety, Kanner described these children as experiencing "major panic" when encountering loud noises or moving objects and "grave emotional crisis" when undergoing medical procedures [1, p. 245]. Further, he described their behavior as "governed by an anxiously obsessive desire for the maintenance of sameness" [1, p. 245].

The DSM-IV also considers anxiety as an associated feature of autistic disorder, as indicated by the statement, "there may be… excessive fearfulness in response to harmless objects" [5]. However, certain anxiety disorders should not be diagnosed in children with ASD unless "the disturbance does not occur exclusively during… a pervasive developmental disorder" as indicated in the criteria for generalized anxiety disorder and separation anxiety disorder, or the "fear or avoidance is not better accounted for by another mental disorder (e.g., pervasive developmental disorder)" as indicated in the criteria for social phobia. Despite this recommendation, there is some preliminary evidence that suggests that anxiety disorders may be separate and distinct disorders in children with ASD. For example, LeCavalier et al. used a confirmatory factor analysis to demonstrate support for the validity of several DSM-IV disorders in children with ASD, including generalized anxiety disorder [16]. In addition, Wood and Gadow cite some very preliminary evidence that has found the same genetic markers for anxiety in typically developing children who have anxiety and children with ASD who have anxiety [3].

Table 1 Diagnostic criteria for autism spectrum disorder

DSM-IV criteria for autism	Proposed DSM-V criteria for ASD
(I) A total of six or more items from (A), (B), and (C), with at least two from (A) and one each from (B) and (C) (A) Qualitative impairment in social interaction, as manifested by at least two of the following: 1. Marked impairments in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body posture, and gestures to regulate social interaction 2. Failure to develop peer relationships appropriate to developmental level 3. A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people 4. Lack of social or emotional reciprocity	(I) Persistent deficits in social communication and social interaction across contexts, not accounted for by general developmental delays, and manifest by all three of the following: (A) Deficits in social–emotional reciprocity, ranging from abnormal social approach and failure of normal back and forth conversation through reduced sharing of interests, emotions, and affect and response to total lack of initiation of social interaction (B) Deficits in nonverbal communicative behaviors used for social interaction, ranging from poorly integrated verbal and nonverbal communication, through abnormalities in eye contact and body language, or deficits in understanding and use of nonverbal communication, to total lack of facial expression or gestures (C) Deficits in developing and maintaining relationships, appropriate to developmental level (beyond those with caregivers), ranging from difficulties adjusting behavior to suit different social contexts through difficulties in sharing imaginative play and in making friends to an apparent absence of interest in people
(B) Qualitative impairments in communication as manifested by at least one of the following: 1. Delay in, or total lack of, the development of spoken language not accompanied by an attempt to compensate through alternative modes of communication 2. In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others 3. Stereotyped and repetitive use of language or idiosyncratic language 4. Lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level	(II) Restricted, repetitive patterns of behavior, interests, or activities as manifested by at least two of the following: (A) Stereotyped or repetitive speech, motor movements, or use of objects (such as simple motor stereotypies, echolalia, repetitive use of objects, or idiosyncratic phrases) (B) Excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change (such as motoric rituals, insistence on same route or food, repetitive questioning or extreme distress at small changes) (C) Highly restricted, fixated interests that are abnormal in intensity or focus (such as strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests) (D) Hyper-or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment (such as apparent indifference to pain/heat/cold, adverse response to specific sounds or textures, excessive smelling or touching of objects, fascination with lights or spinning objects)

(C) Restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least two of the following:
1. Encompassing preoccupation with 1 or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
2. Apparently inflexible adherence to specific, nonfunctional routines or rituals
3. Stereotyped and repetitive motor mannerisms
4. Persistent preoccupation with parts of objects

(II) Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play

(III) The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder

(III) Symptoms must be present in early childhood (but may not become fully manifest until social demands exceed limited capacities)

(IV) Symptoms together limit and impair everyday functioning

Differentiating ASD symptoms from those of certain anxiety disorders can be challenging because of overlapping symptoms between the two conditions. In particular, there is significant symptom overlap between ASD and social phobia, and ASD and obsessive-compulsive disorder (OCD). For instance, symptoms such as preference for being alone, refusal to speak in public situations, and social withdrawal are common to both HFA and social phobia [17]. A few studies of anxiety prevalence have attempted to differentiate the social characteristics underlying these two conditions by modifying common assessment measures. For example, in a study of HFA, Kuusikko et al. excluded all symptoms related to behavioral avoidance (e.g., "I try to avoid social situations," "I leave social situations," and "I usually do not speak to anyone until they speak to me") from the social phobia and anxiety inventory for children (SPAI-C) [17, 18]. Additionally, the question, "It is hard for me to ask other kids to play with me" was excluded since this symptom may reflect social skills deficits rather than social anxiety symptoms. One other study removed items with symptom overlap between different diagnoses [19], while another added in clarification questions to assess the child's understanding of the emotional words in the questions [11]. With these various modifications in place, the samples of children with ASD were found to have clinically significant symptoms of anxiety independent of ASD symptoms.

Similarly, repetitive and ritualistic behavior is a core feature of both ASD and OCD. Both disorders can include symptoms of repetitive body movements, touching, ordering, and adherence to senseless routines. In OCD, compulsions are often preceded by obsessions that are characterized as ego-dystonic, intrusive, and unwanted [5]. In ASD, it is unknown whether obsessions precede compulsive behavior. Further, many children with ASD often appear to enjoy and are comforted by their rituals and overfocused interests (i.e., behaviors are ego-syntonic). Currently, very little is known about the relationship between OCD and ASD, and researchers debate whether OCD should even be diagnosed in individuals with ASD given the overlapping symptoms [20]. To date, two studies [21, 22] have been conducted which compare repetitive behavior in individuals with ASD and individuals with OCD. Both of these studies have found that the type of compulsions experienced by individuals with ASD may be less sophisticated compared to those experienced by individuals with OCD. However, both of these studies have limitations and more research on this issue is clearly needed.

Although researchers have begun to document the presence of different DSM-IV anxiety disorders in children with ASD over the last decade, specific guidelines about how to make differential or dual diagnoses are lacking, and current conceptualizations about overlapping symptoms vary across clinicians and researchers. Wood and Gadow suggest that anxiety disorders can only be considered as true comorbid conditions if the anxiety disorder is "phenotypically and etiologically identical to the monomorbid condition (anxiety) in a typically developing individual (i.e., someone with no ASD diagnosis)" [3]. Otherwise, they suggest that professionals use of the term "co-occurring" to describe this relationship.

Prevalence of Anxiety in ASD

Prevalence data on the presence of DSM-IV anxiety disorders and symptoms in children with ASD vary widely across studies, with reported prevalence estimates ranging from 11 % to 84 % [4, 23, 24]. This wide range of prevalence rates likely results from the different methods used across studies with respect to sample characteristics such as age, level of cognitive functioning, informant, and assessment instrument used. One recent meta-analysis of 31 studies ($n = 2{,}121$) reported that almost 40 % of youth under 18 years with ASD had at least one anxiety disorder [23]. Specific phobia was the most frequently endorsed anxiety disorder (almost 30 %), followed by OCD and agoraphobia (17 %), social anxiety disorder (17 %), generalized anxiety disorder (15 %), separation anxiety disorder (9 %), and panic disorder (2 %). Posttraumatic stress disorder (PTSD) prevalence has varied with one study

reporting no cases of the disorder [25] and another reporting a prevalence of up to 17.4 % [26]. Of note, most of the prevalence rates reported in this study are higher than the prevalence of anxiety in typically developing children, reported to be less than 3 % in epidemiological samples [27]. In their review article, MacNeil et al. also found a higher prevalence of anxiety in children with ASD as compared to community samples of children without ASD as well as children with conduct disorder, language impairments, Down's syndrome, and mixed clinical diagnoses [4].

