Koraly Pérez-Edgar · Nathan A. Fox
Editors

Behavioral Inhibition

Integrating Theory, Research, and Clinical Perspectives

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KPE and NAF:
To Jerry Kagan, our mentor, colleague, and friend for these many years.

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Thank you to the authors. They have taken the time to contribute thoughtful and insightful work illustrating the diversity of thinking in behavioral inhibition research. Thank you also to the hundreds of families who have dedicated countless hours to the work and science reflected in this volume.

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The History and Theory of Behavioral Inhibition

Jerome Kagan

Abstract This chapter summarizes the events that led to the concepts of behavioral inhibition (BI) as well as high and low reactive infants. It argues for the need to gather multiple measures and search for patterns that represent categories of individuals rather than treat all measures as reflections of continuous traits. The chapter suggests that infants born with a high reactive temperamental bias are most likely to display inhibited behavior in the toddler years, but with development, many are able to suppress this profile even though they experience an uncomfortable tension in unfamiliar situations. The feeling of tension renders those who were high reactive infants vulnerable to frequent bouts of guilt or shame and, in some, the symptoms of anxiety or depression.

The History and Theory of Behavioral Inhibition

Changes in the balance between gathering evidence on a puzzling phenomenon and testing theoretical predictions often follow an unexpected observation produced by a novel methodology or an observation from a previously untapped source of information that challenges existing understanding. In all disciplines, however, a major theoretical advance usually requires a rich collection of reliable data before imaginative minds can invent a more comprehensive narrative.

Johannes Kepler needed Tycho Brahe's large corpus of observations in order to replace the belief in circular planetary orbits with elliptical ones. Crick and Watson might not have arrived at their remarkable insight if other investigators had not first discovered the equal ratios of adenine and thymine, on the one hand, and guanine and cytosine on the other, and Rosalind Franklin had not taken a photo of her X-ray crystallography image of the wet form of the DNA molecule.

A majority of nineteenth-century scientists interested in psychological phenomena were Baconian empiricists rather than a priori theorists. A major change in

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research tactics occurred in the twentieth century following the bold theoretical statements of Freud, Watson, and their followers. By the 1930s, a large number of academic psychologists were testing the validity of a prediction from one of these theoretical systems. Recognition of the flaws in both theories, by the 1960s, led to a brief interval when investigators were wary of premature predictions from a priori concepts that had a weak foundation in evidence. But this interlude did not last very long because most psychologists are friendlier to research that attempts to affirm an a priori hypothesis than to studies that probe the properties of, and cascades that lead to, a reliable phenomenon. A large proportion of contemporary psychologists perform experiments that evaluate the theoretical utility of an abstract construct that is silent on the properties of the agent, the specific response quantified, and the setting. The concepts anxiety, intelligence, regulation, aggression, and stress are examples.

I have always been suspicious of abstract words that are presumed to name natural kinds and friendly to studying puzzling phenomena of potentially theoretical significance that were amenable to study with available methods, while avoiding Francis Galton's error of assuming that the observations recorded are sensitive indexes of the abstract concept imposed on the evidence. My loyalty to these criteria explains the invention of the concept of behavioral inhibition, or BI.

Years of observing healthy children from affectionate families in diverse contexts persuaded me that some children inherited a temperamental bias to react to harmless, unexpected, or unfamiliar events with excessive caution. I often brooded on the evidence from a longitudinal study of midwestern individuals born during the early decades of the last century, which revealed that the small group of children who displayed the behaviors we now call behavioral inhibition during their first 3 years retained subtle properties of this trait in adulthood (Kagan & Moss, 1962). Other investigators had anticipated the variation in children's responses to unfamiliar events (Arsenian, 1943; Bronson, 1970; Thomas, Chess, Birch, & Hertzig, 1960). In addition, similar differences have been observed within many species (Barnard et al., 2016). Although I have summarized the history of the research on behavioral inhibition in my laboratory in many places (Kagan, 1994; Kagan & Fox, 2006; Kagan & Snidman, 2004; Kagan, Snidman, Kahn, & Towsley, 2007), a brief synopsis is relevant for the readers of this volume.

The Beginning

Cynthia García-Coll conducted the initial study in the late 1970s for her dissertation. Because obvious signs of withdrawal or approach to a variety of harmless, unfamiliar events do not appear until the second year, Cynthia recruited 21-month-old Caucasian children for her sample. The ethnic restriction was necessary because we knew that the major ethnic groups differed in genetic alleles that might affect the behaviors of interest. For example, East Asians are more likely than Africans and Caucasians to have many CAG repeats in the gene for the androgen receptor, which results in a less sensitive receptor (Chong, Uhart, McCaul, Johnson, & Wand, 2008;

Eyre, Fisher, Smith, Wagemakers, & Matyka, 2013; Hill et al., 2015; Polimanti, Piacentini, Manfellotto, & Fuciarelli, 2012). East Asian populations are more likely than Europeans to possess the short allele in the promoter region of the gene for the serotonin transporter receptor, which could affect the level of arousal to novelty (Gelernter, Cubella, Kidd, Pakstis, & Kidd, 1999). Asians are also less likely than Caucasians to possess the GG polymorphism in the third intron of the gene for the oxytocin receptor (Gong et al., 2017). Finally, Caucasians with the GG polymorphism report being more empathic than those with the AA allele (Tost et al., 2010).

A longitudinal study of Chinese-American and European-American infants from Boston attending a day care center or raised only at home from 3 to 29 months supported the expectation of ethnic differences in behavior. The Chinese-American infants had less variable heart rates during every assessment, stayed closer to their mother in unfamiliar settings, and were more likely to cry to temporary separation from the mother (Kagan, Kearsley, & Zelazo, 1978). Four-month-old Chinese infants living in Beijing showed less motor movement and less crying to unfamiliar events than Caucasian infants from Boston or Dublin (Kagan et al., 1994). Cindy Liu has unpublished data revealing that Chinese-American 4-month-olds are less likely to cry to the unexpected appearance of unfamiliar events than European-American infants.

It is relevant that all the events García-Coll classified as unfamiliar had features that engaged the child's knowledge. Many studies have demonstrated that unexpected events that share no features with a person's acquired representations evoke a brief saccade but do not recruit prolonged attention or a large N400 waveform in the EEG (Kagan, 1970; Manfredi, Cohn, & Kutas, 2017). There is an inverted U-shaped relation between the power of an event to recruit focused attention and the magnitude of its degree of discrepancy from the agent's expectations or knowledge.

Cynthia also decided to observe children directly rather than rely on parental reports because the literature implied that the relation between the two sources of evidence ranged from poor to modest. More recent data support that belief (Bishop, Spence, & Mc Donald, 2003; Saudino, Wertz, Gagne, & Chawla, 2004; Smith et al., 2012). Evidence from the Colorado twin study affirms the weak relation between the two sources of evidence. A sample of more than 300 MZ and DZ twins was observed in a laboratory on 4 occasions (at 14, 20, 24, and 36 months), and parents rated their children for inhibited behavior at the same 4 ages. The relations between the ratings and observed behavioral inhibition hovered around the modest value of 0.3 (Saudino & Cherny, 2001).

These facts are not surprising. A parent asked to judge her child's inhibited behaviors cannot avoid the influence represented by her idiosyncratic comparisons with the child's recent behavior as well as the behaviors of siblings and children in the neighborhood. Parents typically award greater weight to behaviors that are both more intense and less frequent, such as crying to a large animal or a thunder storm, than to more subtle, but more frequent, occasions of hesitation before approaching a safe, but unfamiliar, object or person. Parental evaluations are also influenced by the contexts in which they observe their child. The context is usually encountered with strangers in the home or neighborhood. That is why behaviorally inhibited children are most often described as shy. In addition, mothers vary in their interpretation of

the sentences describing the traits they are asked to rate as a function of their personality or social class. Less well-educated mothers on smaller incomes tend to rate their young children as more emotional and aggressive than observations reveal (Abulizi, Pryor, Michel, Melchior, van der Waerden, & EDEN Mother-Child Cohort Study Group, 2017). Parents can have different understandings of words such as fearful, cautious, or sensitive in sentences that ask "Is your child……?".

By contrast, the psychologists who base the classification of behavioral inhibition on contemporary behaviors in one or more standardized settings typically rely on the frequency of withdrawal, prolonged hesitation, or refusal to approach an unfamiliar object or person in a laboratory and compare each child's behaviors with those of others in the sample. Each measure, whether parent report or behavioral observations, has advantages and disadvantages. However, since one is not a proxy for the other, the validity of every conclusion about behavioral inhibition depends on the source of evidence. Estimates of a child's memory provide an analogy. The number of digits a school-age child can remember is regarded as an index of short-term memory. I suspect that this value is unrelated to a parent's rating of her child's memory ability. Therefore, the two measures should not be combined to arrive at a more valid index of memorial talent.

Statements that refer to the same observation can have different validities if they are based on different evidence. A congenitally blind person who has never seen snow nor informed about its color could state that "snow is white." The validity of the statement is tempered by her lack of sight and by her explanation that she guessed the white color from its cold temperature. Clearly this statement differs from the validity of the same statement by a sighted adult.

Linda Bartoshuk (2014) asked adults who possessed different numbers of taste buds for sweetness on the tongue to rate the sweetness of varied liquids on a scale that went from "not sweet" to "very sweet." The results revealed no relation between the ratings and the number of taste buds the subject possessed. Because that observation is counter-intuitive, she introduced a different measure of perceived sweetness. When the adults adjusted the intensity of an auditory stimulus so that it matched the intensity of sweetness, there was a positive relation between number of taste buds and perceived sweetness. One interpretation is that the sounds, like the liquid, evoked a feeling that the words sweet or not sweet did not. Thus, the validity of the statement that the number of taste buds for sweetness influences a person's sensation of sweetness depends on the measure. The same principle applies to conclusions about behavioral inhibition.

The Invention of Behavioral Inhibition

Cynthia presented a large number of Caucasian, 21-month-olds with a variety of unfamiliar, but harmless, events in an unfamiliar laboratory setting and coded from video records the frequency of hesitation to approach, withdrawal, and crying. About one-third of the sample showed consistent signs of caution to,

and withdrawal from, many incentives and preserved this behavioral bias when observed several weeks later. An equal proportion of children displayed the opposite pattern of a rapid approach to the novel events. The former were called behaviorally inhibited; the latter were classified as uninhibited (García-Coll, Kagan, & Reznick, 1984). Observations of 22 behaviorally inhibited and 17 uninhibited children from Cynthia's sample 40 months later, during their first week of kindergarten, revealed that the behaviorally inhibited children were more likely to play alone and stare at another child or the teacher and less likely to laugh (Gersten, 1989).

Nancy Snidman replicated Cynthia's finding with 31-month-old children who were observed with an unfamiliar peer of the same age and sex in a laboratory playroom. Observations of both samples at 5 and 7 years revealed modest, but significant, preservation of behavioral inhibition behaviors. In addition, the consistently behaviorally inhibited children were likely to possess high values on one or more biological measures that included a higher and less variable heart rate, larger pupillary dilation during a cognitive task, less variability in the pitch periods of vocal utterances, and higher concentrations of salivary cortisol (Kagan, Reznick, & Snidman, 1987; Kagan, Reznick, & Snidman, 1988). This evidence led to the speculation that the behavioral inhibition behavioral pattern was the product of an inherited biology (Kagan, 1994). However, the probability that a child who showed a behaviorally inhibited pattern at 21 or 31 months would also display a behavioral inhibition profile at age 7 which was lower than the probability of exhibiting the extreme sociability, rapid approach to novelty, talkativeness, and emotional exuberance of a typical uninhibited child.

We did not write that behaviorally inhibited children possessed a fearful temperament because we appreciated that the term fear could refer to a verbal report, behavior, or biological measure. Further, this word was being used to describe a rat who did not explore a brightly lit alley, a monkey who became immobile upon seeing a human approach the cage, a college student who showed a potentiated eye blink startled to a loud sound while looking at unpleasant pictures, a verbal report of reluctance to attend parties, a rise in salivary cortisol during the Trier Social Stress Test, a less alpha-band power in the right than the left frontal lobe, or a large BOLD signal to the amygdala to unpleasant pictures. The heterogeneity of the referents for fear led LeDoux (2014) to the conclusion that this term should be restricted to a person's conscious state.

When we wrote that behavioral inhibition was modestly preserved from the second to the eighth year, we stipulated that the stability applied to behaviors displayed by predominantly middle-class, Caucasian children from secure families, when presented with unexpected events. We did not assume that the same conclusion applied to parental or teacher reports or adult memories of childhood traits but were receptive to evidence that extended our conclusions to these other sources of evidence.

The behaviors that define behavioral inhibition can be the product of experiences that are independent of a temperamental bias. Because the concept of behavioral inhibition was based on behaviors observed during the early months of the second year, it is reasonable to assume that experiences in and outside the family, as well prenatal events, could produce an inhibited behavioral pattern that was not the product of a temperamental bias. Rubin has pointed out that some children in a social

situation with peers prefer to play alone but do not show withdrawal to novelty. These children should not be classified as behaviorally inhibited (Rubin, Hastings, Stewart, Henderson, & Chen, 1997). The heterogeneity of the causal cascades that lead to behavioral inhibition motivated a search for behaviors in young infants that were a result of the same biology that mediated behaviorally inhibited responses.

High and Low Reactive Infants

Initially, we did not know the infant responses that might be analogues of behavioral inhibition. Fortunately, we had gathered data on a sample of 4-month-old infants exposed to unfamiliar events. I took the video records to a quiet room and watched them with a mental set free of a priori prejudices. The behavioral profiles of the first 18 infants were similar and matched expectations. Therefore, they were uninformative. But the next infant was different. To repeated presentations of a colorful mobile moving slowly in front of her face, she thrashed her arms and legs, cried, and on several occasions arched her back. This last response is significant because it is mediated by a circuit from the central nucleus of the amygdala to the central gray. The unexpected behavior of this infant was the origin of the concept of high reactivity.