While the prevalence data represent a step forward in our understanding of anxiety in children with ASD, several methodological issues constrain the interpretation of the data. First, most prevalence studies of anxiety have been conducted in children with HFA or with school-age children and adolescents with ASD from clinical samples, whereas few, if any, studies report on prevalence of anxiety in lower functioning and younger children [28–30]. Second, the majority of the studies use instruments to assess for anxiety that are validated in typically developing children but not validated for the ASD population [4]. Third, anxiety is typically measured using a single informant, parent report. Few studies use child report because of the underlying belief that youth self-report of anxiety may be compromised by difficulty recognizing and communicating emotions [31–35]. Finally, most studies have small sample sizes, inadequately matched control groups and include heterogeneous ASD groups [4]. Despite these limitations, most studies seem to agree that children with ASD are at greater risk for anxiety disorders than most other individuals.

Correlates of Anxiety in ASD

Several correlates of anxiety have been examined including IQ, ASD severity, ASD subtype, and age, among which the most well-studied correlate is IQ [19, 30, 31, 36–38]. Several studies have reported a positive correlation between IQ and anxiety, when anxiety is studied as a group of disorders [19, 30, 36, 38]. Researchers have hypothesized that children who are higher functioning are more likely to experience higher levels of anxiety due to greater insight and awareness of their differences as well as their enhanced ability to communicate feelings of anxiety [38, 39]. These data however are not conclusive as another study found no correlation between IQ and anxiety [40]. Children with ASD and ID have also been shown to have higher rates of anxiety than individuals with ID but without ASD [28, 41]. Finally, a meta-analysis of the anxiety prevalence data indicates that higher mean IQ and anxiety are correlated only for specific disorders, i.e., OCD and separation anxiety disorder, where as a lower mean IQ is associated with a higher prevalence of anxiety in general and with social anxiety disorder [23].

The severity of ASD symptoms may also relate to anxiety. Mazurek and Kanne reported that children with fewer ASD symptoms are at greater risk for anxiety [38]. Others however have reported that greater ASD severity may increase risk for anxiety [19] or that ASD severity does not relate to anxiety [40]. More research on these relationships is clearly needed.

A few studies have examined the issue of age-related differences in anxiety prevalence, but the findings have been mixed. Using a cross-sectional design, Davis et al. examined age-related patterns in anxiety symptoms from infancy to adulthood. The findings showed that anxiety increased from toddlerhood to childhood, decreased through young adulthood, and then increased in older age (over 50 years old) [42]. Several limitations were noted, including the cross-sectional methodology, different informants and instruments across the age groups, and lack of an adolescent group. Strang et al. conducted a case-control study examining the influence of age (6–11 and 12–18 years) and IQ on emotional symptoms in youth with HFA [40]. Results showed that levels of anxiety were unaffected by age, IQ, ASD severity, or their interaction. Limitations of this study include its small sample size and lack of control group. A recent meta-analysis found that anxiety was positively correlated with age for anxiety disorders as a group and more specifically for generalized anxiety disorders [23]; lower mean age was associated with higher rates of OCD and separation anxiety disorder.

Aside from the correlates discussed above, there is little evidence that suggests other factors are related to anxiety in individuals with ASD. Thus far, the prevalence data do not indicate a relationship between anxiety in children with ASD and gender, race, or socioeconomic status. Additionally, very little research has examined the relationship between anxiety and other psychiatric disorders in children with ASD. In typically developing children, anxiety disorders frequently co-occur with depression and ADHD. In children with ASD, there is some evidence indicating that anxiety may be associated with externalizing disorders [2, 19, 25, 43, 44]; however, further research investigating these patterns is needed.

Etiology

There are currently no established etiological models that explain the development of anxiety in children with ASD. Several hypothetical models that are beginning to gain empirical support are discussed below.

Neuropsychological

Weak central coherence theory, which was an early theory of ASD, may contribute to anxiety [45]. This theory postulates that children with ASD tend to overfocus on small details and have difficulty seeing "the big picture" and that this underlying piecemeal approach may relate to differences in visual attention [46]. This compromised ability to integrate multiple sources of information may lead to confusion and distress in certain situations. Children may subsequently perceive certain situations as scary [47]. The data on weak central coherence theory as a contributing factor to ASD however is equivocal, with some data showing group differences [48, 49] on central coherence tasks between ASD and typically developing children and others finding no difference [50, 51].

Neurobiological

A wealth of literature indicates that the amygdala plays a critical role in the pathophysiology of both adult [52–54] and child anxiety disorders [55–58]. Together with influence from other brain regions such as the orbitofrontal cortex and anterior cingulate cortex, this region regulates an individual's responses to incoming emotional stimuli [59–62]. Functional magnetic resonance imaging (fMRI) data show that children and adolescents with anxiety disorders exhibit increased activation of the amygdala compared to typically developing youth when performing a variety of threat processing tasks, usually involving responses to facial expressions of fear and anger [63].

There has been enthusiasm for an "amygdala theory of autism" implicating this region in the underlying social cognitive impairments of the disorder including difficulties with the perception of, recognition of, and memory for emotion in facial expressions [64–66]. Empirical support for amygdala dysfunction in ASD however has yielded some inconsistent findings. For example, several postmortem studies report decreased cell size and increased cell density in this region [67, 68]. However, a later study reported fewer neurons in the amygdala of individuals with ASD compared to controls [69]. Volumetric studies have also reported inconsistent results with some data showing increased amygdala volumes [70–74] and other data reporting decreased [75–77] or no difference [78, 79] in amygdala volumes compared to control subjects. Finally, fMRI data report increases [80], decreases

[77, 81], or no differences [82–84] in amygdala function between individuals with ASD and control subjects during tasks involving emotional displays. Methodological differences across the imaging studies may account for the discrepant findings, including differences in the types of cognitive tasks and the degree to which attention was manipulated [84].

Very few studies have examined amygdala function in relation to anxiety in individuals with ASD. Juranek et al. examined a heterogeneous group of youth with ASD [85]. Positive correlations were reported between increased total and right amygdala volume and scores on the child behavior checklist anxious/depressed scale in children with ASD. In a study of adults with ASD, the level of self-reported social anxiety as measured by the social avoidance and distress scale (SADS) was positively correlated with right amygdala activation, indicating that the neural response to emotional faces in ASD may be mediated by the degree of social anxiety [86]. Further research on the neural underpinnings of anxiety and its impact on social functioning is needed in children with ASD.

Genetic

Anxiety and depression are frequently comorbid and transmissible disorders [87, 88]. Therefore, high rates of these disorders in family members of children with ASD, particularly first-degree relatives, may confer risk for anxiety disorders in the offspring with ASD. Research on the relationship between familial psychopathology and proband anxiety is important for early prevention, treatment of affected individuals, as well as providing insight into potential genetic and environmental mechanisms of anxiety in children with ASD [34].

The literature shows that parents and relatives of children with ASD have higher levels of anxiety and mood disorders compared to family members of children with other developmental disabilities, such as Down's syndrome [89–91]. The majority of parents of children with ASD report the onset of their emotional disorders prior to having any children [89–92] indicating that caregiver stress is not the sole contributor to anxiety disorders in the parents.

Studies comparing the prevalence of emotional disorders in children with ASD and their relatives are gradually emerging. Mazefsky et al. examined the prevalence of emotional disorders in a sample of 17 adults with ASD and their first-degree relatives [92]. Results showed that 88 % of probands had a mood or anxiety disorder. Higher rates of mood disorders were present in probands who had mothers with depressive disorders compared to probands who had mothers without a mood disorder (80 % versus 16 %). Associations between anxiety disorders in the proband and parent however were not found due to the low rate of parental anxiety disorders. The results were viewed as preliminary due to the study's small sample size.

In a later study, Mazefsky et al. examined the relationship between emotional symptoms in adolescents with HFA ($n = 38$) and their mother's mood symptoms [34]. Anxiety and depression were present in 39 % and 32 % of the adolescents, respectively. Maternal phobic anxiety and hostility were significant predictors of adolescent anxiety. The researchers interpreted these data as preliminary due to the small sample size as well as lack of structured diagnostic interviews to measure psychopathology.

A small body of research has explored the hypothesis that maternal mood disorders predict a specific subtype of ASD that is characterized by higher cognitive functioning and the presence of co-occurring internalizing disorders. DeLong proposed two "taxa" of ASD: one that is higher functioning, associated with comorbid anxiety and mood disorders, and linked to a family history of mood disorder and another that is lower functioning and not linked to a family history of mood disorder [93]. Cohen and Tsiouris found that recurrent maternal depression was associated with higher cognitive and adaptive functioning, increased behavior problems, and an internalizing behavioral style in offspring with ASD [94]. All mothers with recurrent major depression reported onset of their mood disorder prior to having children, providing support for the hypothesis that depression in mothers of children with ASD may result from genetic contributions rather than solely from caregiver stress.