The biologist Stuart Firestein (2016) favored this route to discovery over trying to prove a favored hypothesis. I recall a paper by Torsten Wiesel in which he admitted that he and David Hubel had no idea what they would observe when they measured the responses of neurons in a cat's primary visual cortex to simple visual stimuli. Their fishing expedition led eventually to discoveries that earned them a Nobel Prize.

Research with animals provided clues to an explanation of this infant's behavior. Many laboratories had confirmed that the amygdala is excited by unexpected events, whether threatening or rewarding. The unexpected onset or offset of an event, pleasant or unpleasant, is usually followed by an increase in dopamine and/or norepinephrine which affects the amygdala (Holly & Miczek, 2016; Schultz, 2015). Further, the amygdala projects to targets that mediate bodily movement, arches of the back, distress cries, and the cardiovascular system (Amaral & Adolphs, 2016; Herry et al., 2007; Strange & Dolan, 2001).

A small proportion of domestic cats who do not approach or attack rats display heightened excitability in a circuit from the basomedial amygdala to the ventromedial hypothalamus which, in turn, projects to the neurons in the central gray that mediate arches of the back (Adamec & Stark-Adamec, 1989). Human infants display limb movements, distress cries, and back arches. Hence, we entertained the possibility that infants who became motorically aroused and distressed by unexpected events possessed a temperamental bias we called high reactive that predisposed them to display a behavioral inhibition profile in the second year. Infants who were minimally active and rarely cried were classified as low reactive and were expected to become uninhibited in the second year.

Our intuition was confirmed. The behaviors of over 500 4-month-old healthy, Caucasian infants to unfamiliar visual, auditory, or olfactory events revealed that

about 20% showed the combination of vigorous motor activity and distress cries that define the high reactive infant and 40% displayed the opposite pattern characteristic of the low reactive infant. High reactive infants from both the Kagan and the Fox laboratories were more likely than low reactive infants to display inhibited behavior at 14 months (Fox, Snidman, Haas, Degnan, & Kagan, 2015). The details of our continued study of our groups of high and low reactive infants from 4 months to 18 years are summarized in many books and papers but especially in Kagan (1994), Kagan and Snidman (2004), and Kagan et al. (2007). Fox and his students, as well as the authors of the chapters in this volume, have extended our understanding of behavioral inhibition or a high reactive temperament in a major way (Calkins & Fox, 1992; Fox, Henderson, Rubin, Calkins, & Schmidt, 2001).

Current Understanding

Our current view is that the 4-month-old infants classified as high reactive, based on a combination of frequent motor movement and crying to unfamiliar events, inherit a neurochemistry, not yet known, that lowers the threshold of responsivity of the amygdala, and perhaps the hippocampus as well, to unexpected or unfamiliar events. Because the amygdala sends projections to many bodily targets, high reactive children and adults are likely to experience an unexpected rise in heart rate or tightening of muscles that they cannot explain. The fact that infants who would be classified as high reactive at 4 months had higher than average heart rates and greater sympathetic tone on the cardiovascular system 2 weeks before delivery, as well as during sleep at 2 and 16 weeks postnatally, supports this suggestion (Snidman, Kagan, Riordan, & Shannon, 1995).

Children become consciously aware of the feelings that originate in the cardiovascular system, muscles, and gut during the second year. Their interpretation of the feeling depends on its quality and the setting. If the feeling occurs when the child is confronting a large dog or hearing a loud sound, the child is likely to interpret the feeling as fear of harm. Because 2-year-olds are not yet capable of controlling all the actions prompted by this feeling, they show the behaviors that define behavioral inhibition.

But with each passing year, these children become better able to control behavioral inhibition responses. Only 46% of high reactive 4-year-olds interacting with two unfamiliar peers of the same age and gender were obviously behaviorally inhibited, compared with 10% of low reactive peers (Kagan, Snidman, & Arcus, 1998). Only one in five high reactive children displayed a consistent behavioral inhibition profile on four assessments from 14 months to 7 years. Many 15- and 18-year-olds who had been high reactive infants and had behavioral inhibition in the second year were no longer shy with strangers. One adolescent boy who was a high reactive infant who showed inhibited behavior in the second year wrote an essay describing how he successfully copes with his feelings: “I have found that the manifestation of my anxiety can be overcome by using simple mind over matter techniques. …..Because I now understand my predisposition towards anxiety, I can talk myself out of simple fears.”

It is likely that parental practices contribute to the variation in inhibited behavior among high reactive infants. Doreen Arcus's evidence supports that suggestion. She analyzed observations gathered in the homes of a sample of high reactive and other infants on five occasions between 5 and 13 months. The high reactive infants raised by mothers who picked them up immediately when they cried were reluctant to yell when they were in danger and tried to protect them from situations that might evoke fear displayed more inhibited behavior at 14 months than high reactive infants whose mothers were less protective (Arcus, 1991).

Although high reactive infants become better able to suppress behaviorally inhibited responses as they develop, many continue to experience a vulnerability to the tense feeling tone that is a component of this temperamental bias. A proportion of high reactive 18-year-olds who did not display an obvious behavioral inhibition persona showed signs of an excitable amygdala (Schwartz et al., 2012), as well as a thicker cortex in a small area in the ventromedial prefrontal cortex of the right hemisphere that projects to the neurons in the lateral periaqueductal gray that mediate arches of the back (Schwartz et al., 2010). This biological feature renders these youths sensitive to uncertainty. Some high reactive adolescents confessed to an uncomfortable tension whenever they were uncertain of the future. One 15-year-old said that he feels "nervous before any vacation because I don't know what will happen."

The Need for Patterns of Measures

The evidence implies that future studies of behavioral inhibition should add biological measures that might separate children with a behaviorally inhibited profile into those who possess a high reactive temperament and those whose behavioral inhibition pattern is primarily the result of experience. The 5-year-olds from the García-Coll and Snidman samples who preserved a behavioral inhibition profile from the 2nd to the 5th year had high values on several biological measures that were absent in children who did not preserve their earlier behavioral inhibition pattern (Kagan et al., 1987).

The measures that show promise of being informative, when added to inhibited behavior, include a high and minimally variable heart rate at rest, a large wave 5 from the inferior colliculus in the brain stem which evoked potential to a series of clicks, a right frontal activation in the resting EEG, a large and shallow rate of habituation of the P3a or N400 wave form to unfamiliar pictures, an activity in the corrugator and infrahyoid muscles to novelty, a large increase in pupillary dilation to challenge, and a large BOLD signal to the amygdala to novelty (Baas, Milstein, Donlevy, & Grillon, 2006; Dietrich & Verdolini Abbott, 2012; Hatfield, Cotlam, & Fowler, 1986; Kagan & Snidman, 2004; Kagan, Snidman, Mc Manis, Woodward, & Hardway, 2002; Schmidt, 2008). Among Caucasian samples, eye and hair color, height and weight, and facial width are also useful variables because high reactive infants who show inhibited behavior are more likely than others to have light blue eyes, a smaller body size, and a narrower face (Kagan & Snidman, 2004).

A behavioral inhibition profile in an older child or adult, without any biological measures, does not guarantee an origin in a high reactive temperamental bias. This claim restates the reasonable assumption that most behaviors are the result of more than one causal cascade. Even a particular level of spiking activity in a collection of neurons can be the result of different inputs to those neurons (Marder, 2015). Suicide, homicide, grade point average, and every DSM-5 diagnosis are heterogeneous categories that must be parsed into subgroups with similar causal cascades. Gathering patterns of measures is one way to accomplish this goal.

Instead of treating a behavioral or biological measure as reflecting a continuous trait, it will prove more fruitful to create categories of people based on their profiles on a pattern of measures (Bergman, 1998). About one in four high reactive infants showed inhibited behavior at 14 months and, at age 11, were reserved with the examiner, reported disliking novel events and crowds, and displayed one or more of the biological signs of an excitable limbic system (right frontal activation, large wave 5, high and minimally variable heart rate, and large N400 to unfamiliar pictures). Not one low reactive infant showed this pattern, and only 5% of high reactive children developed the opposite profile of sociable traits, a preference for new experiences, and a less excitable limbic system. Further, evidence from the Colorado twin study, described earlier, revealed that the heritability of observed behavioral inhibition was higher when the sample was restricted to children whose behavioral inhibition scores were greater than 1 standard deviation from the mean of the entire sample (Manke, Saudino, & Grant, 2001; Robinson, Kagan, Reznick, & Corley, 1992).

The data imply that a high reactive temperamental bias is a better predictor of the traits that will not develop rather than the profile that does emerge. Few adolescents who had been high reactive infants would say to an interviewer, as one low reactive participant did, “Everything is fun.” Nor would many low reactive children report a chronic mood of worry and melancholy. The power of each temperamental bias is to limit the likelihood of acquiring certain traits rather than determine a particular profile in adolescence (Kagan & Snidman, 2004). The evidence invites a conception of high and low reactivity as categories rather than continuous traits (Kagan et al., 1998). This perspective provides a deeper understanding of behavioral inhibition than reporting a correlation of 0.40 between continuous measures of behavioral inhibition at ages 2 and 11 or an effect size of 0.30 based on an ANOVA performed on a single measure that compared behaviorally inhibited children with others.

Susceptibility to Shame or Guilt

The heightened amygdalar excitability of high reactive individuals should be accompanied by a susceptibility to an awareness of an intrusive bodily feeling when the child or adolescent violates a moral standard. The intensity and quality of bodily feeling are partly the result of the brain’s projections to bodily targets whose activity feeds back to the insula and anterior cingulate via fibers that travel the spinothalamic tract or the vagal or glossopharyngeal nerves to the nucleus of the solitary

tract in the medulla (Murphy, Brewer, Catmur, & Bird, 2017). The vagus nerve transmits activity occurring in the heart, lung, and gut; the glossopharyngeal nerve carries inputs from the carotid sinus, which is activated by changes in blood pressure, and the spinothalamic tract brings inputs from the skin to the brain. Because the specific neurons of the insula and cingulate that are activated depend on the particular inputs they receive, the quality of the feeling that pierces consciousness varies with the input pattern. The feeling, however, invites more than one interpretation. Hence, the person relies on thoughts about the immediate past and the setting to decide on the most reasonable interpretation.

A youth who has violated a standard and believes that respected others will entertain demeaning thoughts is likely to interpret an intrusive feeling as shame. If the same adolescent decides that the violation could have been avoided had he or she been more thoughtful, the feeling will invite an interpretation of guilt. If both kinds of feelings occur, a blend of shame and guilt will be reported. However, these words are the person's interpretation of a feeling in a particular context. The same feeling in a different setting is likely to invite a different emotional word.

This suggestion shares features with Lisa Barrett's hypothesis that popular terms for emotions are the brain's constructions (Barrett, 2016). However, I prefer to write that the person, not the brain, constructs the interpretation because the content that emerges depends on a very large number of possible interactions among neuronal profiles that can originate in a dozen sites (Venkatraman, Edlow, & Immordino-Yang, 2017). The interactions among the neuronal profiles of only 6 of 12 activated sites would produce more than a half million possible interactions, none of which can be predicted with confidence from the neural profiles that gave rise to them.

The pattern of swirling water molecules produced by a temporal sequence of six jets of water provides a visual metaphor. The final shape of a protein furnishes another appropriate analogy. Although a specific collection of genes determines the sequence of amino acids that comprise each protein, its final shape, which affects its function, is determined by what happens during a rapid sequence of chemical interactions among atoms as the string of amino acids undergoes the folding process. The final shape is not knowable from the genes that supplied the molecular components of the protein.

Analogously, a person's interpretation of a feeling that emerged from brain profiles triggered by an event in a setting, comprised of inputs from body to brain followed by outputs from brain to body and modulatory processes, is a function of interactions among neural patterns that are not predictable, at least at present, from the neuronal profiles evoked by the event. For that reason, I prefer to write that the person imposes an interpretation on his or her feelings in a setting.

Eleven-year-olds who were high reactive infants told an interviewer that they regularly felt guilty whenever a parent told them they had done something wrong. Studies by Kochanska, Gross, Lin, and Nichols (2002) support the relation between a behavioral inhibition profile and a susceptibility to self-blame. Women who were blind to the history of each adolescent interviewed the 15-year-olds in our sample in their home. Those who had been high reactive as infants reported more frequent and more intense bouts of guilt than low reactive infants. One of four high reactive

infants said that two of their most salient traits were excessive seriousness and thinking too much about their behaviors. A larger proportion of high than low reactive infants were religious and felt their faith helped them control bouts of uncertainty (Kagan & Snidman, 2004).

These observations imply that children who were high reactive should be at a higher risk for anxiety or depressive disorders because chronic guilt or shame can provoke these symptoms. A clinical psychologist who was blind to the history of each adolescent administered a standard psychiatric interview to high and low reactive participants when they were 18 years old. Youth who had been high reactive infants were far more likely than those who had been low reactive to meet criteria for a diagnosis of depression, social anxiety, or general anxiety disorder. Further, 90% of the high reactive participants with one or more of these diagnoses had been behaviorally inhibited in the 2nd year and showed frequent arches of the back at 4 months. Not one of the smaller number of low reactive participants who received one of these diagnoses showed a behavioral inhibition profile or arches (unpublished data).