Another study found that boys with high activity of the monoamine oxidase A (MAOA) gene were more likely to exhibit fears and rituals as well as aggression if their mother had certain homozygous compared to heterozygous MAOA alleles [95]. These preliminary findings suggest that certain combinations of maternal–child genotypes may influence the expression of anxiety in the child.

Environmental Factors

Wood and Gadow hypothesized that the interaction between ASD symptoms and several environmental stressors may increase risk for anxiety [3]. Specific stressors include increased academic demands, expectations to focus on assigned activities rather than preferred interests, hypersensitivity to sensory stimuli, and teasing and bullying. The transition to middle and high school can be a particularly stressful time, especially for children and adolescents with HFA who are integrated in mainstream educational settings. This transition requires adjustment to a larger academic setting with a greater number and diversity of students [96]. Academic demands suddenly increase and can be associated with diminished environmental supports. Social interactions become more complex and individuals with ASD may have difficulty navigating these challenges due to their core ASD impairments, including communication deficits and limited theory of mind capabilities. As a result, ASD youth may experience academic deterioration, negative peer interactions, victimization, and social isolation, all of which can increase risk for anxiety and depression [96–99].

Assessment

General Considerations

Multimodal and multi-informant approaches are generally recommended for assessing child anxiety in typically developing youth and children with ASD [3, 4]. Anxiety is generally thought to include behaviors from multiple domains, specifically behavioral, physiological, verbal/cognitive, and affective [100]. Multimodal assessment includes direct observation of behavior as well as self-report of cognitions, affective states, and sometimes physiological responses evoked by feared stimuli [101, 102]. However, for individuals with ASD, cognitive and communication deficits may make the assessment of cognitions, and affective and physiological states through self-report challenging, and in some cases not possible [103].

Thus, multi-informant assessment is recommended. The tendency for clinicians to attribute symptoms of psychopathology to the cognitive deficits of the individual, a phenomenon known as diagnostic overshadowing [104], makes accurate diagnosis of anxiety in individuals with ASD who also have ID challenging. Additionally, parental reporting may be biased if a parent attributes certain symptoms to anxiety or if the parent experiences his/her own anxiety [105–107]. Previous studies among the general population [108, 109] and in children with ASD [35, 110] have also found low parent–child agreement on specific measures of anxiety. Concordance between parent and teacher report of internalizing symptoms is also low [111]. Some authors have argued that parent report may be more valid among children with ASD given children's difficulties with emotional insight [19, 35], whereas others have stressed the importance of obtaining data from multiple sources and contexts using different types of assessment methods [111]. In summary, while multi-informant methods have been recommended, issues related to informant selection have not yet been fully resolved.

Another issue that complicates the assessment of anxiety is determining whether behavioral difficulties or negative emotional states are due to anxiety or some other type of problem. Great caution must be taken in inferring the presence of anxiety in this population based primarily on the observation of behavioral avoidance and apparent negative emotional states. Individuals with ASD may display negative emotional behaviors and behavioral avoidance when encountering situations that are simply non-preferred as opposed to aversive situations that induce fear. Functional behavioral assessment of avoidant behavior can help make this distinction [112]. For example, demands to complete academic tasks, removal of preferred items, or transitions from higher to lower preferred activities have been shown to elicit problem behavior and negative emotional responses in this population. In the case of noncompliance, avoidance may occur as a function of the individual lacking the necessary skills, insufficient reinforcement to support the desired response, or the failure to discriminate what response is expected. Avoidance and escape of academic demand situations through the display of problem behavior is one of the more commonly observed operant functions of problem behavior [112] in children with ASD. In the case of competing reinforcement, the individual may avoid a situation because there is relatively more reinforcement associated with an alternative response that competes with the one being prompted (e.g., the individual refuses to go to school because there is more reinforcement available at home) [113].

Despite these caveats, the presence of avoidance in combination with other indicators of fear including fearful facial expressions and intense physiological arousal should alert the clinician to the possible presence of anxiety. In addition to the intensity of the emotional response, the continued display of fearful responses long after the eliciting stimulus has been removed might also suggest anxiety. In contrast, avoidant behavior related to noncompliance or decrements in reinforcer density may not be associated with extremely intense or lengthy displays of the classic indicators of fear, but often quickly abate once the eliciting stimulus conditions are removed. Such observations in combination with other sources of assessment data (interviews, rating scales, and other observational data) can be important to differential diagnosis.

Described below are methods for assessment that are aimed at overcoming some of these assessment challenges. Methods that will be discussed include screening and diagnostic instruments, behavioral interviews, direct observation of behavior, and physiological measures.

Screening and Diagnostic Instruments

In general, there are two categories of instruments available for the assessment of anxiety in individuals with ASD. These include (1) instruments designed to assess a broad range of psychopathology, including anxiety disorders, in individuals with ASD and (2) instruments originally designed to assess anxiety in typically developing individuals, which have been extended to individuals with ASD.

Instruments Designed to Assess a Broad Spectrum of Psychopathology in Individuals with ASD

There are only a few instruments that have been developed specifically for the ASD population. These involve both semi-structured interviews and rating scales. All of these instruments are in their infancy and require additional study of their psychometric properties.

The Autism Comorbidity Interview—Present and Lifetime Version (ACI—PL) [11] is a semi-structured diagnostic interview based on the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS) [114]. It was modified to make it appropriate for use with individuals with ASD. For each psychiatric disorder, additional screening questions are included which ask about common observable

features and presenting concerns of parents of children with ASD with each comorbid disorder. Additional questions ascertain whether the child with ASD understands the emotion being assessed before inquiring about specific symptoms. This instrument also has the ability to distinguish whether impairment is due to the comorbid psychiatric disorder or due to the core features of ASD. Thus far, the ACI—PL has found to be reliable and valid only for certain psychiatric disorders, with OCD as the only anxiety disorder [11].

A few studies have used modified versions of other instruments designed for typically developing children by removing symptoms that overlap between anxiety and ASD [17, 19] as well. The Autism Spectrum Disorders—Comorbidity for Children (ASD—CC) [115] and the Baby and Infant Screen for Children with Autism Traits (BISCUIT—Part 2) [116] are informant-based rating scales used to examine comorbid conditions, including anxiety, in children with ASD. Parents or other caregivers are asked to endorse items on a 3-point Likert scale. The ASD—CC was designed for children with ASD ages 2–16, and the BISCUIT was designed for toddlers with ASD ages 17–37 months. Both scales have good reliability [115, 116] and the ASD—CC has good validity [117].

Instruments Designed for Typically Developing Children and Extended to Individuals with ASD

There are several well-established instruments developed to assess anxiety in typically developing children. Although these instruments have been extended to individuals with ASD, none have been tested for reliability or validity in this population. These instruments involve semi-structured interviews, informant-based rating scales, and self-report measures. The Anxiety Disorders Interview Schedule—Child and Parent Version (ADIS—C/P) [118] is a semi-structured interview based on DSM-IV criteria. Its reliability and validity are well established with typically developing children [119, 120]. Additionally, there are many rating scales available for the assessment of anxiety in typically developing children, but the most widely used include the Multidimensional Anxiety Scale for Children (MASC) [121], Revised Children's Manifest Anxiety Scale (RCMAS) [122], Spence Children's Anxiety Scale (SCAS) [123], and Screen for Child Anxiety and Related Emotional Disorders (SCARED) [124]. The latter two scales also have parent versions available. Although these scales generally have good psychometric properties for typically developing children [125], the use of self- report measures with children with ASD is cautioned [34]. These instruments have been described in more detail in chapter "Assessment of Anxiety Disorders: Categorical and Dimensional Perspectives."

Behavioral Interviews

Interviews should be conducted with individuals with ASD to the extent possible with consideration of the individual's cognitive and language capabilities. Interviewing care providers (parents, teachers, and support staff) may be the primary source of information about anxiety-related behaviors in some cases. Information should be gathered on the nature of the anxiety response, the relevant antecedents that occasion anxiety, as well as the consequences the behavior produces.

When interviewing care providers, it is important to distinguish between the respondent's observation of events versus his or her interpretation of what the individual with ASD may be experiencing and why. While care providers' own hypotheses about the individual's anxiety may be useful, the clinician must also gather descriptive information and form his or her own hypotheses. In particular, it is important to identify what particular situations or stimuli are avoided by the child, elicit escape, and occasion negative emotional states suggesting anxiety, e.g., fearful facial expressions, crying, shaking, and panic-like states. For young children and individuals with ASD who may be unable to verbally express fear or their desire to avoid a situation, avoidance sometimes co-occurs with other

responses such as aggression, property destruction, and self-injury—particularly when initial attempts to avoid or escape are ineffective [126, 127]. Although avoidant and escape responses are generally maintained by negative reinforcement (i.e., escape or avoidance of the feared stimulus), it is important to identify how care providers respond (or what other events occur) after the individual displays anxious or avoidant behavior. Reactions on the part of care providers, including attention (in the form of consoling the individual or talking about their anxiety) as well as access to preferred activities, can inadvertently reinforce these behaviors.

The interview can also provide information about how the individual's anxiety affects the care provider. For many parents, observing one's child in an anxious or upset state is often unpleasant and anxiety inducing. Reacting in a way that reduces child anxiety (e.g., by permitting the child to avoid the feared situation) also reduces the parent's anxiety and thus reinforces these parent behaviors. Understanding these interactions is important for understanding the broader context in which anxiety occurs and has important implications for designing treatment. For example, different treatments would be indicated in a case where the parent has a very low tolerance for his/her child becoming anxious versus one where the parent has a higher threshold and shows little anxiety.

Direct Observation of Behavior

Direct observation of behavior can be more effortful and time-consuming than other methods of assessment because the conditions that induce anxiety must be present. This is accomplished either by observing the child in the natural environment or by simulating those conditions in the clinic setting. Therefore, information obtained via interviews of the individual and care providers and findings obtained from self- and other-report should be used to guide initial behavioral observations.

Determining whether the stimuli that induce anxiety can be precisely identified and presented in a controlled manner is critical to designing formalized behavior observational procedures. For example, some studies have described cases in which anxiety was elicited by specific stimuli such as water, needles, or dental care [128–130]. Certain anxiety disorders, such as specific phobias, OCD, social phobia, and separation anxiety disorder, are characterized by anxiety that is often elicited by a specific stimulus or classes of stimuli. In these cases, presentation of the anxiety-inducing stimulus in a controlled fashion may be possible. In other cases, however, the stimuli that occasion anxiety may be difficult to identify or control. For example, individuals with generalized anxiety disorder may not be able to identify specific stimuli that reliably elicit fear. In other cases, stimuli may be identifiable but difficult to present and terminate with the level of control required in treatment—such as the behavior of peers and certain internal stimuli (e.g., physiological sensations).

Naturalistic Behavioral Observation and Behavioral Monitoring

In cases where the anxiety-inducing stimulus cannot be readily presented in a controlled manner, direct observations in the settings where the anxious behavior has been known to occur can be helpful at various points in the assessment and treatment process. In cases where this is impractical (e.g., the behavior is infrequent or unpredictable), enlisting care providers to monitor anxious behavior may yield the most complete information. In contrast to self- and other-report measures, which involve the retrospective reporting of behavioral patterns or tendencies, behavioral monitoring involves the observation and recording of discrete behaviors in real time or within a brief time frame. For example, behavioral monitoring may involve a mother recording each time she observes her child checking to see if a door is locked along with any observable antecedents and consequences for this behavior. Parents can also provide ratings of subjective distress based on observable indices of affect such as crying, trembling, or facial expressions. In addition to helping identify antecedents and consequences

during the assessment phase, data obtained using behavioral monitoring can be used to establish a pretreatment baseline and evaluate treatment effects. Parental monitoring of anxiety in children without ASD has been reported in several studies [131–133]. Although all of these examples involved children without ASD, a similar type of monitoring can also be used with children with ASD and, in some cases, may be the best source of data.

Behavioral Avoidance Test

In cases where the anxiety-inducing stimulus is identifiable and can be presented in a controlled fashion, it is possible to arrange conditions to directly observe the anxious response in vivo. A Behavioral Avoidance Test (BAT) [134] is a highly structured method of assessing avoidant behavior associated with the feared stimulus. Generally, this procedure involves progressively exposing the individual to the feared stimulus along some dimension (e.g., distance, time) and recording the point at which the avoidant response is displayed. BATs can be highly individualized based on the specific stimuli that elicit fear in the person being observed. In addition to the benefit of observing the anxiety responses directly and in a controlled manner, one can use the same method of stimulus presentation during graduated exposure treatment (see below). Although the BAT has been a widely utilized observational measure for assessing certain anxiety disorders across populations, it may be especially important to include a BAT in the assessment of anxiety disorders in individuals with ASD given that self-report and interview data may be limited. Many of the available clinical case studies that report on the assessment and treatment of anxiety in this population describe the use of a BAT [135, 136].

Physiological Measures

The use of psychophysiological measurement for the assessment of anxiety is commonly recommended by researchers [101, 137] but rarely used. Although only a couple of studies [138, 139] have included physiological measures for assessing anxiety in individuals with ASD, these studies demonstrate the potential feasibility of this method. Both of these studies utilized store-bought heart rate monitors and were able to appreciate differentiated results across conditions. However, knowledge is still limited with regard to the selection of measures, appropriate conditions under which to measure physiological responding, and the validity of this measure [140]. Moreover, for some individuals with ASD, physiological measurement may be even more challenging because they may have difficulty tolerating the equipment and procedures. Despite these limitations, the potential use of physiological measures should continue to be explored as these could provide additional information regarding the situations that cause increased arousal in individuals with ASD, especially for those individuals who are unable to reliably verbalize or report this information due to language deficits.

Treatment

Treating anxiety disorders in children with ASD can be a challenge given the paucity of the research in this area, despite an extensive body of research on the treatment of anxiety in typically developing children. As described below, there are some promising treatment options, but caution needs to be taken when recommending these treatments until more evidence of their efficacy has been established for children with ASD. These treatment options include (1) behavioral treatment, which is aimed at

treating specific phobia; (2) cognitive behavioral treatment (CBT) for children with HFA, which is aimed at treating a wide range of anxiety disorders; and (3) pharmacological treatment for repetitive and ritualistic behaviors. Unfortunately, there are not many rigorous studies on specific anxiety disorders or symptoms in this population. Therefore, the treatments described are limited to the anxiety disorders for which there is the most research, and some of our conclusions are drawn from the literature on both individuals with ID and typically developing children.

Behavioral Treatment

A recent review by Jennett and Hagopian identified behavioral treatment as an evidence-based treatment for specific phobia in individuals with ID [141]. The authors identified 38 studies published over a 35-year time period. These studies were mainly case reports, single-case experimental designs [142], as well as some uncontrolled group studies. Among the studies were 12 well-designed single-case experimental studies that met the American Psychological Association (APA) Divisions 12 and 16 criteria for empirically supported treatments. Participants in the reviewed studies varied widely in their demographics, with approximately 30 % also having an ASD diagnosis and representing the full range of impaired intellectual functioning (i.e., mild to profound). In addition, a wide variety of age groups from childhood to adulthood were represented. A significant proportion of these studies described the clinical nature of the problems in detail, but failed to include formal DSM diagnoses. However, most of the clinical problems described involved avoidance of feared situations or stimuli, such as dogs, needles, or water, and could be characterized as specific phobia. This review revealed that behavioral treatment, involving the use of graduated exposure and reinforcement, has been sufficiently researched to characterize this class of interventions as a "well-established" evidence-based treatment for individuals with ID. This finding is consistent with literature on the treatment of specific phobias in typically developing children [143]. Although there is not much research specifically on the use of behavioral treatment for individuals with ASD, it is reasonable to believe that this intervention may be efficacious for this population based on the research support in both typically developing children and individuals across the range of intellectual functioning.