Circumstances Select Symptoms

Each person's biology and life history create diverse vulnerabilities that increase the probability of developing habits or emotions that make it difficult for the person to honor the demands of their particular society. But the actualization of a maladaptive outcome in vulnerable individuals depends in a major way on the person's current life circumstances. There would be fewer cases of ADHD in children who possessed a compromise in attentional processes if they lived in a society with no schools. The dramatic rise in addiction to opioids required the easy availability of opioid pain killers. I suggest that the high incidence of social anxiety disorder is due partly to the fact that many adults are living in a large city far from family and childhood friends. If comparable data were available for eighteenth-century Americans, I suspect that the frequency of this profile would be far lower. The high reactive youth who received a diagnosis of depression, general anxiety, or social anxiety disorder were coping with life conditions that triggered these symptoms. A high reactive 18-year-old who never left the small town in which she grew up in would be less likely to develop social anxiety than her identical twin sister who left home at age 17 to attend a large university in a big city.

The results of a 30-year longitudinal study of three generations of depressed and healthy adults are relevant. The members of the third generation who had a mental illness, and, in addition, had a depressed parent and grandparent, displayed a variety of symptoms other than depression (Weissman et al., 2016). A similar result emerged from a study of more than 800,000 Danes. When both a parent and his or her adolescent had a psychiatric diagnosis, the youth's diagnostic category was frequently different from that of the parent because the two probands had to cope with different circumstances (Dean, Stevens, & Mortensen, 2010). The popular strategy of searching for interactions between biological and experiential variables with respect to an

outcome ignores the person's current life conditions. An adult with the short allele in the promoter region of the serotonin transporter gene who had to cope with a bitter divorce and few friends during the childhood years, but managed to combine a satisfying career with a happy marriage, is unlikely to develop depression.

Summary

High and low reactivity appear to be temperamental categories, rather than continuous dimensions, generated by a neurochemistry that remains unknown. It is possible that these two categories are the products of different genes. Although these genes remain unknown, there are reasons to assume that the genes influencing the migration of the neural crest cells to their final form as melanocytes, autonomic ganglia, or bony tissue of the skull and face contribute to these categories (Anderson, 1993).

Because a behavioral inhibition profile can be the result of distinct causal cascades, it will be necessary to gather a pattern of measures, including biological variables, to detect those whose behavioral inhibition profile has a temperamental origin. There is at present no pattern of measures that guarantees this separation. Two popular premises are slowing progress. One is the assumption that the underlying trait of behavioral inhibition or reactivity is continuous. The second is the assumption that verbal reports are valid proxies for behavioral observations in varied contexts.

The neurochemistry that is the foundation of the high reactive temperamental bias is more likely to be conserved than the profile of observable behaviors. These facts imply that the biological bases of high reactivity can be likened to the disappearance of a drop of black ink in a glass of glycerine that has been stirred for several minutes. This conception is reminiscent of Carl Jung's contrast between the invisible anima or animus, on the one hand, and the observable traits that comprise the person's persona. The former, which cannot be easily inferred from the latter, can be likened to the invisibility of the tightly woven black and white threads comprising a gray cloth.

References

Abulizi, X., Pryor, L., Michel, G., Melchior, M., van der Waerden, J., & EDEN Mother-Child Cohort Study Group. (2017). Temperament in infancy and behavioral and emotional problems at age 5.5. *PLoS One, 12*, e0171971.

Adamec, R. E., & Stark-Adamec, C. (1989). Behavioral inhibition and anxiety. In J. S. Reznick (Ed.), *Perspectives on behavioral inhibition* (pp. 93–124). Chicago, IL: University of Chicago Press.

Amaral, D. G., & Adolphs, R. (Eds.). (2016). *Living without an Amygdala*. New York, NY: The Guilford Press.

Anderson, D. J. (1993). Molecular control of cell fate in the neural crest. *Annual Review of Neuroscience, 16*, 129–158.

Arcus, D. (1991). *Experiential modification of a temperamental bias in inhibited and uninhibited children*. Unpublished doctoral dissertation, Harvard University.

Arsenian, J. M. (1943). Young children in an insecure situation. *Journal of Abnormal and Social Psychology, 38*, 225–249.

Baas, J. M., Milstein, J., Donlevy, M., & Grillon, C. (2006). Brainstem correlates of defensive states in humans. *Biological Psychiatry, 59*, 588–593.

Barnard, S., Marshall-Pescina, S., Passalacqua, C., Beghelli, V., Capra, A., Normando, S., … Valsecchi, P. (2016). Does subjective rating reflect behavioural coding? Personality in 2 month-old dog puppies. *PLoS One, 11*, e0149831.

Barrett, L. F. (2016). The theory of constructed emotion. *Social Cognitive and Affective Neuroscience, 12*, 1–23.

Bartoshuk, L. (2014). The measurement of pleasure and pain. *Perspectives on Psychological Science, 9*, 91–93.

Bergman, L. R. (1998). A pattern-oriented approach to studying individual development. In R. B. Cairns, L. R. Bergman, & J. Kagan (Eds.), *Methods and models for studying the individual* (pp. 83–121). Thousand Oaks, CA: Sage.

Bishop, G., Spence, S. H., & Mc Donald, C. (2003). Can parents and teachers provide a reliable and valid report of behavioral inhibition? *Child Development, 74*, 1899–1917.

Bronson, G. W. (1970). Fear of visual novelty. *Developmental Psychology, 2*, 33–40.

Calkins, S., & Fox, N. A. (1992). The relations among infant temperament, security of attachment, and behavioral inhibition at 24 months. *Child Development, 63*, 1456–1472.

Chong, R. Y., Uhart, M., McCaul, M. E., Johnson, E., & Wand, G. S. (2008). Whites have a more robust hypothalamic-pituitary adrenal axis response to a psychological stressor than blacks. *Psychoneuroendocrinology, 33*, 246–254.

Dean, K., Stevens, H., & Mortensen, P. B. (2010). Full spectrum of psychiatric outcomes among offspring with parental history of mental disorder. *Archives of General Psychiatry, 67*, 822–829.

Dietrich, M., & Verdolini Abbott, K. (2012). Vocal function in introverts. *Journal of Speech, Language, and Hearing Research, 55*, 973–987.

Eyre, E. L., Fisher, J. P., Smith, E. C., Wagemakers, A. J., & Matyka, K. A. (2013). Ethnicity and long term heart rate variability in children. *Archives of Diseases in Children, 98*, 292–298.

Firestein, S. (2016). *Failure*. New York, NY: Oxford University Press.

Fox, N. A., Henderson, N. A., Rubin, K. H., Calkins, S. D., & Schmidt, L. A. (2001). Continuity and discontinuity of behavioral inhibition and exuberance. *Child Development, 72*, 1–21.

Fox, N. A., Snidman, N., Haas, S. A., Degnan, K. A., & Kagan, J. (2015). The relation between reactivity at 4 months and behavioral inhibition in the second year. *Infancy, 20*, 98–114.

García-Coll, C., Kagan, J., & Reznick, J. S. (1984). Behavioral inhibition in children. *Child Development, 51*, 1005–1009.

Gelernter, J., Cubella, J. F., Kidd, J. R., Pakstis, A. J., & Kidd, K. K. (1999). Population studies of polymorphisms of the serotonin transporter protein gene. *American Journal of Medical Genetics, 88*, 61–66.

Gersten, M. (1989). Behavioral inhibition in the classroom. In J. S. Reznick (Ed.), *Perspectives on Behavioral Inhibition* (pp. 71–91). Chicago, IL: University of Chicago Press.

Gong, P., Fan, H., Liu, J., Yang, X., Zhang, K., & Zhou, X. (2017). Revisiting the impact of OXTR rs53576 on empathy. *Psychoneuroendocrinology, 80*, 131–136.

Hatfield, M. E., Cotlam, G. L., & Fowler, S. C. (1986). Anxiety and striate muscle activation. *Journal of Abnormal Psychology, 95*, 228–236.

Herry, C., Bach, D. R., Esposito, F., Di Salle, F., Perrig, W. J., Scheffler, K., … Seifritz, E. (2007). Processing of temporal unpredictability in human and animal amygdala. *The Journal of Neuroscience, 27*, 5958–5966.

Hill, L. K., Hu, D. D., Koenig, J., Sollers, J. J., Kapuku, G., Wang, X., … Thayer, J. F. (2015). Ethnic differences in resting heart rate variability. *Psychosomatic Medicine, 77*, 16–25.

Holly, E. N., & Miczek, K. A. (2016). Ventral tegmental area dopamine revisited. *Psychopharmacology, 233*, 163–186.

Kagan, J. (1970). The determinants of attention in the infant. *American Scientist, 58*, 298–306.

Kagan, J. (1994). *Galen's prophecy*. New York, NY: Basic Books.

Kagan, J., Arcus, D., Snidman, N., Feng, W. Y., Hendler, J., & Greene, S. (1994). Reactivity in infants: A cross-national comparison. *Developmental Psychology, 30*, 342–345.

Kagan, J., & Fox, N. A. (2006). Biology, culture and temperamental biases. In N. Eisenberg, W. Damon, & R. M. Lerner (Eds.), *Handbook of child psychology* (6th ed., pp. 167–225). New York, NY: John Wiley.

Kagan, J., Kearsley, R. B., & Zelazo, P. R. (1978). *Infancy*. Cambridge, MA: Harvard University Press.

Kagan, J., & Moss, H. A. (1962). *Birth to maturity*. New York, NY: John Wiley.

Kagan, J., Reznick, J. S., & Snidman, N. (1987). The physiology and psychology of behavioral inhibition in children. *Child Development, 58*, 1459–1473.

Kagan, J., Reznick, J. S. & Snidman, N. (1988). Biological bases of childhood shyness. *Journal Science, 240*, 167–171.

Kagan, J., & Snidman, N. (2004). *The long shadow of temperament*. Cambridge, MA: Harvard University Press.

Kagan, J., Snidman, N., & Arcus, D. (1998). The value of extreme groups. In R. B. Cairns, L. R. Bergman, & J. Kagan (Eds.), *Methods and models for studying the individual* (pp. 65–80). Thousand Oaks, CA: Sage.

Kagan, J., Snidman, N., Kahn, V., & Towsley, S. (2007). The preservation of two infant temperaments into adolescence. *Monographs of the Society for Research for Child Development, 72*, 1–75.

Kagan, J., Snidman, N., Mc Manis, M., Woodward, S., & Hardway, C. (2002). One measure, one meaning; multiple measures, clearer meaning. *Development and Psychopathology, 14*, 463–475.

Kochanska, G., Gross, J. N., Lin, M. H., & Nichols, K. E. (2002). Guilt in young children. *Child Development, 73*, 461–482.

LeDoux, J. E. (2014). Coming to terms with fear. *Proceedings of the National Academy of Sciences, 111*, 2871–2878.

Manfredi, M., Cohn, N., & Kutas, M. (2017). When a hit sounds like a kiss. *Brain and Language, 169*, 28–38.

Manke, B., Saudino, K. J., & Grant, J. D. (2001). Extremes analyses of observed temperament dimensions. In R. N. Emde & J. K. Hewitt (Eds.), *Infancy to early childhood* (pp. 52–72). New York, NY: Oxford University Press.

Marder, E. (2015). Understanding brains. *PLoS Biology, 13*, e1002147.

Murphy, J., Brewer, R., Catmur, C., & Bird, G. (2017). Interoception and psychopathology. *Developmental Cognitive Neuroscience, 23*, 45–56.

Polimanti, R., Piacentini, S., Manfellotto, D., & Fuciarelli, M. (2012). Human genetic variation of CYP450 superfamily. *Pharmacogenomics, 13*, 1951–1960.

Robinson, J. L., Kagan, J., Reznick, J. S., & Corley, R. (1992). The heritability of inhibited and uninhibited behavior: A twin study. *Developmental Psychology, 28*, 1030–1037.

Rubin, K. H., Hastings, P. D., Stewart, S. L., Henderson, H. A., & Chen, X. (1997). The consistency and concomitants of inhibition. *Child Development, 68*, 467–483.

Saudino, K. J., & Cherny, S. S. (2001). Sources of continuity and change in observed temperament. In R. N. Emde & J. K. Hewitt (Eds.), *Infancy to early childhood* (pp. 89–109). New York, NY: Oxford University Press.

Saudino, K. J., Wertz, A. E., Gagne, J. R., & Chawla, S. (2004). Night and day: Are siblings as different in temperament as parents say they are? *Journal of Personality and Social Psychology, 87*, 698–706.

Schmidt, L. A. (2008). Patterns of second-by-second resting frontal brain (EEG) asymmetry and their relation to heart rate and temperament in 9-month old human infants. *Personality and Individual Differences, 44*, 216–225.

Schultz, W. (2015). Neural reward and decision signals. *Physiological Reviews, 95*, 853–951.

Schwartz, C. E., Kunwar, P. S., Greve, D. N., Kagan, J., Snidman, N., & Bloch, R. B. (2012). A phenotype of early infancy predicts reactivity of the amygdala in male adults. *Molecular Psychiatry, 17*, 1042–1050.

Schwartz, C. E., Kunwar, P. S., Greve, D. N., Moran, L. R., Viner, J. C., Covino, J. M., … Wallace, S. R. (2010). Structural differences in adult orbital and ventromedial prefrontal cortex predicted by infant temperament at 4 months of age. *Archives of General Psychiatry, 67*, 78–84.

Smith, A. K., Rhee, S. H., Corley, R. P., Friedman, N. P., Hewitt, J. K., & Robinson, J. L. (2012). The magnitude of genetic and environmental influences on parental and observational measures of behavioral inhibition and shyness in toddlerhood. *Behavior Genetics, 42*, 764–777.

Snidman, N., Kagan, J., Riordan, L., & Shannon, D. C. (1995). Cardiac function and behavioral reactivity during infancy. *Psychophysiology, 32*, 199–207.