The main components of behavioral treatment are graduated exposure and reinforcement. These components are also among the main components in CBT (as described below) and, therefore, can be applied to both low functioning individuals (i.e., IQ < 70) with ASD and those with HFA. If a child needs help understanding or participating in the exposure, supplemental behavioral components such as prompting, modeling, response prevention, or the use of distracting stimuli can be used in order to facilitate it. The determination of whether these components are necessary should be based on the needs and functioning level of the individual requiring treatment, but may be used as part of any treatment package utilizing graduated exposure.

Graduated Exposure

As described in chapter "Cognitive-Behavioral Treatment for Pediatric Anxiety Disorders," graduated exposure is most appropriate for anxiety disorders in which there is a specific stimulus that the individual is attempting to avoid and, therefore, is most applicable to disorders such as specific phobia, social phobia, and OCD. With typically developing individuals, graduated exposure involves developing a fear hierarchy ranging from least to most feared stimuli based on the individual's verbal report. The individual is gradually exposed from lesser to more feared stimuli while maintaining appropriate approach responses and low levels of anxiety. For individuals with ASD who may not be able to generate a fear hierarchy based on verbal report, the hierarchy may be developed based on the

results of a BAT (as described above) or derived by the therapist based on other assessment findings. In the latter case, the therapist may generate a range of stimulus variations by altering the feared stimulus along a physical dimension, such as its distance from the individual, the duration of contact, or size of the stimulus. Regardless of how the hierarchy is developed, graduated exposure involves systematically exposing the participant to variations of the feared stimulus that progress to closer approximations of the actual feared stimulus. Progression along the hierarchy is based on the participant successfully completing the previous step, ideally with minimal anxiety. Based on the participant's progress, the hierarchy can be changed by including intermediate stimulus variations.

Based on the basic learning process of extinction, exposure aims to extinguish any associations between the feared stimulus and aversive events (such as intense physiological arousal) by presenting the feared stimulus in the absence of those aversive events. Consequently, for this approach to successfully result in extinction, it is critical that exposure to the feared stimulus not be paired with any aversive events (including extreme anxiety), or result in escape/avoidance from the stimulus that could strengthen avoidance and produce counter-therapeutic effects. Ideally, the exposure session should be arranged to minimize the likelihood that the target stimulus will be avoided by (1) gradually progressing from lesser to more anxiety-provoking stimuli and (2) programming reinforcement for successful approach during stimulus presentations.

For example, if a child is fearful of dogs, the hierarchy should involve exposing the child to a dog starting at a distance that is comfortable and then progressively getting closer to the dog until the child is within arm's reach or is able to touch it [135, 138]. Reinforcement should be programmed for successfully completing the steps of the hierarchy (see below for more information). If no starting distance is comfortable, the first step may involve showing the child a picture or video of a dog or having the child observe a dog behind a gate (these variations will largely be a function of the child's individual ability to understand symbols or representations of feared stimuli). The progression through the hierarchy should be based on the child's pace so that avoidance or escape from the dog is not reinforced and low levels of anxiety can be maintained throughout the exposure. For example, if the child resists the next step of the hierarchy, he or she should be allowed to back up to a distance that is more comfortable but should not be allowed to leave the situation entirely. If a particular step remains difficult, such that the child is always resisting, an intermediate step can be programmed and/or the reinforcement for approach behavior can be modified or increased.

Reinforcement

In addition to systematically exposing the individual to the feared situation, treatment should involve reinforcement for approach responses. In anxiety disorders, the maintaining consequence for avoidant behavior is typically negative reinforcement, in the form or either avoidance or escape from the feared situation. Therefore, it is important to impose reinforcement procedures targeting approach responses that are strong enough to counter or compete with the negative reinforcement maintaining escape or avoidance. Although typically developing individuals may be able to identify powerful reinforcers based on verbal report, for lower functioning individuals with ASD, a systematic preference assessment (based on nonverbal choice responses) should be conducted to identify preferred items that may potentially serve as reinforcers. Hagopian et al. provide a comprehensive review of the preference assessment procedures for individuals with ASD and other developmental disabilities [144].

Reinforcers are typically delivered using response contingent schedules. For example, in a study by Hagopian and colleagues, tokens were provided every 10 s during participation in each step of a hierarchy for a blood draw for an individual with ID [126]. The tokens were then traded in at the completion of the session for preferred items or activities that were identified via a preference assessment. Tangible reinforcers, such as toys or preferred snacks, may also be used to reinforce approximations of the approach response [142].

Other Behavioral Treatment Components

Other behavioral components, based on the principles of learning, may be necessary to help the child to cooperate with or understand the exposure. Some children, including those with lower functioning ASD, may learn how to participate in the graduated exposure simply through learning the contingency that approximations of an approach response lead to reinforcement. For other children, additional treatment components may be needed to facilitate this process.

Prompting may be included in the treatment package as way to assist the child to comply with the steps of the exposure hierarchy and come into contact with the reinforcement contingencies in place. This may especially be important when he or she is exhibiting intense anxiety or not approximating the targeted approach response. Prompting involves supporting the child in performing the desired task, in this case, approaching the feared stimulus. It may involve telling the child what to do in order to approach the feared stimulus, showing the child how to approach the feared stimulus, or physically helping the child to approach the feared stimulus. For example, in a study by Runyan and colleagues, a least-to-most prompting hierarchy was used to help the participants complete the steps of the hierarchy in order to successfully ride an escalator [145]. The prompting sequence consisted of a model (e.g., showing the participant how to step on the escalator), verbal prompt (e.g., telling the participant, "step up"), physical prompt (e.g., touching elbow or holding hands to help the participant to step on the escalator), and finally manually guiding the participant's body through the step. A wide variety of prompting methods are available and routinely used with individuals with ASD [146], although the prompts used may depend on the individual's functioning level and ability to perform the required task.

Modeling involves arranging for the participant to observe another person (model) engaging with or approaching the feared stimulus appropriately. Models may either be live [142] or observed via video [128]. In a study by Love and colleagues, two young children with ASD were treated for fear and avoidance of going outside and running water [142]. Prior to prompting each participant to engage in an approach step of the exposure hierarchy, their mothers would model the step and verbalize their lack of fear. Similarly, in a study by Erfanian and Miltenberger, two adults diagnosed with moderate to profound ID were treated for fear of dogs: prior to exposure along the hierarchy, each participant would engage in a preferred activity with the therapist at a far distance from a dog while observing another adult interact positively with the dog [135].

Response prevention is another component that is sometimes used in conjunction with prompting or modeling in order to ensure that the individual comes into contact with the feared stimulus. Response prevention is typically done in order to implement extinction, which may involve preventing an escape response or prompting a behavior that is incompatible with avoidance (e.g., approach). In either case, it typically involves not allowing the individual to leave the feared situation until the targeted step is completed. For example, Rapp and colleagues treated an adolescent with ASD and severe ID for self-injurious behaviors, elopement, and dropping associated with the avoidance of swimming pools [129]. The participant was physically guided to approach and then occupy the pool. Attempts to drop or elope were blocked by prompting the participant to sit in a rolling chair. Two therapists physically guided her toward the pool by rolling the chair. When she reached the pool, another therapist provided her with edible reinforcement. Although this study describes an effective response prevention procedure, most studies published to date that describe the behavioral treatment of anxiety in individuals with ASD do not include response prevention or escape extinction [141]. That is, in most cases, the individual is permitted to escape or avoid the situation. However, not enough research has been conducted to determine whether this component should be routinely included as part of a treatment package.

Finally, use of distracting stimuli is another component that may be used in conjunction with graduated exposure and reinforcement. This involves the noncontingent access to items during exposure, ostensibly as a means of providing alternative reinforcement of responses incompatible with avoidance. Luscre and Center incorporated distracting stimuli along with an exposure hierarchy, modeling,

and reinforcement for the treatment of children with autism displaying anxiety and resistance during dental exams [147]. Each participant was provided with access to items such as music and preferred toys with the intent to promote relaxation. The intervention was effective for all cases; however, data on the participants' level of relaxation were not reported (nor is it possible to determine the contribution of each treatment component). Although providing distracting stimuli during exposure is relatively easy and a seemingly benign component, it is possible that free reinforcement can weaken the effects of contingent reinforcement provided for successful approach behavior. Additional research is needed before the routine use of distracting stimuli can be recommended.

Although there is not much research to date specifically on the use of graduated exposure and reinforcement with individuals with ASD, the collective findings that it is a well-established treatment for both individuals with and without cognitive limitations with specific phobia [141, 143] may be sufficient evidence for the use of this treatment with individuals throughout the ASD population. Behavioral treatment, as described above, can be highly individualized based the functioning level and needs of the individual, utilizing additional treatment components when necessary.

Cognitive Behavioral Treatment

Recently, there has been an increase in research on the treatment of anxiety disorders specifically for individuals with HFA. Lang and colleagues identified nine studies on modified CBT for anxiety in individuals with ASD [148]. These studies include a range of experimental and nonexperimental designs, with five studies that included a waitlist control group [149]. The majority of participants across the reviewed studies were diagnosed with Asperger's disorder, and few participants were diagnosed with PDD-NOS or high functioning autism. The ages of the participants ranged from preadolescence to postadolescence. Finally, the majority of studies included individuals with multiple anxiety diagnoses, including OCD, GAD, separation anxiety disorder, panic disorder, social phobia, and specific phobia. CBT has been classified as an evidence-based treatment for social phobia, OCD, school refusal, and general anxiety symptoms for typically developing children [150, 151] according to guidelines established by the APA Division 12. Thus, in the absence of other information, and coupled with the promising preliminary evidence from investigations of CBT with individuals with HFA, it is reasonable to believe that this type of treatment may also be efficacious for this population.

All of the research studies published to date on the use of CBT with individuals with ASD have used a manualized approach based on commonly used treatments for typically developing children with anxiety disorders that has been modified based on the characteristics of individuals with ASD (see Table 2 for more information on each study) [20, 32, 110, 149, 152–162]. Most of the treatment manuals describe the steps for individual CBT, including "Building Confidence" [159], "Coping Cat" [160], and the manual developed by March and Mulle for OCD [161]. One describes the steps for a group CBT approach ("Cool Kids") [162]. Finally, some researchers [39, 153, 155, 158] created their own manuals specific to their studies. As described in chapter "Cognitive-Behavioral Treatment for Pediatric Anxiety Disorders," manualized CBT for typically developing children usually involves (1) affect recognition, (2) coping strategies, (3) cognitive restructuring, and (4) graduated exposure. The adapted manuals for individuals with ASD include these components as well, but with modifications such as increased structure during sessions, use of visual cues to teach key concepts, use of perseverative interests and behavioral reward systems to increase motivation for participation, and simplified cognitive restructuring [20, 32, 149, 152, 155, 156]. The majority of manuals have also been modified to include more parent involvement in the treatment sessions. In addition, a few studies have investigated the efficacy of CBT plus skills training that focus on areas of deficit commonly seen in individuals with ASD such as social skills or daily living skills [39, 149, 158].

Table 2 Cognitive behavioral treatment in children with autism spectrum disorders

Author (year)	*N*	Sample characteristics	Anxiety diagnoses	Type of treatment	Treatment manual	Control group	Treatment outcomes
Chalfant et al. [32]	47	HFA ($n=13$), AS ($n=34$); age 8–13	SAD ($n=8$), GAD ($n=14$), SP ($n=20$), SpP ($n=3$), PD (n=2)	12-week group CBT with concurrent parent sessions	Adapted "Cool Kids" Program (Lyneham et al. [162])	Waitlist control (random assignment)	71.4 % of treatment group no longer met DSM-IV criteria for anxiety disorder (vs. 0 % in control group)
Lehmkuhl et al. [152]	1	HFA; age 12	OCD	10 sessions individual CBT with parent involvement	Adapted manual by March and Mulle [161]	N/A	Subject no longer endorsed clinically significant symptoms of OCD on Y-BOCS
Reaven et al. [153]	33	ASD ($n=15$), PDD-NOS ($n=4$), AS ($n=14$); age 8–14	GAD ($n=22$), SAD ($n=6$), SP ($n=5$)	12-week group CBT with concurrent parent sessions	Original treatment manual written by authors	Waitlist control	Parents of children in treatment group reported significant decrease in severity of anxiety symptoms according to SCARED (vs. no reported decrease in control group)
Reaven and Hepburn [20]	1	AS; age 7	OCD	14 sessions individual CBT with parent involvement (sertraline was initiated during treatment)	Adapted manual by March and Mulle [161]	N/A	65 % decrease in parent-reported symptoms on CY-BOCS after treatment
Schleismann and Gillis [154]	1	AS, age 6	SP	12 sessions individual CBT with parent involvement	Adapted "Coping Cat" manual (Kendall [160])	N/A	Subject no longer met diagnostic criteria for social phobia (based on clinical judgment)
Sofronoff et al. [155]	71	AS; age 10–12	PD, OCD, SP, SAD, GAD (n's not reported)	6-week group CBT or 6-week group CBT with parent involvement	Study-specific manual	Waitlist control (random assignment)	Significant decrease in parent-reported anxiety symptoms (according to SCAS-P) in both groups, but greater improvement with parental involvement

(continued)

Table 2 (continued)

Author (year)	*N*	Sample characteristics	Anxiety diagnoses	Type of treatment	Treatment manual	Control group	Treatment outcomes
Sze and Wood [156]	1	HFA; age 11	SAD, GAD, OCD	16-week individual CBT with parent involvement	Adapted "Building Confidence" program (Wood and McLeod [159])	N/A	Subject no longer met diagnostic criteria for SAD, GAD, or OCD (according to ADIS-C/P)
Sze and Wood [157]	1	AS; age 10	GAD, SP	Not reported	Adapted "Building Confidence" program (Wood and McLeod [159])	N/A	Subject no longer met diagnostic criteria for GAD or SP (according to ADIS-C/P)
White et al. [158]	4	AS ($n=3$), PDD-NOS ($n=1$); age 12–14	GAD ($n=3$), SP ($n=3$), SpP ($n=2$)	12–13 sessions individual CBT with parent involvement + 5 sessions group social skills training	Manual created by authors "Multimodal Anxiety and Social Skills Intervention" (MASSI; White et al. [110])	N/A	Three of the four subjects no longer met diagnostic criteria for targeted anxiety disorder. Variable improvement in social competence based on parent report (according to SRS)
Wood et al. [149]	40	AS ($n=3$), ASD ($n=20$), PDD-NOS ($n=17$); age 7–11	SP ($n=35$), SAD ($n=24$), OCD (n = 17), GAD (n = 19)	16-week individual CBT with parent involvement	Adapted "Building Confidence" program (Wood and McLeod [159])	Waitlist control (blinding, random assignment)	64.3 % of treatment completers no longer met diagnostic criteria for anxiety disorders (vs. 9.1 % of control group)

Affect Recognition

Affect recognition involves identifying physiological symptoms or behaviors that occur when one is anxious. The goal of this step is to increase self-awareness of symptoms or situations that may lead to anxious feelings. Emotion recognition is impaired in some individuals with ASD [163–165]. In order to decrease the communication demands and possible challenges with emotion recognition, Reaven modified this step by presenting a written menu of possible physical symptoms and allowing the participant to choose from among them instead of asking him to generate this information on his own [166].

Acquisition and Use of Coping Strategies

After the individual is able to identify his or her physical symptoms of anxiety, coping strategies are taught so that he or she has the tools to manage anxiety when confronted with a feared situation. The most commonly used coping strategy for individuals with ASD is behavioral relaxation. Behavioral relaxation usually involves progressive muscle relaxation and deep breathing. Some modified CBT programs [32] devote the most time to teaching relaxation skills since it is a concrete exercise and does not rely on the child's communication skills. Other commonly taught coping strategies involve the use of positive self-statements (see below) and distraction [20]. The majority of studies have enhanced skills training with visual supports. For example, in a case study, Reaven and Hepburn's participant made a "toolbox" with cutout "tools" that were each labeled with a coping strategy and could be used as a visual reminder to utilize that strategy during exposure sessions [20]. Other case studies describe the use of social stories which outline the coping strategies that can be used when facing a fear [20, 154].