Strange, B. A., & Dolan, R. J. (2001). Adaptive anterior hippocampal responses to oddball stimuli. *Hippocampus, 11*, 690–698.

Thomas, A., Chess, S., Birch, H., & Hertzig, M. E. (1960). A longitudinal study of primary reaction patterns in children. *Comprehensive Psychiatry, 1*, 103–112.

Tost, H., Kolachana, B., Hakimi, S., Lemaitre, H., Verchinski, B. A., Mattay, V. S., … Meyer-Lindenberg, A. (2010). A common allele in the oxytocin receptor gene (OXTR) impacts prosocial temperament and human hypothalamic-limbic structure and function. *Proceedings of the National Academy of Sciences, 107*, 13936–13941.

Venkatraman, A., Edlow, B. L., & Immordino-Yang, M. H. (2017). The brainstem in emotion. *Frontiers in Neuroanatomy, 11*, 15. https://doi.org/10.3389/fnana.2017.00015

Weissman, M. M., Berry, O. O., Warner, V., Gameroff, M. J., Skipper, J., Talati, A., … Wickramaratne, P. (2016). A 30-year study of 3 generations at high and low risk for depression. *JAMA Psychiatry, 73*, 970–977.

Behavioral Inhibition in Nonhuman Primates: The Elephant in the Room

John P. Capitanio

Abstract Behavioral inhibition (BI) refers to a pattern of timidity and avoidance in the face of novel people, objects, or situations. It was a concept originally identified in humans, but there is no a priori reason to assume that it is specific to our species. Here, we examine some of the conceptual and methodological issues associated with studying behavioral inhibition in nonhuman primates and review two sets of studies, those in which behavioral inhibition (or something looking like behavioral inhibition) was *induced* by some manipulation and those in which behavioral inhibition was *naturally occurring* in populations. The review indicates that there is no consensus on how to define this temperament pattern behaviorally in nonhuman primates, and some have used this term inappropriately: "behavioral inhibition" is not the same thing as "inhibition of behavior." We conclude that more attention needs to be paid to the dynamic aspects of behavior (specifically the fact that behavior can show multifinality and equifinality) and to methodological issues, such as those involving reliability and validity. Animal models in general, and primate models in particular, can be extremely valuable in understanding the underlying mechanisms and later health consequences of possessing a behaviorally inhibited phenotype, but their value can be diminished by lack of agreement—the elephant in the room—on how to measure behavioral inhibition in nonhumans.

Behavioral inhibition (BI) refers to a pattern of timidity and avoidance when faced with novel people, objects, or situations. Most often, behavioral inhibition is identified through behavioral tests conducted in the laboratory (e.g., García-Coll, Kagan, & Reznick, 1984), although rating scales, completed by parents or teachers, are also used (e.g., van Brakel & Muris, 2006). Behavioral inhibition is, perhaps, most commonly identified in the second and third years of life, but evidence suggests it is preceded in infancy by a pattern of negative reactivity to novelty—"frequent thrashing of limbs, motor tension in the arms and legs, occasional arching of the back, and

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frequent crying (Kagan, 2012, p. 71).” Kagan (2012) estimates a prevalence of approximately 15–20% for this pattern of negative reactivity among middle-class, European-American infants born at term. Importantly, behavioral inhibition has been linked to later social anxiety (Pérez-Edgar & Guyer, 2014), although evidence suggests that social factors such as parenting style and peer relationships can moderate the relationship between behavioral inhibition and later psychopathology (Frenkel et al., 2015; Williams et al., 2009). Considerably more detail about each of these topics can be found in other chapters in this volume (see the chapter “The Social World of Behaviorally Inhibited Children: A Transactional Account” by Henderson and the chapter “Peer Relations and the Behaviorally Inhibited Child” by Rubin).

Is behavioral inhibition a distinctly human phenomenon? There’s no reason to assume that it is. At its essence, behavioral inhibition is an extreme manifestation of a behavioral strategy that makes adaptive sense. When an individual encounters a novel individual, object, or situation, its choices are largely limited to approaching, withdrawing, or standing one’s ground, each of which may involve varying degrees of affective display. “Standing one’s ground” could take a variety of forms, ranging from preparation for battle, simple vigilance to get more information, or freezing—reducing one’s motor and vocal output in the hope that the novel stimulus (typically an individual in this case, either a conspecific or a potential predator) won’t notice the subject and will move away. Extreme versions of freezing abound in the animal literature and include tonic immobility and thanatosis, both of which involve considerable inhibition of behavior. Assuming, then, that behavioral inhibition is an aspect of an individual’s fear response (and evidence suggests that it is), then individuals that inhibited their behavior in the face of challenging circumstances may well have had an evolutionary advantage, enabling them to live (and reproduce) another day.

Animal studies have been important in understanding the neurobiological, physiological, and genetic bases of behavioral inhibition (see the chapter “Behavioral Inhibition in Rodents: A Model to Study Causes and Health Consequences of Temperament” by Cavigelli; also Clauss, Avery, & Blackford, 2015). My focus in this chapter is on studies with nonhuman primates, which I believe can be especially valuable. This is largely due to the shared ancestry of humans and Old World monkeys such as the rhesus macaque, the nonhuman primate species most often used in research of this type. Evidence indicates that the common ancestor of humans and Old World monkeys (such as rhesus macaques) existed about 23 million years ago, compared to the common ancestor with rodents, which was about 90 million years ago (Nei & Glazko, 2002).

The value of studying an animal model with recent common ancestry, of course, is that this increases the likelihood that the similarity between the human and nonhuman species in the process of interest is homologous (i.e., owing to common descent) rather than analogous (i.e., owing to convergent evolution, where different species separately evolve the same solution to a problem, such as flight in birds, bats, and bees). Homologous processes are much more likely to share similar or identical underlying mechanisms; this is not necessarily the case with analogous comparisons (Campbell & Hodos, 1970). The brains of human and nonhuman primates show greater similarity than do the brains of humans and rodents, for example (Phillips et al., 2014).

Conceptual and Methodological Issues in Studying Behavioral Inhibition in Nonhuman Primates

There is a wide variety of studies, conducted with nonhuman primates, that have employed the concepts of "behavioral inhibition" or "inhibited temperament." Some studies have focused on factors that can increase risk for developing a behavioral inhibition phenotype, while others have been more focused on the behavioral, physiological, and disease sequelae of possessing a behavioral inhibition phenotype. The question of interest for the present chapter is, are we all studying the same thing? Note that this is not an issue that is specific to behavioral inhibition—labels for many psychological constructs are used differently by different individuals (see the chapter "The History and Theory of Behavioral Inhibition" by Kagan). In relation to behavioral inhibition, however, this is the elephant in the room, referred to above, and it is partly a conceptual issue, and partly a measurement issue.

One aspect of the conceptual issue involves whether the inhibition of one's behavior is a state or a trait. There are circumstances in which everyone should inhibit their behavior—at a classical music concert, in church, or at a museum. That is not the kind of "behavioral inhibition" that is typically referred to, however, in the scientific literature. Rather, the focus is on a pattern of behavior that is more trait-like—a pattern that shows consistency across time and situations—and is evident in situations in which most others are *not* inhibiting their behavior.

A second conceptual issue is whether the inhibition of behavior that one sees is a manifestation of something other than an inhibited temperament. Depressed individuals, for example, can display a reduction in behavioral output in multiple contexts, even in situations when other individuals are not inhibiting their behavior. While there is good evidence that behavioral inhibition in childhood is a risk factor for depression (and other psychological conditions) in adolescence and beyond (e.g., Rotge et al., 2011), depression and behavioral inhibition are considered distinct. For example, anhedonia is an important characteristic of childhood depression (Tandon, Cardeli, & Luby, 2009) but is not a characteristic of behavioral inhibition.

Behavior is the principal way in which animals satisfy their needs and wants (Capitanio, 2017a). Behavior is generally much more flexible than the latent traits that underlie behavior. What this means is that the same trait can be manifested in different types of behavior depending on the situation or the developmental stage: behavior shows multifinality (Wilden, 1980). For example, Kagan and colleagues (described in Kagan, 2012) indicate that behavioral inhibition, as typically determined in the second or third year of life, is preceded by a pattern of increased negative reactivity (described above) and is followed by social inhibition. Presumably these three types of behavior are manifestations of the same underlying trait, but their differential expression during development is a reflection of the organism's capabilities and changes in the environment.

In infancy, for example, the individual's behavioral repertoire is limited, and it is unable to move away on its own from novel situations that it finds fearful. The next best thing is to exhibit displays of negative affect (crying, thrashing) that would

hopefully achieve the same goal by attracting a caregiver who could move the infant. Later, in adolescence, the increasing importance of the individual's social environment is likely to result in this inhibited style of interacting with the world having a more social aspect to it. Thus, even in the human literature, from which the concept of behavioral inhibition arose, behavioral inhibition can be reflected in different behavioral outcomes (Fox, Henderson, Marshall, Nichols, & Ghera, 2005). (It is also worth noting, for the sake of completeness, that behavior also shows equifinality (von Bertalanffy, 1952), in that the same behavioral outcome can be a manifestation of different underlying processes or traits, as indicated in the previous paragraph's example of depression. I will return to this concept below.)

The idea that behavior can be multifinal leads to the methodological issue associated with behavioral inhibition: how do we measure it? In human studies, a variety of methods have been employed, including laboratory assessments, parent questionnaires, teacher questionnaires, and even self-questionnaires, the intercorrelations of which are often quite variable (Broeren & Muris, 2010; van Brakel & Muris, 2006). Studies of behavioral inhibition in nonhumans are, of course, generally more limited methodologically, relying almost exclusively on laboratory assessments. Although it is worth noting that rating scales, completed by observers who are familiar with the animals, and with demonstrated reliability and validity, are increasingly common in nonhuman primate research (Gosling, 2001).

The remainder of this chapter will be focused on describing how the concept of "behavioral inhibition" has been used in the nonhuman primate literature. In some cases, behavioral inhibition has been the main concept under study, while in other cases, a manipulation resulted in a pattern of behavior that the investigator (or others) labeled post hoc as behavioral inhibition. What are the measures that have been used, and how similar or different are they? My goal is not to indicate that one method is better than another, but rather to reveal that, in the nonhuman primate literature, there is little consensus in how the concept is measured. Nowhere is that more evident than in my own research program, where I've used the term in at least three different ways. I will conclude with some thoughts on where we might go from here, to facilitate study of behavioral inhibition in nonhuman primates.

Behavioral Inhibition in the Nonhuman Primate Literature

As just described, the concept of behavioral inhibition has been used in multiple ways in the nonhuman primate literature. For the sake of discussion, I will classify the research in this area as falling into one of two categories and will discuss the studies in each. I will refer to the first category as "Induced Studies." In these studies, some manipulation resulted in an outcome that the authors (or others) described as reflecting behavioral inhibition. I will label the second class of studies "Naturally Occurring Studies." These studies share a common methodology involving broad surveys of a number of animals in order to identify the animals possessing a behavioral inhibition phenotype. The focus in these studies has been less on the factors

that lead to behavioral inhibition and more on (a) the neurobiological correlates and (b) the later consequences, of having a behavioral inhibition phenotype (see the chapter "The History and Theory of Behavioral Inhibition" by Kagan, discusses the implications for temperament theory when making the distinction between "induced" and "naturally occurring" behavioral inhibition). My emphasis throughout this discussion is on the *behavioral* phenomenon of behavioral inhibition, and less on the underlying mechanisms, although I recognize that studies of mechanisms can be extremely valuable in showing that the phenomenon in different species could, indeed, be homologous. Unfortunately, too few nonhuman primate research programs have focused on mechanisms.

Induced Studies

Studies conducted with monkeys in the 1950s and 1960s (and even into the 1970s) identified the important role that early experience can have on social and personality development; although probably because of the dominance of the behaviorist paradigm in Psychology at the time, the term "personality" was rarely invoked (for reviews see Capitanio, 1986; Capitanio & Mason, 2019). One series of studies, conducted by Bill Mason, was especially innovative in that contrasts were made between monkeys reared in the wild versus in captivity, with mobile versus stationary surrogates, and with dogs versus inanimate hobbyhorses as companions (see Mason, 1979). Of these and other studies, Clarke and Boinski (1995, p. 111) wrote, in their review of temperament in the primate literature, that "Primate infants reared in artificial environments providing relatively more stimulation or in those that more closely approximate the species-typical norm appear to have less inhibited behavioral responses to novelty challenges (e.g., show more exploration and less inhibition) and appear to approach novel situations in a more bold and instrumental manner." While it is true that the animals reared under restricted conditions tended to be less responsive when confronted with novelty, Mason did not refer to these as "behaviorally inhibited" monkeys. Rather, he referred to their behavior as reflecting a coping style, not a temperament.

In fact, while there were long-term social consequences of some of these more restricted forms of rearing (e.g., Capitanio, 1985), the deficits were more often described as cognitive than affective (Mason, 1978)—restricted rearing often resulted in animals that didn't seem to understand that their own behavior could impact their world (both social and nonsocial) in adaptive ways. Their more passive approach to the world often resulted in them not even trying to solve simple problems that would get them a preferred food item, for example (Mason, 1978). Moreover, their affective responses often seemed out of proportion and not modulated by the receipt of social signals (e.g., of submission) that would often inhibit the further display of aggression in more normally reared animals. Finally, when heart rate data were obtained in novel situations, the animals reared under the more restrictive conditions (e.g., reared with a hobbyhorse instead of a dog, Mason & Capitanio,

1988) had significantly lower heart rate, a pattern opposite to that found in behaviorally inhibited humans (Pérez-Edgar & Guyer, 2014). Thus, while their behavior was often "inhibited" in their confrontations with novelty, the overall pattern reflects a more complex amalgam of passivity, affective reactivity, physiological organization, and overall social ineptitude.

A research program by Schneider and Clarke described rhesus monkeys born to mothers that had experienced stress during pregnancy. The stressor was carefully controlled, comprising a relocation of the pregnant female to another room, and exposure to three 1-sec bursts of loud noise during a 10-min period. The stressor was administered 5 day/week during mid- to late gestation (days 90–145 of a typical 165-day gestation). Control mothers were undisturbed in their living cages. These animals were followed for about 4 years and were observed in a number of situations (summarized in Clarke & Schneider, 1997). Following a new group formation, the prenatally stressed (PNS) animals showed more locomotion, self-directed and disturbance behavior, and less play. When observed alone in an open-field environment, PNS animals showed less exploratory behavior, more time inactive (interpreted as "freezing"), and reduced vocalizing. The critical criteria in these studies suggesting to the authors that PNS led to an inhibited temperament style was the greater inactivity and disturbance-type behavior, and reduced exploration and play.

Finally, a retrospective study conducted in my laboratory examined the consequences of exposure to ketamine (an immobilizing agent used in veterinary practice) during gestation (Capitanio, Del Rosso, Calonder, Blozis, & Penedo, 2012). Animals were assessed as 3–4-month-old infants in our BioBehavioral Assessment (BBA) program, which comprises a variety of behavioral and physiological tests over a 25-h period (details are provided below). Results indicated an interaction between number of ketamine exposures in the first trimester and genotype for the monoamine oxidase A (*MAOA*) gene. Monoamine oxidase A is an enzyme that inactivates monoamine neurotransmitters such as dopamine, serotonin, and norepinephrine. The transcription of the gene that codes for this protein is controlled by a regulatory region that, in humans and rhesus monkeys, is polymorphic and has been linked to impulsive aggression and psychopathology (Barr & Driscoll, 2014). Our results indicated that, for animals possessing the low-transcriptional variant of the *MAOA* gene, more ketamine exposures during the first trimester (the number of exposures ranged from 1 to 7) were associated with reduced Emotionality, as well as reduced contact with novel objects during the somewhat stressful BBA testing. These results were suggestive to us of an inhibited temperament.

Naturally Occurring Studies

Steve Suomi examined behavioral inhibition in two separate lines of research in rhesus monkeys. In one line of research, Suomi (1991, p. 178) identified as "high reactive" those mother-reared infants that "react to brief social separations with unusually high cortisol and ACTH elevations, exaggerated noradrenalin turnover,

and much more 'depressive' behavioral reactions than the other mother-reared subjects." They were described as exhibiting extreme behavioral and physiological reactions to novel, challenging circumstances, including high and stable heart rates, as well as minimal exploration in a playroom full of toys.

Later (p. 179), Suomi noted that "we have been struck by the degree to which our high-reactive young monkeys resemble human children identified as shy or 'behaviorally inhibited,' in terms of their characteristic behavioral and physiological response to environmental novelty and challenge, as well as the developmental stability of the respective phenomena (cf. Kagan, Reznick, & Snidman, 1988)." Interestingly, Suomi reported that approximately 20% of their mother-reared infants fit this profile, a figure similar to that reported by Kagan (1989, above). Finally, Suomi suggested that this high-reactive profile was heritable. Unfortunately, there were few details presented about the specific behavioral measures examined, although the designation of "reactive" also incorporated the physiological measures described above.

In a second line of research by Suomi, animals living in social groups were simply rated by trained observers on a three-point scale (low, moderate, or high) for behavioral inhibition, defined as "(a) least likely to approach new stimuli; (b) most anxious; (c) most constrained in social interactions; and (d) least likely to enter new, challenging situations" (Boyce, O'Neill-Wagner, Price, Raines, & Suomi, 1998, p. 286). Bolig, Price, O'Neill, and Suomi (1992) reported that animals that were rated high on this scale at one time point were significantly more likely to be rated as least confident, curious, and equable and most excitable, fearful, irritable, and tense, on a personality inventory completed by the same raters several weeks after the initial behavioral inhibition rating. In addition, Boyce et al. (1998) examined clinical veterinary records and determined that, during a period of exogenously imposed stress for the entire group, the inhibited animals, defined as having been rated "high" on the behavioral inhibition item, showed a significantly higher incidence of injuries compared to animals rated "low" or "moderate" on the item. It was unclear from their study whether the inhibited animals were targeted by others or whether their behavior elicited aggression from others. Importantly, though, the rates of injury of the inhibited animals during non-stressful periods were equivalent or lower than were the rates for non-inhibited animals.

It is likely that the most productive research program investigating behavioral inhibition (or inhibited temperament) is that of Kalin and colleagues. Their approach has been to broadly survey rhesus monkeys in their colony using a procedure called the human intruder paradigm (HIP) and to identify animals that demonstrate a particular pattern of response. While there have been some changes to the procedure over time, the basic paradigm involves removing the animal from its social group and/or familiar housing environment and relocating the animal to a single cage in an unfamiliar room for up to 30 min. Next, an unfamiliar human intruder enters and stands ~2.5 m from the cage, presenting his profile without eye contact. This is sometimes referred to as the NEC (no eye contact) condition. The principal measure used to identify behaviorally inhibited animals is the behavior "freeze" in the NEC condition, where freezing is defined as "remaining motionless, except for slow head movements, for at least 3 s" (Kalin & Shelton, 1989).

In the most recent paper by this group, for example, Shackman et al. (2017) used the HIP on two occasions 1 week apart, when animals were about 2 years of age, and found it to be reasonably stable across all animals ($r = 0.74$, $n = 109$). From those initial screening sessions, two extreme groups (high BI and low BI, $n = 12$ per group) were identified and were exposed to the HIP approximately 1.5 years later. The correlation in their responses was $r = 0.56$. Furthermore, in a variant of the usual HIP, animals were exposed to the intruder for three times over a 30-min period or were left alone for the same amount of time (all animals were tested in both conditions in randomized order). Then the animals were left alone for 30 min, and the amount of freezing was recorded. High-behavioral inhibition animals showed significantly more freezing in the "alone after intruder" condition than they did in the "alone after alone" condition; low-behavioral inhibition animals did not show this pattern. Finally, approximately 2 years after the initial screening, the 24 animals were tested for their willingness to take a preferred food item when it was placed on top of a box that contained a live snake, artificial snake, roll of tape, or nothing. High-BI and low-BI groups differed, though only in the most intense (live snake) condition: High-BI animals were twice as likely, compared to the low-BI animals, to refrain from reaching for the food item when the snake was present (Shackman et al., 2017).

Other work by this group has also shown that, among the free-ranging colony of rhesus monkeys on Cayo Santiago, Puerto Rico, anxious temperament (their broader concept, which includes behavioral inhibition) was associated with social inhibition (Fox & Kalin, 2014). Together these data demonstrate predictive validity in the behavioral realm—animals identified as behaviorally inhibited versus non-inhibited from the HIP showed persisting differences up to 2 years after the initial screening—and in contexts that were different from those that defined the phenomenon in the first place.

Fairbanks and colleagues studied variation in inhibited temperament in a captive colony of vervet monkeys (*Chlorocebus aethiops*), with a particular emphasis on how temperament of young animals is related to maternal style. Factor analyses of maternal behaviors revealed a two-factor structure: protectiveness and rejection. Maternal protectiveness was characterized by high levels of contact-seeking by the mother and high levels of interest in the infant. Protectiveness was associated with infants spending more time in contact with their mothers and less time at a distance of 1 m or greater. Maternal protectiveness was associated, among juveniles, with less time looking outside of the animals' enclosures and with a longer latency to enter a novel environment (Fairbanks & McGuire, 1988).

A later study induced greater levels of maternal protectiveness by introducing new breeding males into the existing groups. As expected, in the birth season following introductions of new males, females were indeed more protective, and maternal protectiveness was associated with their infants having longer latencies to approach novel stimuli (Fairbanks & McGuire, 1993). In both studies, the longer latencies to approach novel stimuli were identified as evidence of behavioral inhibition. Finally, in another line of research, Fairbanks (2001) developed an intruder challenge test, involving exposing vervet monkeys to an unfamiliar animal located in a cage outside of the resident animals' enclosure. Factor analyses of seven behaviors that were coded as responses to the intruder (e.g., latency to approach within

1 m) revealed a single dimension identified as reflecting inhibition to impulsivity. Thus, unlike in their earlier studies (Fairbanks & McGuire, 1988, 1993), this definition of the term "inhibition" reflected performance in a specifically social context.

A fourth set of studies was conducted in my laboratory and began with an investigation into the temperamental underpinnings of asthma. This line of research was based upon an early study of children (Kim, Ferrara, & Chess, 1980) suggesting a temperamental component (stressful responding to novelty, "slow-to-warm-up") in children with asthma. Our research facility has a unique program in primate respiratory biology, with a group of core faculty that model asthma in monkeys. An important measure is the airways response, which is quantified by determining what dose of methacholine (a muscarinic receptor agonist) is required to increase airways resistance by a standard amount. Airway hyperresponsiveness (AHR), a hallmark of asthma, is indicated when only a very small dose is needed to increase resistance.

Our first study was retrospective, involving 19–35-month-old monkeys for whom AHR data had already been collected. A subset of those animals had participated in our BioBehavioral Assessment (BBA) program (described in detail in Capitanio, 2017a, 2017b; Golub, Hogrefe, Widaman, & Capitanio, 2009). Briefly, the BBA program comprises a standardized series of assessments, conducted over a 25-h period, when infant rhesus monkeys are between 90 and 120 days of life. Assessments include observations at the beginning (Day 1) and the end (Day 2) of the 25-h period, while the animals are alone in their temporary holding cage, four blood samples to assess hypothalamic-pituitary-adrenal regulation, and temperament ratings at the end of the 25-h period. The goal of the retrospective study (Capitanio et al., 2011) was to identify whether BBA measures related to behavioral inhibition predicted the airways response.

The result indicated that three measures were significant predictors: animals that had more sensitive airways showed reduced Emotionality (i.e., lower rates of vocalizing and other affective behaviors) on the Day 1 observations, had a blunted stress-induced cortisol response, and had higher values on our temperament measure of Vigilance. These three measures correctly classified 95% of our sample based on their airways data.

The idea of reduced emotional output after having been relocated (within 30 min) to a novel setting, and maintenance of Vigilance throughout the 25-h period, was suggestive to us of behavioral inhibition, and we labeled this pattern as such. Based upon these retrospective data, we created a prediction equation from the results of the logistic regression and then performed a prospective study, identifying a new sample of 3–4-month-old infants that had extreme values on both ends of the continuous distribution. We then gave them the methacholine challenge test at 1.25 years of age and found a similar result (Chun, Miller, Schelegle, Hyde, & Capitanio, 2013, Fig. 2): behavioral inhibition status was significantly associated with AHR. A third study, recently concluded, has also found this result.

As the previous paragraph indicates, three separate studies at our facility have now found a significant relationship between, on the one hand, reduced Day 1 Emotionality and increased Vigilance (suggestive to us of behavioral inhibition) and blunted cortisol response, and on the other hand, AHR 1–2 years later. Further study,

however, revealed that these animals also showed later behavioral outcomes that are consistent with the human literature (Chun & Capitanio, 2016). For example, in response to a short-term stressor—relocation—as juveniles, behaviorally inhibited animals showed greater evidence of anxiety than did non-inhibited animals. In addition, in their familiar outdoor corrals, behaviorally inhibited animals spent significantly more time alone than did non-inhibited monkeys. Later, as young adults, there were no group differences in the amount of time spent in social behavior between behaviorally inhibited and non-inhibited animals. We did find wide variation in the amount of time that young adult behaviorally inhibited animals spent alone when in their familiar cages, however, and an exploratory analysis revealed that the behaviorally inhibited animals that spent the LEAST amount of time alone as adults had had higher quality social interactions at the earlier juvenile time point. This result is similar to those described in the first paragraph of this chapter indicating that social factors can moderate the relation in humans between behavioral inhibition and later behavior (Kagan, 1989).

The definition of behavioral inhibition used in our asthma studies (reflecting high Vigilance and low Day 1 Emotionality and including blunted cortisol responsiveness to stress) was empirically derived. Lately, however, we have been exploring a second indicator of behavioral inhibition that is more theoretically based. If an important indicator of behavioral inhibition is that such individuals continue to display inhibition during novel circumstances beyond the point when non-inhibited individuals have resumed a more normal pattern of behavior, then we ought to identify an inhibited phenotype in our BBA program based upon how animals behave at the beginning of the 25-h assessment program as well as at the end of the testing period. As described above, we conduct behavioral observations on animals in their temporary holding cage on Day 1 and on Day 2 to assess their general behavioral responsiveness to being apart from their companions and in a novel environment.

Factor analyses have revealed a two-factor structure underlying the behavioral data (Golub et al., 2009), and scales reflecting Activity (which includes proportion of time spent locomoting, rate of environment exploration, and whether the animal ate food) and Emotionality (described above as incorporating rates of vocalizing) were calculated for each of the 2 days.

It is a low score on the Day 1 Emotionality measure that is a component of our asthma-related indicator of behavioral inhibition (which we can designate henceforth as aBI). During the BBA testing, the general pattern of responsiveness is that many behavioral indicators of Activity are higher on Day 2 than on Day 1 and behavioral indicators of Emotionality are lower on Day 2 compared to Day 1. Presumably this is because animals have become more comfortable in the situation. It seemed to us that "behavioral inhibition" might be indicated by animals that were below the mean on Day 1 Activity and Emotionality and who remained below the mean on Day 2 Activity and Emotionality.