Cognitive Restructuring

Cognitive restructuring involves recognizing and challenging negative automatic thoughts. For individuals with ASD, this typically involves replacing negative automatic thoughts with more helpful statements. For example, a child with social phobia may be taught to replace the negative automatic thought "Those kids think I'm stupid because I don't know what to say" with the statement "Everyone has something interesting to say." For individuals who are unable to identify automatic thoughts, generic positive self-statements can be offered, such as "Nothing bad will happen" or "It's no big deal." Chalfant et al. used worksheets with lists of helpful and unhelpful thoughts that the participants could choose from rather than relying on their limited communication skills to generate them on their own [32]. Sze and Wood also relied on visual materials, rather than spoken language, and included a participant's special interests to facilitate learning of these skills [156]. In particular, the participant was allowed to draw her favorite cartoon characters and then wrote "icky" and "calm" thoughts into thought bubbles. Across all studies of individuals with ASD, cognitive restructuring was significantly simplified and typically was conceptualized as affect recognition and positive coping statements, as described above [32, 152].

Graduated Exposure

Graduated exposure, as described in the behavior treatment section, is a main component of CBT. Individuals with HFA can take a more active role in creating the hierarchy of anxiety-provoking situations. Some of the original treatment manuals [160, 161] include visual cues such as "fear

thermometers" to assess the level of anxiety experienced throughout the exposure, and similar to typically developing children, this strategy is effective in many of the HFA case studies as well [154]. When engaging in exposure tasks, individuals are reminded to use their coping techniques and report the levels of anxiety at different points in the exercise using these visual cues. As described above, reinforcement is a necessary component to increase motivation and adherence to the exposure exercises and in some cases involves the use of the child's perseverative interests [153, 156]. For example, in one case [156], a points system was used to keep track of homework completion, and the child was rewarded with access to activities and movies with which she was preoccupied.

Parent Involvement

Parent involvement generally involves (1) psychoeducation about the nature of anxiety and basic principles of CBT, including how to facilitate appropriate extinction of avoidance behaviors and reinforce appropriate alternative behaviors, and (2) homework assignments for which the parents complete exposure exercises with their children outside of therapy sessions. In most cases, parent involvement is woven throughout all therapy sessions [20, 39, 153, 158] in order to enhance generalization of the skills learned in session. Parents may be involved in the development of fear hierarchies and coping skills training and then given coaching by the therapist to implement exposure sessions with their children. Subsequent homework assignments are given where parents are asked to practice systematically exposing their child to items on the fear hierarchy outside of the therapy session so that the gains made by the child in the session are generalized to the natural setting. Studies have found that CBT with parental involvement is an important component for individuals with ASD and leads to more treatment gains compared to child-focused CBT [149, 155].

Skills Training

Skills training involves a focus on deficits specific to children with ASD that may impact the efficacy of CBT. White and colleagues have hypothesized that social deficits in individuals with HFA may contribute to the promotion of social anxiety in this population [39, 158]. Adolescents with HFA may develop and maintain social anxiety because of their awareness of their own social difficulties. As a result, they may avoid social situations and, therefore, have few opportunities to practice appropriate social skills. Based on this hypothesis, a multicomponent manual-based program was developed which targets both anxiety and social deficits as reciprocal influences on one another. This treatment package includes individualized CBT, group social skills training, and parent education/involvement. It contains the components described above plus the use of social skills training through the use of modeling, feedback, and reinforcement. Social skills that may be targeted include initiating with peers, conversational skills, flexibility, recognizing the cues of others, and handling rejection; see Table 2 for more information on outcomes. Other researchers have preliminarily focused on other areas of skill deficit, such as self-help skills and the presence of circumscribed interests [149].

Despite the promising results in the literature to date, there still remain several questions regarding the use of CBT with individuals with HFA. More research needs to be conducted in order to determine the contribution of the cognitive components of this treatment with this population. According to Lang and colleagues, the fundamental mechanism of action in CBT involves a correction of dysfunctional cognitions and a reliance on introspection [148]. However, most of the modifications necessary to gear this treatment to individuals with ASD have been behavioral in nature, and many of the cognitive components have been significantly reduced. Therefore, it is possible that behavioral components alone, as described above, would be sufficient and potentially more efficient for treating the HFA population. Additionally, there still remain several questions concerning for whom this treatment

works best. As described above, the majority of the participants in the collective research to date have been diagnosed with Asperger's disorder, with only a few having high functioning autism or PDD-NOS. Given the differences in communication and cognitive skills across these diagnoses, it should not be assumed the CBT would be equally effective for all individuals in the higher range of functioning on the autism spectrum. Finally, since participants in these studies typically have more than one anxiety disorder or the groups of participants have different anxiety diagnoses, it is unclear as to which anxiety disorders are being treated or for which anxiety disorders these treatments are most effective.

Pharmacological Treatments

Research on the pharmacological treatment of anxiety in children with ASD is relatively lagging in comparison to studies in typically developing children. To date, there are no controlled studies of medications for separation anxiety disorder, generalized anxiety disorder, social phobia, or OCD in children and adolescents with ASD. The current literature focuses on the treatment of anxiety symptoms as well as repetitive and ritualistic behaviors in children and adolescents with ASD. Relevant adult data are also presented to illustrate developmental differences in treatment response. This section will focus primarily on data from open-label and controlled drug trials of anxiety and repetitive behaviors. Select case report studies are presented if these are the only data available for a particular medication; these data however should be interpreted cautiously until data from controlled trials are available. The effects of each medication reported in this section are limited to anxiety and repetitive behaviors and not inclusive of the full range of benefits of the drug.

Selective Serotonin Reuptake Inhibitors

The selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed medications for children with ASD [167, 168]. Three lines of evidence spark enthusiasm for using SSRIs in children with ASD. First, serotonergic abnormalities have been implicated in the pathophysiology of ASD [169]. Second, double-blind placebo-controlled trials have demonstrated the effectiveness of multiple SSRIs in the treatment of anxiety disorders, including OCD, in typically developing children [170, 171]. Although not yet known, it is possible that the clinical presentation and pathophysiology of anxiety disorders may be similar in children with and without ASD [85, 172]. Lastly, SSRIs have a relatively benign side profile compared to other psychotropic medications (e.g., risperidone) that are often prescribed in children with ASD, making them a preferable first-line agent for treatment for anxiety.

The data on SSRIs in the treatment of anxiety and repetitive behavior in children and adolescents with ASD are mixed with some studies demonstrating efficacy of select SSRIs (fluoxetine), whereas other SSRIs (citalopram) show no effect. The doses of SSRIs used in these studies are lower than the doses typically used to treat emotional disorders in typically developing children and adolescents. For example, the mean dose of citalopram used in children with ASD was 16.5 mg [173] compared to the mean dose of 25 mg used to treat depression in typically developing children and adolescents [174]. Similarly, the mean doses of fluoxetine were 9.9 mg [175] and 20 mg [176] in children and adolescents with ASD and a same age typically developing sample, respectively. Developmental differences in dosing of SSRIs as is also present in ASD, with adults tolerating higher doses and demonstrating greater efficacy than children [173, 177].

Findings from several case report studies suggest that sertraline may improve anxiety in children with ASD. Ozbayrak reported an improvement in anxiety and repetitive behavior with sertraline in two children with Asperger's disorder [178]. One child was a 6-year-old boy who was described to

have anxiety, excessive clinginess, repetitive questioning, preoccupations with death and blood, and physical aggression. His anxiety, clingy behavior, and questioning improved with 25 mg of sertraline. He became hyperactive on 50 mg of sertraline. The second child was a 13-year-old boy with an impairing compulsive counting ritual that responded to 50 mg of sertraline.

Results from a case study of nine children with ASD, ages 6–12 years, found that sertraline 25–50 mg was beneficial in reducing transition-related anxiety and agitation [179]. Three children demonstrated relapse after 3–7 months, whereas six children demonstrated continued benefits for a few months. Sertraline was generally well tolerated with one child developing stomachaches and two children exhibiting agitation on 75 mg of sertraline.

Another case report documented improvement in separation anxiety in a school-age girl with ASD who received 150 mg sertraline [180]. The child had classic DSM-IV symptoms of separation anxiety as assessed by an established structured diagnostic interview. Symptoms included fear of her sister being harmed, wanting to sleep near her sister, and anxiety and restlessness when separated from her sister. Her symptoms resolved with 6 months of sertraline treatment.