Thus, behaviorally inhibited animals start low and remain low, reflecting an initial inhibition (Day 1) that persists into the second day, a time point when the behavior of other animals has normalized somewhat. If we calculate this index (which we will refer to as our responsiveness-inhibition measure, rBI), we find that 17.9% of

the ~4200 animals assessed to date in the BBA program fit this profile, a number that meshes well with the ~15% of human infants reported by Kagan (1989) that show behavioral inhibition, and with the ~20% of infant monkeys that Suomi (1991) found. We cannot calculate the percentage of animals for aBI, as it is a continuously distributed measure resulting from a prediction equation based on the initial logistic regression (see Chun et al., 2013).

How do our two measures of "behavioral inhibition," aBI and rBI, interrelate? If we identify the top ~15% of animals for aBI and compare, using chi-squared, aBI vs. non-aBI with rBI vs. non-rBI, we find a highly significant ($p < 0.001$) relation. Unfortunately, it is negative—animals identified as inhibited using the rBI criteria were significantly more likely to be identified as non-inhibited using the aBI criteria. Why would two measures that appear to be face valid for the construct of interest be inversely related? We've noted above that aBI does predict some outcome measures obtained months to years later: AHR, anxious behavior, and social behavior, suggesting both predictive and construct validity. What is rBI related to? Unfortunately, with one exception, the types of data that we have collected examining aBI and the types of data we have collected examining rBI do not overlap, making direct comparisons difficult. The one exception, however, is instructive.

At our facility, animals can be relocated from their large, outdoor social cages either temporarily or permanently, for a variety of reasons. We have developed a simple food retrieval task that we administer to animals on their first morning following such a relocation: each animal is presented with a preferred food item by hand or via placement on a food tray if the animal does not take the item by hand. Three such trials are administered in a 5-min period, and we record whether the animals take the food item, as well as any affective displays that they make during the trials.

rBI is a highly significant predictor of responses in this food retrieval task—rBI animals are significantly more likely to not take the food item on any of the three trials, whereas non-rBI animals are significantly more likely to take the treat by hand on all three trials. Similarly, rBI animals are significantly less likely to perform affective displays compared to non-rBI animals. Thus, in this novel situation, animals identified in infancy (using BBA data) as behaviorally inhibited with the rBI criterion continue to show inhibited behavior well into adulthood (up to 11 years after BBA participation), as indexed by a reluctance to take a preferred food item and a reduced tendency to display affective responses in a moderately stressful situation. Importantly, aBI is not related to any measure in this task—food retrieval or affective displays.

Both measures show predictive validity (albeit to different outcome measures). What about concurrent validity? Both measures were derived from performance on specific tasks in the BBA program. How do these measures map onto the other tasks in our assessment battery? We do perform a human intruder test in the BBA program, though it is a more abbreviated version than Kalin's protocol (Kalin & Shelton, 1989). Exploratory and confirmatory factor analyses (Gottlieb & Capitanio, 2013) revealed a four-factor structure underlying the behavioral data—Activity (e.g., active, environment explore), Emotionality (grimace, coo), Aggression (threat, bark), and Displacement (i.e., anxiety-related behaviors such as tooth grind and yawn).

Using our full BBA database of more than 4100 animals, rBI animals show significantly lower scores, compared to non-rBI animals, on all four factors. Unlike Kalin, we do not score "freeze" in our human intruder testing, inasmuch as this is not a significant component of our infant animals' responses (Gottlieb & Capitanio, 2013, discuss differences between the two human intruder paradigms). However, Activity is likely to be the dimension in our analysis that would reflect the reduction in Activity seen in "freezing." In our analysis, rBI animals showed significantly lower levels of Activity compared to non-rBI animals. In contrast to these results, an analysis using the aBI measure revealed that aBI animals showed significantly GREATER Activity and Emotionality compared to non-aBI animals in our human intruder test. They also showed significantly lower Aggression, as did the rBI animals. There were no differences between aBI and non-aBI animals in Displacement behaviors.

A second task to examine involves contact with novel objects. Throughout the 25-h BBA testing, each monkey has in its cage a novel object that contains an actimeter, which records any force exerted on the object. If we examine the proportion of time the animals are in contact with the object, we find that rBI animals show significantly less contact than do their non-rBI counterparts. There are no differences between aBI and non-aBI animals on this measure. We note that in the description of our study of prenatal ketamine exposure, above, we found greater exposure among animals with the low transcriptional variant of the *MAOA* promoter, resulted in reduced Emotionality and reduced contact with novel objects—the same measures that we are comparing in this analysis. Together, this validity analysis suggests to us that the rBI measure is more reflective of what "behavioral inhibition" is all about, a suggestion further supported by some very preliminary RNA-seq and imaging data showing significant differences particularly in areas of the amygdala (paper in preparation). Consequently, we now believe that our asthma-related measure of behavioral inhibition is misnamed.

Discussion and Conclusions

As the discussion above indicates, the concept of "behavioral inhibition" has captured the attention of a variety of research groups that work with nonhuman primates. The notion that there is naturally occurring variation in fearfulness, which manifests as reduced behavioral output, has led to a variety of paradigms to quantify this phenotype in the primate literature. The diversity of operational definitions, however, does create some problems that would be useful to address, in order that the full value of animal models (e.g., experimental control, greater access to tissue for understanding mechanisms) can be realized. Herewith are some thoughts about the state of research into "behavioral inhibition" in nonhuman primates.

"Behavioral inhibition" is an imprecise term

It is likely that the vast majority of human developmental psychologists have a clear reference point when they hear the phrase "behavioral inhibition," and this reference point likely encompasses the work done by Kagan, Fox, and others in the field of human development. Colleagues whose principal interests are in behavioral processes in nonhuman animals may not have the same reference point.

An obvious reason for this may be because of a lack of familiarity with the substantial literature on behavioral inhibition in humans, and the fact that, in that literature, the phrase refers to something specific. "Behavioral inhibition," as a phrase, sounds a lot like "inhibition of behavior," which is a label for phenomena that are hugely more common than is the temperament-oriented referent of the phrase. Scientists who study animal behavior see "inhibition of behavior" a lot—animals may inhibit their behavior when a potential predator flies overhead, or when a higher-ranked animal approaches a subordinate, or when a technician enters an animal room to perform a procedure on an animal living in a cage. As described above, there are many specific circumstances in which inhibiting one's behavior makes sense, but this is not what is typically referred to as behavioral inhibition. A critical defining feature of behavioral inhibition is that it describes a set of individuals who are inhibiting their behavior in circumstances when the majority of conspecifics are not—that is, it is a concept that refers to individual differences in responsiveness that are largely a characteristic of the individual, and not specifically characteristic of the situation (e.g., a concert hall), per se. So, in short, "behavioral inhibition" is not the same thing as "inhibition of behavior."

Behavior Is Equifinal

As indicated earlier, behavior, as the output of a living system, is a dynamic means for the individual to get its needs and wants met. As a result, the same behavior can be displayed for different reasons. For example, the research described above by Mason (1979) was referred to by others as involving behavioral inhibition, but I (and he) would argue that it is more a reflection of motivational/cognitive processes than affective ones (although affective processes are involved). As such, the inhibition of behavior by these animals in novel circumstances reflects a more fundamental deficit in how they approach the world, resulting from having experienced abnormal early rearing environments of a kind that would never (hopefully) be experienced by human children. This "inhibition of behavior" is probably not simply because of a strong fear of the novel, as is the case with behaviorally inhibited children. Similarly, depressed individuals can show a reduction in behavioral output that has some similarities with behavioral inhibition. Even if one uses a definition of behavioral inhibition that does refer to the notion of individual differences in responsiveness, then, it is important to recognize that the same behavioral endpoints can result from very different underlying processes.

More Attention Needs to Be Paid to Measurement Issues

While the notion of behavioral inhibition has captured the attention of primatologists, associated measurement issues have generally not. As described above, each laboratory that has studied (or is studying) this phenomenon tends to employ its own tasks to identify the phenotype. No studies have been performed, which we are aware of, that attempt to assess this construct using a multi-method approach. In a collaboration originating with a new colleague, A. Fox, however, we are planning to examine whether my lab's measures of behavioral inhibition map onto the freezing behavior seen in the NEC condition in the Kalin laboratory's HIT. (My money is on the rBI measure, and not the aBI measure.) In addition, as with any psychometric effort, attention must be paid to issues of reliability (i.e., are the measures of behavioral inhibition stable over time) and validity (does behavioral inhibition relate in expected ways to other behavioral phenomena, in either a predictive or concurrent fashion).

Overall, the study of behavioral inhibition as a temperament style has benefitted greatly from the use of animal models, in which greater access to tissue permits an understanding of underlying brain mechanisms in a way that cannot be obtained from humans (e.g., Fox et al., 2005; Roseboom et al., 2014). Animal models can also provide other perspectives on the phenomenon of behavioral inhibition, however. For example, while temperament is often construed as "biological," with an implication of "inherited," three studies described above suggest experiential origins of behavioral inhibition (i.e., they suggest experiential origins if we agree that they are all likely measuring behavioral inhibition): Schneider and Clarke's studies of prenatal stress, our own study of prenatal ketamine exposure and *MAOA* genotype, and Fairbanks's work on maternal protectiveness in vervet monkeys. Captive colonies of nonhuman primates can provide the large numbers of animals needed to identify relatively rare phenotypes, and the detailed record keeping that is common at such facilities permits exploratory analyses of factors that impact the development of behavioral inhibition, as well as its persistence over the life span. Finally, the ability to manipulate the animals, such as with a cross-fostering design, can help disentangle genetic and experiential contributions. The benefits of a comparative perspective, however, rely on careful definition (and labeling) of the process of interest and a demonstration that the phenomenon in nonhumans is strongly related to the phenomenon in humans. We believe that such work will be greatly facilitated by a more explicit recognition of the complexity of behavior (i.e., that it is equifinal and multifinal) and by adopting measures that have demonstrated reliability and validity.

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References

Barr, C. S., & Driscoll, C. (2014). Neurogenetics of aggressive behavior: Studies in primates. *Current Topics in Behavioral Neuroscience, 17*, 45–71.

Bolig, R., Price, C. S., O'Neill, P. L., & Suomi, S. J. (1992). Subjective assessment of reactivity level and personality traits of rhesus monkeys. *International Journal of Primatology, 13*, 287–305.

Boyce, W. T., O'Neill-Wagner, P., Price, C. S., Raines, M., & Suomi, S. J. (1998). Crowding stress and violent injuries among behaviorally inhibited rhesus macaques. *Health Psychology, 17*, 285–289.

Broeren, S., & Muris, P. (2010). A psychometric evaluation of the behavioral inhibition questionnaire in a non-clinical sample of Dutch children and adolescents. *Child Psychiatry and Human Development, 41*, 214–229.

Campbell, C. B., & Hodos, W. (1970). The concept of homology and the evolution of the nervous system. *Brain, Behavior, and Evolution, 3*, 353–367.

Capitanio, J. P. (1985). Early experience and social processes in rhesus macaques (*Macaca mulatta*): II. Complex social interaction. *Journal of Comparative Psychology, 99*, 133–144.

Capitanio, J. P. (1986). Behavioral pathology. In G. Mitchell & J. Erwin (Eds.), *Comparative primate biology: Volume 2A. Behavior, conservation, and ecology* (pp. 411–454). New York, NY: Alan R. Liss.

Capitanio, J. P. (2017a). Variation in biobehavioral organization. In S. Schapiro (Ed.), *Handbook of primate behavioral management* (pp. 55–73). Boca Raton, FL: CRC Press.

Capitanio, J. P. (2017b). Naturally-occurring nonhuman primate models of psychosocial processes. *ILAR Journal*., in press*, 58*, (2):226–234

Capitanio, J. P., Del Rosso, L. A., Calonder, L. A., Blozis, S. A., & Penedo, M. C. T. (2012). Behavioral effects of prenatal ketamine exposure in rhesus macaques are dependent on *MAOA* genotype. *Experimental and Clinical Psychopharmacology, 20*, 173–180.

Capitanio, J. P., & Mason, W. A. (January 2019). Personality as adaptation: Perspectives from nonhuman primates. In D. R. Lynam & D. B. Samuel (Eds.), *Using basic personality research to inform the personality disorders*. New York, NY: Oxford University Press.

Capitanio, J. P., Miller, L. A., Schelegle, E. S., Mendoza, S. P., Mason, W. A., & Hyde, D. M. (2011). Behavioral inhibition is associated with airway hyper-responsiveness but not atopy in a monkey model of asthma. *Psychosomatic Medicine, 73*, 288–294.

Chun, K., & Capitanio, J. P. (2016). Developmental consequences of behavioral inhibition: A model in rhesus monkeys (*Macaca mulatta*). *Developmental Science, 19*, 1035–1048.

Chun, K., Miller, L. A., Schelegle, E. S., Hyde, D. M., & Capitanio, J. P. (2013). Behavioral inhibition in rhesus monkeys (*Macaca mulatta*) is related to the airways response, but not immune measures, commonly associated with asthma. *PLoS One, 8*(8), e71575. https://doi.org/10.1371/journal.pone.0071575

Clarke, A. S., & Boinski, S. (1995). Temperament in nonhuman primates. *American Journal of Primatology, 37*, 103–125.

Clarke, A. S., & Schneider, M. L. (1997). Effects of prenatal stress on behavior in adolescent rhesus monkeys. *Annals of the New York Academy of Science, 807*, 490–491.

Clauss, J. A., Avery, S. N., & Blackford, J. U. (2015). The nature of individual differences in inhibited temperament and risk for psychiatric disease: A review and meta-analysis. *Progress in Neurobiology, 127–128*, 23–45.

Fairbanks, L. A. (2001). Individual differences in response to a stranger: Social impulsivity as a dimension of temperament in vervet monkeys (*Cercopithecus aethiops sabaeus*). *Journal of Comparative Psychology, 115*, 22–28.

Fairbanks, L. A., & McGuire, M. T. (1988). Long-term effects of early mothering behavior on responsiveness to the environment in vervet monkeys. *Developmental Psychobiology, 21*, 711–724.

Fairbanks, L. A., & McGuire, M. T. (1993). Maternal protectiveness and response to the unfamiliar in vervet monkeys. *American Journal of Primatology, 30*, 119–129.

Fox, A. S., & Kalin, N. H. (2014). A translational neuroscience approach to understanding the development of social anxiety disorder and its pathophysiology. *American Journal of Psychiatry, 171*, 1162–1173.

Fox, N. A., Henderson, H. A., Marshall, P. J., Nichols, K. E., & Ghera, M. M. (2005). Behavioral inhibition: Linking biology and behavior within a developmental framework. *Annual Review of Psychology, 56*, 235–262.

Frenkel, T. I., Fox, N. A., Pine, D. S., Walker, O. L., Degnan, K. A., & Chronis-Tuscano, A. (2015). Early childhood behavioral inhibition, adult psychopathology and the buffering effects of adolescent social networks: A twenty-year prospective study. *Journal of Child Psychology and Psychiatry, 56*, 1065–1073.

García-Coll, C., Kagan, J., & Reznick, J. S. (1984). Behavioral inhibition in children. *Child Development, 55*, 1005–1009.

Golub, M. S., Hogrefe, C. E., Widaman, K. F., & Capitanio, J. P. (2009). Iron deficiency anemia and affective response in rhesus monkey infants. *Developmental Psychobiology, 51*, 47–59.

Gosling, S. D. (2001). From mice to men: What can we learn about personality from animal research? *Psychological Bulletin, 127*, 45–86.

Gottlieb, D. H., & Capitanio, J. P. (2013). Latent variables affecting behavioral response to the human intruder test in infant rhesus monkeys (*Macaca mulatta*). *American Journal of Primatology, 75*, 314–323.

Kagan, J. (1989). Temperamental contributions to social behavior. *American Psychologist, 44*, 668–674.

Kagan, J. (2012). The biography of behavioral inhibition. In M. Zentner & R. L. Shiner (Eds.), *Handbook of temperament* (pp. 69–82). New York, NY: Guilford Press.

Kagan, J., Reznick, J. S., & Snidman, N. (1988). Biological basis of childhood shyness. *Science, 240*, 167–171.

Kalin, N. H., & Shelton, S. E. (1989). Defensive behaviors in infant rhesus monkeys: Environmental cues and neurochemical regulation. *Science, 243*, 1718–1721.

Kim, S. P., Ferrara, A., & Chess, S. (1980). Temperament of asthmatic children: A preliminary study. *Journal of Pediatrics, 97*, 483–486.

Mason, W. A. (1978). Social experience and primate cognitive development. In G. M. Burghardt & M. Bekoff (Eds.), *The development of behavior: Comparative and evolutionary aspects* (pp. 233–251). New York, NY: Garland Press.

Mason, W. A. (1979). Wanting and knowing: A biological perspective on maternal deprivation. In E. Thoman (Ed.), *Origins of the infant's social responsiveness* (pp. 225–249). Hillsdale, MI: Erlbaum Associates.

Mason, W. A., & Capitanio, J. P. (1988). Formation and expression of filial attachment in rhesus monkeys raised with living and inanimate mother substitutes. *Developmental Psychobiology, 21*, 401–430.

Nei, M., & Glazko, G. V. (2002). The Wilhelmine E. Key 2001 invitational lecture. Estimation of divergence times for a few mammalian and several primate species. *Journal of Heredity, 93*, 157–164.

Pérez-Edgar, K. E., & Guyer, A. E. (2014). Behavioral inhibition: Temperament or prodrome? *Current Behavioral Neuroscience Reports, 1*, 182–190.

Phillips, K. A., Bales, K. L., Capitanio, J. P., Conley, A., Czoty, P., t'Hart, B. A., … Voytko, M. L. (2014). Why primate models matter. *American Journal of Primatology, 76*, 801–827.

Roseboom, P. H., Nanda, S. A., Fox, A. S., Oler, J. A., Shackman, A. J., Shelton, S. E., … Kalin, N. H. (2014). Neuropeptide Y receptor gene expression in the primate amygdala predicts anxious temperament and brain metabolism. *Biological Psychiatry, 76*, 850–857.

Rotge, J.-Y., Grabot, D., Aouizerate, B., Pelissolo, A., Lepine, J.-P., & Tignol, J. (2011). Childhood history of behavioral inhibition and comorbidity status in 256 adults with social phobia. *Journal of Affective Disorders, 129*, 338–341.

Shackman, A. J., Fox, A. S., Oler, J. A., Shelton, S. E., Oakes, T. R., Davidson, R. J., & Kalin, N. H. (2017). Heightened extended amygdala metabolism following threat characterizes the early phenotypic risk to develop anxiety-related psychopathology. *Molecular Psychiatry, 22*, 724–732.

Suomi, S. J. (1991). Early stress and adult emotional reactivity in rhesus monkeys. In *The childhood environment and adult disease*, *Ciba foundation symposium 156* (pp. 171–188). Chichester, England: Wiley.

Tandon, M., Cardeli, E., & Luby, J. (2009). Internalizing disorders in early childhood: A review of depressive and anxiety disorders. *Child & Adolescent Psychiatric Clinics of North America, 18*, 593–610.

van Brakel, A. M. L., & Muris, P. (2006). A brief scale for measuring "behavioral inhibition to the unfamiliar" in children. *Journal of Psychopathology and Behavioral Assessment, 28*, 79–84.

von Bertalanffy, L. (1952). *Problems of life*. New York, NY: John Wiley & Sons.

Wilden, A. (1980). *System and structure*. London, England: Tavistock.

Williams, L. R., Degnan, K. A., Pérez-Edgar, K. E., Henderson, H. A., Rubin, K. H., Pine, D. S., … Fox, N. A. (2009). Impact of behavioral inhibition and parenting style on internalizing and externalizing problems from early childhood through adolescence. *Journal of Abnormal Child Psychology, 37*, 1063–1075.

Behavioral Inhibition in Rodents: A Model to Study Causes and Health Consequences of Temperament

Sonia A. Cavigelli

Abstract Behavioral inhibition (BI), a trait related to fearful temperament and withdrawal/avoidance of novelty, is an important predictor of adult health trajectories. However, specific mechanisms underlying this temperament-health relation are poorly understood. In order to model underlying physiological and developmental processes associated with behavioral inhibition to identify causal mechanisms for specific health trajectories, we developed a rodent model of early emerging behavioral inhibition. This behavioral trait of low exploration has been documented in many species and represents a relatively basic behavioral phenotype, which supports the goal of developing a non-human animal model. In this chapter, I review the behavioral and physiological characteristics of the rodent behavioral inhibition model, with an eye toward identifying biological mechanisms that may bias behaviorally inhibited individuals toward certain health trajectories. In addition, I review information on developmental correlates and influences on behavioral inhibition, with an eye toward identifying and testing interesting social and environmental interventions that could minimize health biases. I complete the chapter with a discussion of areas of future research with a rodent behavioral inhibition model.

Temperament, personality, and individual differences are of interest in multiple disciplines. A key question of intrigue for a long time has been: "What is it that makes one individual respond to a set of circumstances in one way while another responds to the same situation quite differently?" This question has been posed by psychologists and philosophers trying to understand the development and function of behavioral diversity, by medical professionals trying to understand variability in disease progression and outcomes, and by biologists trying to understand evolutionary and ecological processes underlying variance. Variance is present in all systems and often regarded as meaningless noise. However, when this variance is systematically

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characterized, quantified, and understood, the potential implications are large, particularly in a clinical setting (e.g., Cavigelli, 2005; Forster, Finn, & Brown, 2017; Gatt et al., 2007; Gurevitz, Geva, Varon, & Leitner, 2014; O'Leary-Barrett et al., 2017; Reeb-Sutherland et al., 2009).

For example, in the case of behavioral inhibition, if we can identify specific physiological or cognitive processes associated with this trait, and predispose an individual to specific health outcomes, then we can better identify interventions to minimize specific negative health outcomes associated with the behavioral trait (e.g., Cavigelli, Michael, & Ragan, 2013; Morales, Pérez-Edgar, & Buss, 2015; Pérez-Edgar et al., 2011). To better understand the origins and the health implications of behavioral inhibition, we examined the validity of a potential rodent model of this trait. Such a model would allow for experimental and longitudinal research on the causal mechanisms leading to trait development and on mechanisms involved in trait-specific health outcomes. Specifically, a rodent model of this relatively basic trait allows for complementary experimental, developmental, functional, and mechanistic studies on the causes and consequences of behavioral inhibition (see the chapter "Behavioral Inhibition in Nonhuman Primates: The Elephant in the Room" by Capitanio). Here, we present current knowledge on this rodent model of human behavioral inhibition.

Behavioral Inhibition as a Basic Trait

Human behavioral inhibition (BI) refers to a behavioral predisposition that indicates an initial, general fear response to unfamiliar situations, for example, slower approach and faster retreat from novel objects or situations (García-Coll, Kagan, & Reznick, 1984; Kagan, Reznick, & Snidman, 1987). This is a relatively basic behavioral response pattern, and there is a wealth of historical animal and human research to indicate that an approach-withdrawal spectrum of individual differences is likely universal across species and cultures (Blanchard, Flannelly, & Blanchard, 1986; Rothbart, Ahadi, Hershey, & Fisher, 2001; Schneirla, 1965; Stevenson-Hinde, Stillwell-Barnes, & Zunz, 1980; Suomi, 1987; Thomas & Chess, 1977).

In the field of animal personality research, investigators have identified five broad behavioral dimensions that involve stable within-species individual variance: boldness, exploration, activity, sociability, and aggressiveness (Réale, Reader, Sol, McDougall, & Dingemanse, 2007). Interestingly, these five broad dimensions identified from a review of the literature are similar to broad personality dimensions identified in humans using a data-driven approach—i.e. the "Big Five" dimensions of neuroticism, extraversion, openness to new experiences, agreeableness, and conscientiousness (Costa & McCrae, 1992; Gosling & John, 1999). Within these two broad personality frameworks, behavioral inhibition likely lies along the dimensions of "exploration" (willingness to engage novelty) and "openness to new experience" or "emotional stability/neuroticism" (e.g., curiosity/creativity or calmness/balance). The field of personality and temperament research is very complex, but for

the purpose of this chapter, I highlight that behavioral inhibition is one basic characteristic that defines reliable differences among individuals within a species and that this trait has been identified both in humans and animals.

Developing a Rodent Model of Behavioral Inhibition

In the United States, early laboratory-based tests indicated that 15–20% of children displayed signs of generalized behavioral inhibition (García-Coll et al., 1984; Kagan et al., 1987; Kagan & Snidman, 1999). These tests consisted of exposing children to a battery of conditions that involved different forms of novel or unfamiliar stimuli (e.g., novel toys, unfamiliar people, etc.). The trait was relatively stable across age and could be characterized as early as infancy (Kagan & Snidman, 1991; Reznick et al., 1986). Follow-up studies have identified physiological correlates of behavioral inhibition, including increased autonomic nervous system activity, greater basal (i.e., "unstimulated") hypothalamic-pituitary-adrenal (HPA) axis activity, greater HPA reactivity to novelty in certain cases, and increased activation of the amygdala in response to novel stimuli (e.g., Buss, Davidson, Kalin, & Goldsmith, 2004; Kagan et al., 1987; Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996; Schwartz, Wright, Shin, Kagan, & Rauch, 2003). All of these physiological response biases, and others to be identified yet, may "set the stage" for the development of specific health outcomes.

Children that display signs of behavioral inhibition are more prone to allergies and anxiety disorders (e.g., Hirshfeld et al., 1992; Kagan & Snidman, 1991, 1999; Turner, Beidel, & Wolff, 1996). Capitanio (see the chapter "Behavioral Inhibition in Nonhuman Primates: The Elephant in the Room") notes in his work a link between behavioral inhibition in nonhuman primates and airway hyperresponsiveness, a marker of allergic asthma. In particular, there is long-standing evidence that behavioral inhibition is one of the best predictors of later social anxiety (Biederman et al., 1990; Chronis-Tuscano et al., 2009; Clauss & Blackford, 2012; Hirshfeld et al., 1992; Hirshfeld-Becker et al., 2007; Kagan, Reznick, Clarke, Snidman, & García-Coll, 1984; Pérez-Edgar & Fox, 2005; Reeb-Sutherland et al., 2009; Schwartz, Snidman, & Kagan, 1999). Finally, older community-dwelling adults that self-identified as low in curiosity (information/stimulation seekers) had higher mortality rates than more curious adults (Swan & Carmelli, 1996). The physiological correlates of behavioral inhibition (i.e., enhanced limbic activation/physiological stress activation) could be one mechanism that predisposes individuals to develop allergies and anxiety. For example, cChronically elevated physiological stress (e.g., allostatic load) can have long-term consequences on neuronal, immune, and metabolic function associated with allergies and anxiety (Brindley & Rolland, 1989; Dhabhar & McEwen, 1999; Wilckens & De Rijk, 1997).