The largest and most rigorous SSRI study in children with ASD is a multisite, double-blind, placebo-controlled 12-week trial of citalopram (mean dose of 16.5 mg) in 149 children with ASD. Results showed no significant difference in repetitive behaviors between the citalopram (32.9 % responders) and placebo groups (34.2 % responders) [173]. Significantly more side effects occurred in the citalopram versus control group (97.3 % versus 86.8 %). In the citalopram group, the most common side effects were increased energy, impulsivity, diminished concentration, hyperactivity, stereotypy, diarrhea, and insomnia. Two children in the study had seizures, one of whom had preexisting seizures.

Studies of fluvoxamine indicate beneficial effects in adults but not children. In a double-blind controlled study of adults with ASD, fluvoxamine (mean dose 276.7 mg/day) was effective in reducing repetitive behavior, maladaptive behavior, and repetitive speech in 8 of 15 (53 %) patients on active drug compared to a 0 % response in the placebo group [181]. Side effects in adults taking fluvoxamine were mild and transient. In contrast, a placebo-controlled trial of fluvoxamine (25–250 mg/day, mean dose = 106.9 mg/day) in 18 of 34 children with PDD showed benefit in only one (6 %) subject [182]. Side effects emerged in 14 out of 18 children and most commonly included insomnia, hyperactivity, agitation, and aggression. The high rate of side effects may have overshadowed any type of treatment response. An open-label study of fluvoxamine (1.5 mg/kg/day, mean maximum dose = 66.7 mg) in 18 children and adolescents also showed a less robust response than in adults [183]. There were no differences between the active drug and placebo groups on the primary and secondary outcome measures. However, 8 of the 18 (44 %) children were noted to exhibit a partial or complete response based on the intent-to-treat analysis. Half of the children exhibited agitation, akathisia, or behavioral activation; three dropped out due to severe symptoms.

Unlike the findings from the fluvoxamine studies, data on fluoxetine indicate comparable responses in both adults and children. In a pediatric double-blind study ($n = 45$), low-dose fluoxetine (mean dose 9.9 mg/day) was superior to placebo in reducing repetitive behaviors [175]. Side effects were comparable between the two groups. Similarly, a recent double-blind study in adults with ASD ($n = 37$) showed that fluoxetine (mean dose 64.8 mg/day) significantly decreased repetitive behaviors compared to placebo [184].

There is one open-label trial of escitalopram (mean dose 11.1 mg) that showed some improvement in stereotypies, as well as irritability and hyperactivity, in 28 children with ASD. Only five children tolerated the highest possible dose of escitalopram (20 mg) without experiencing side effects. Dose-related side effects emerged in 18 subjects and included irritability ($n = 7$), hyperactivity ($n = 6$), or both ($n = 5$) [185].

Collectively, these data indicate that the SSRIs work differently in children, adolescents, and adults with ASD. Children with ASD benefit from lower doses of medications when compared to doses given to typically children with anxiety disorders and to adults with ASD and anxiety or repetitive behaviors. Moreover, children with ASD are more susceptible to side effects such as behavioral activation.

Other Medications

Several other medications have been tested in either placebo-controlled or open-label trials for the treatment of anxiety and repetitive behaviors. First, two atypical antipsychotics, risperidone and aripiprazole, which are FDA approved for the treatment of irritability in ASD, both have beneficial effects on reducing stereotypies. Findings from the Research Units of Pediatric Psychopharmacology's multisite double-blind placebo-controlled trial of risperidone (0.5–3.5 mg/day) in 101 children and adolescents with ASD showed a reduction in stereotypic behavior, among other symptoms, in the active drug compared to placebo group [186]. Weight gain (2.7 ± 2.9 kg in 8 weeks), fatigue, and drowsiness were more prevalent in the active drug versus placebo group. Two double-blind controlled trials of aripiprazole (Marcus et al. [187]: $n = 218$, 5–15 mg/day; Owen et al. [188]: $n = 98$, 5–15 mg/day) showed a significant reduction in stereotypies compared to those receiving placebo [187, 188]. Aripiprazole resulted in less weight gain than risperidone (approximately 1.3 kg over 8 weeks in Marcus et al. [187]; 2.0 kg over 8 weeks in Owen et al. [188]).

Second, there is one open-label trial of buspirone (mean dose 29.3 mg/day) that demonstrated a moderate to significant reduction in anxiety and irritability in 16 of 22 children with ASD [189]. Buspirone was well tolerated except by one child who exhibited oral-lingual dyskinesia, which resolved after the drug was discontinued.

Third, clomipramine may be effective in reducing repetitive behavior. A double-blind placebo-controlled study of 24 children and adolescents with ASD indicated that clomipramine (mean dose 152 mg/day) was moderately effective in reducing anger and compulsive behaviors compared to either desipramine or placebo [190]. A later double-blind placebo-controlled study in adults found that clomipramine was superior to placebo in reducing stereotypies and irritability [191]. Side effects of clomipramine in these studies included tachycardia, fatigue, and tremor [190, 191].

Fourth, in a double-blind, placebo-controlled study of 13 individuals with ASD, Divalproex (mean dose 822.92 mg/day) was effective in improving repetitive behaviors. Divalproex was well tolerated, with no subjects dropping out due to adverse events [192].

Finally, atypical antidepressants have been examined in open-label trials. In an open-label retrospective study of 10 youth and young adults, venlafaxine (mean dose 24.4 mg/day) was beneficial in reducing repetitive behaviors, ADHD symptoms, and social deficits [193]. Similarly, mirtazapine (30.3 mg/day) reduced anxiety, maladaptive behaviors, and irritability in an open-label naturalistic study in 26 youth and young adults with ASD [194].

Case Follow-Up

Case 1: Before starting treatment, a behavioral avoidance task is done with Jessica. It reveals that she is unable to approach a live dog behind a fence from 50 feet. Using this benchmark at a starting point, a graduated hierarchy is developed to expose Jessica to the dog by slowly and systematically fading the distance between her and the dog 5 feet at a time. Her preferences are assessed in order to identify potential rewards for following the steps of the hierarchy. For the first step of the hierarchy, a marker is placed at 45 feet from the dog and moved along the steps of the hierarchy when Jessica is successful. For each step, she is prompted to approach the marker and, if she is successful, she is allowed to play with her preferred toys at that distance. After systematically working through the hierarchy, Jessica is successfully able to touch her neighbor's dog briefly and no longer tries to run away when leaving for school in the morning.

Case 2: After completing the assessment, Danny begins individual therapy sessions with his mother. An individualized, manual-based treatment plan is created that includes both child-focused and parent-focused components. During the first few sessions, Danny is introduced to the visual stimulus

of a "fear thermometer" to express his level of fear in different situations. He is also taught coping skills such as behavioral relaxation and "talking back to the fear monster" using social stories and picture schedules. Concurrent with this, his mother meets with the therapist to receive psychoeducation on the nature of anxiety and phobias. Using the fear thermometer, Danny and his mother assist the therapist with creating a hierarchy. During therapy and for homework assignments, Danny and his mother participate in the graduated exposure sessions. Danny receives rewards for using his fear thermometer and coping skills. By the end of therapy, Danny is able to go out with his parents without his teddy bear and is able to briefly approach peers at school.

Summary

Review of the existing literature suggests that many of the behavioral assessment strategies traditionally employed with non-ASD populations may be applicable to individuals with ASD, despite the communication deficits and problems with emotion recognition that may make self-report limited or entirely unavailable. Direct behavioral observation via BATs and behavioral monitoring in natural settings may be the primary sources of information during both the assessment and treatment evaluation phases. Treatment should be individualized based on the characteristics and functioning level of the individual. Behavioral treatment procedures consisting of graduated exposure and reinforcement can be used across the spectrum. Data on modified CBT with adolescents with HFA is promising. Pharmacological trials focus primarily on treatment of repetitive behaviors rather than DSM-IV anxiety disorders; these data show differential responses across medications and age groups. Despite significant gaps in the literature, research conducted thus far is sufficient to guide clinicians on how to proceed clinically with assessment and treatment of anxiety in individuals with ASD. Nevertheless, additional research designed to examine the presence of other types of anxiety disorders, to develop additional assessment strategies, and to further examine treatment efficacy for anxiety in individuals with ASD is needed.

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