Because behavioral inhibition emerges early in life, can be a stable trait over years, and is associated with elevated physiological responses associated with emotion and stress regulation and health consequences, it would be beneficial to determine the relative causal relations among temperament, developmental experiences, physiological response biases, and health outcomes. If a certain temperament is

causally related to specific developmental experiences and/or with a physiological response bias that is detrimental to a particular health outcome, then "interventions" that target these specific mechanisms may be particularly effective in maintaining quality of life. (In this case, "interventions" may involve social or environmental alterations.) The relative benefit of interventions could be assessed in the short-term by capturing the amount of change observed in the physiological response bias that is associated with poor health outcomes.

These motivations drove us to develop a rodent model of behavioral inhibition. Our goals in developing a short-lived animal model was to provide a means to (1) identify BI-associated physiological response biases that may have important health consequences for humans; (2) test causal relations among temperament, peripheral physiology, and health using experimental methods that are not possible in human research; and (3) conduct reasonable lifelong longitudinal studies to document the development and stability of temperament, associated physiological biases, and health outcomes. Results from a short-lived rodent model can provide preclinical insights into physiological and developmental mechanisms that bias health trajectories in fearful or inhibited children and adults.

In the early 2000s, we began to test the viability of a rodent model of behavioral inhibition. For several reasons, we chose rats as an ideal rodent model species to study the causes and long-term consequences of behavioral inhibition. Rats are a relatively complex social species, with a great deal of background literature on behavior, development, and physiology. They are also relatively short-lived which allows for life-span studies on the influence of early life factors on adult health and physiology. In addition, rats are a relatively large rodent which allows for ample and repeated physiological sampling over the life span. Finally, prior studies had documented a trait similar to behavioral inhibition in many species (e.g., "neophobia," "emotionality," or "shyness"), including rats, suggesting that the trait is relatively well-conserved across species, even those that undergo experimental breeding (Buss & Plomin, 1984; Einon & Morgan, 1976; Gosling & John, 1999; Takahashi & Kim, 1994; Wilson, Clark, Coleman, & Dearstyne, 1994). These preliminary studies supported the notion that the equivalent of behavioral inhibition in humans could be identified in other species and that an animal model with naturally occurring variance in this trait was theoretically viable.

To develop a valid rodent model of behavioral inhibition, we had several goals. First, we wanted to use behavioral tests with rodents that were similar to those used to test behavioral inhibition in humans. Second, we wanted to determine the relative stability of the trait within an individual across development and begin at the earliest point at which the trait could be reliably identified. Last, we wanted to verify that the physiological response biases identified in human behavioral inhibition, which may be responsible for specific health trajectories, were present in rodent behavioral inhibition. We conducted the bulk of this work with outbred rats (Sprague-Dawley) in order to test these questions in a genetically heterogeneous population that would maximize behavioral variance.

Given the above goals, we conducted initial studies to quantify infant, juvenile, and adult rat behavioral and physiological responses to test arenas that were made to be comparable to laboratory behavioral assessment conditions in early studies of

childhood behavioral inhibition (e.g., novel toys and novel social partners; García-Coll et al., 1984; Kagan et al., 1984; Reznick et al., 1986). We tested whether fearful responses generalized across different environmental conditions (both social and nonsocial unfamiliar environments) and whether the inhibited phenotype was seen in a similar percentage of rats as had been documented in humans (i.e., ~15% of those tested). To mimic human laboratory test conditions, we studied rat responses to controlled novel conditions in which threatening stimuli were minimized—i.e., low light and noise, well-protected and simple arenas, and tests conducted during waking hours (Cavigelli et al., 2007; Cavigelli & McClintock, 2003).

Rats were tested in two different novel conditions on separate occasions—one that included a novel social partner and one that included only novel objects (i.e., novel social vs. nonsocial environments). To estimate behavioral inhibition or fear-related responses, we documented latency to approach novelty, overall locomotion, and frequency to inspect novelty. Latency to approach a novel social partner is one of the behavioral responses most linearly associated with basal and reactive corticosterone production, although many of the behavioral responses to novelty are closely associated with one another and with glucocorticoid production (Cavigelli et al., 2007, 2009).

Given these characteristics of behavioral responses, we defined rodent behavioral inhibition as a longer-than-median latency to approach novelty in both a social and nonsocial arena. Using this definition, behaviorally inhibited rats make up approximately 30% of any tested group (Cavigelli et al., 2007). We have found that defining a rat's temperament relative to others within a specific cohort is an important method to control for slight variations among cohorts and testing conditions among studies. Importantly, a rat's response to one arena (e.g., social novelty) did not necessarily predict its behavioral response to the other arena (e.g., nonsocial novelty; correlation of individual approach latencies in each arena: $r_{58} = 0.194$, ns) suggesting the importance of varied behavioral testing to identify generalized inhibition to multiple forms of novelty (Cavigelli et al., 2007; Kagan, Snidman, McManis, Woodward, & Hardway, 2002). The lack of correlation also reflects Kagan's (see the chapter "The History and Theory of Behavioral Inhibition") argument that behavioral inhibition reflects a specific category of temperament, rather than a constellation of continuous traits.

To test trait stability over time, we documented behavioral responses to the social and nonsocial novel arenas across multiple test ages and also tested trait stability over relatively long stretches of the rat's life span. In one case, we were able to test stability in the nonsocial arena over the life span, and in another case we tested stability in the two different arenas over a shorter span of 4 months (~20% of the median rat life span in laboratory conditions; Cavigelli & McClintock, 2003, Cavigelli et al., 2007, Caruso, McClintock, & Cavigelli, 2014). Behavioral responses to the nonsocial arena were linearly stable over time ($r_{28–51} = 0.32–0.75$, $p < 0.05–0.001$) with higher stability when shorter test-retest intervals were used (i.e., 4 vs. 10 months; Cavigelli & McClintock, 2003, Cavigelli et al., 2007, Caruso et al., 2014). In addition, in both arenas, males were slower to approach novelty and moved less than females (Cavigelli, Michael, West, & Klein, 2011). *Mean* response to both arenas was also relatively stable over time. For rats retested in both arenas at two test ages, 4 months apart, the mean approach latency in the novel social and nonsocial

arenas at test age 1 was linearly related to mean latency at test age 2 ($r_{59} = 0.39$, $p < 0.01$). Lastly, 65% of rats classified as "inhibited" at time point one continued to display inhibition 4 months later (again, with behavioral inhibition defined as longer than median latency to interact with novelty in both a nonsocial and social test situation; Cavigelli et al., 2007, 2009). Overall, repeat testing on both arenas at two ages led to an identification of stable inhibition in 17% of rats tested, and a similar percentage of stably non-inhibited rats (i.e., shorter than median approach latency on both arenas at both test ages). This behavioral inhibition percentage is comparable to the percentage of behavioral inhibition in humans (Cavigelli et al., 2007).

In a complementary model of rodent behavioral inhibition, Kalin and colleagues have experimentally elicited similar behavioral characteristics in male and female Sprague-Dawley rats by exposing them to predator cues (Campeau, Nyhuis, Sasse, Day, & Masini, 2008; Nanda, Qi, Roseboom, & Kalin, 2008). This model allows for greater experimental control of behavioral inhibition (here defined as freezing and decreased locomotion/hypervigilance) and allows for repeated testing/elicitation of the phenotype since rats do not habituate to predator cues (Blanchard et al., 1998). With this model, individual differences in BI-related responses to acute predator exposure were stable across repeat testing and with greater stability when repeat tests were conducted closer together in time (e.g., test-retest interval of 2 days, in adolescence, $r_{22} = 0.538$, $p < 0.01$, or adulthood, $r_{22} = 0.723$, $p < 0.001$; test-retest interval of 28 days, from adolescence to young adulthood, $r_{35} = 0.475$, $p < 0.01$; Qi et al. 2010). Further, individuals could be characterized as either high or low behavioral inhibition based on the stability of their behavioral response to predator exposure tested 2 days apart. Rats with high stability during this short test-retest interval also showed much more stability in behavior over the longer test-retest interval (28 days, $r_{94} = 0.902$, $p < 0.001$; Qi et al. 2010). Finally, similar to behavioral inhibition elicited by exposure to a more benign arena with a novel rat or objects, adult males showed more inhibited behavior in response to a predator than adult females (Cavigelli et al., 2011; Qi et al., 2010).

In this complementary model of rodent behavioral inhibition, the inhibited behavior (but not other behaviors, such as grooming and rearing) was decreased by an injection of anxiolytic drug (diazepam) just prior to predator exposure (Qi et al., 2010). Thus, based on results from two models of rodent behavioral inhibition (predator vs. benign novelty exposure), trait stability in Sprague-Dawley rats was relatively high, with greater stability with shorter test-retest intervals and a greater number of repeat tests, and males displaying more behavioral inhibition than females.

The above work has been conducted with rats. However, there would be some advantages to extending this work to mice. Laboratory mice present an attractive complementary rodent species because they cost about half as much to maintain in the laboratory (because of smaller body size), and because of this, there has been more extensive work conducted to modify their genetic makeup. To minimize genetic variance and maximize certain traits in a rodent population, selective breeding has been conducted with both rats and mice, but in mice, there is a longer history of conducting more refined genetic modifications compared to rats. For example, there are more established "knockout" and transgenic mouse vs. rat models, and these models,

which involve targeted modification of specific genes, allow for more targeted experimental tests of how a specific physiological mechanism affects phenotype.

Given some of these benefits of mouse models, we have tested whether the results described above for outbred rats translate to mice. With several mouse strains (in- and outbred; e.g., C57BL/6, Balb/c, CD-1), we have conducted pilot studies to determine the relative stability of behavioral inhibition within individuals. To date, we have no good evidence of stable behavioral inhibition across time or any evidence of a reliable relation between fear-related behavior and physiology in these mouse strains. This lack of relation may result from methodological or species differences between mice and rats. For example, behavioral tests and measures with mice may require additional modifications to identify subtle behavioral differences in a species that is one-tenth the size of rats. In addition, in a smaller prey species, there may be less variance in exploratory behavior since high exploration is particularly detrimental in a small species that is easily consumed by predators. Last, by chance or design, mouse breeding histories may have led to less behavioral variance among individuals, which would minimize power to identify reliable individual behavioral differences.

Developing models in mice may require different behavioral tests; however, movement to a viable mouse population could be beneficial, both economically and scientifically. A mouse model may provide more genetic tools to study underlying physiological mechanisms involved in behavioral inhibition and associated health outcomes. However, there are also distinct advantages to a rat model. For example, refined genetic modifications are being used with rats now, and rats carry certain physiological advantages such as a larger body size that allows for more feasible and accurate physiological manipulations and measures. Additionally, many behavioral and physiological processes are more similar between humans and rats as compared to between humans and mice (reviewed in Ellenbroek & Youn, 2016). Thus, additional refinement of a mouse model could provide a specific complement to the rat model, primarily in providing a means to study behavioral inhibition in two rodent species to strengthen the ability to identify a range of mechanisms that support the presentation and maintenance of behavioral inhibition.

Physiological Processes Underlying Rodent Behavioral Inhibition

Based on arguments made at the beginning of this chapter, we are interested in modest physiological response biases associated with behavioral inhibition. Even slight modifications in physiological responses associated with behavioral inhibition could lead to significant cumulative impacts on health over the life span. In a rodent model, the physiological measures that can be most accurately collected are slightly different from those in humans. For example, in humans, minimally invasive fMRI provides an excellent measure of central neurobiological function, and noninvasive methods can be used to measure cardiovascular function (blood pressure, heart rate variability, etc.). In rodents, these technologies are retrofit for a small species, and

involve involuntary and relatively long-term restraint, which may lead to less reliable indices of basal neurobiological or cardiovascular function. However, collecting peripheral blood samples to measure metabolic, endocrine, and immunological responses, and conducting controlled experimental manipulations, can be easily, accurately, and humanely collected in a rodent as compared with children. Given these slight differences in procedural efficacy, we have focused primarily on documenting peripheral physiological correlates of rodent behavioral inhibition, although we have also documented more static alterations in neurobiological function (e.g., receptor binding, receptor gene expression).

Before reviewing physiological response biases present in inhibited rats, we touch on a brief but important issue about different cross-disciplinary use of the term "behavioral inhibition" (see also the chapter "Behavioral Inhibition in Nonhuman Primates: The Elephant in the Room" by Capitanio). Across research domains, the term "behavioral inhibition" refers to slightly different concepts. In classic preclinical biomedical research (i.e., mechanistic/molecular level research with nonhuman animals), "behavioral inhibition" is used to refer to an acute behavioral response to potentially rewarding conditions and is thought to involve behavioral control and clamped impulsivity associated with resilience to drug addiction. Neuronal mechanisms underlying this behavioral response have been studied in an acute fashion, and there is ample information to indicate that this acute behavioral response is related to prefrontal cortex and hippocampus function. This definition of behavioral inhibition is not used in the current chapter.

In the current chapter, I focus on the temperamental aspect of behavioral inhibition, that is, a stable trait associated with chronically altered physiological regulation. Specifically, I review physiological response biases that exist in individuals that regularly show inhibited behavioral responses to novel conditions as opposed to reviewing acute neuronal responses/mechanisms involved in the acute display of behavioral inhibition. Given our focus on developing a model to understand cumulative influences of altered physiological regulation on long-term health conditions, we have focused our research on peripheral rather than central physiological processes that are associated with behavioral inhibition. These peripheral responses influence long-term health trajectories and may help us understand the processes that bias health outcomes in inhibited individuals. In addition, these peripheral physiological processes can be measured in a minimally invasive fashion and therefore documented over time to determine relative stability of physiological response biases associated with behavioral inhibition.

Life Span

In the rodent model, we have documented several physiological correlates of behavioral inhibition. One of the more striking and well-supported results is the shorter life span: stable behaviorally inhibited rats die, on average, 7–8 months earlier than non-BI rats (Cavigelli & McClintock, 2003, Cavigelli et al., 2009). Contextualized

as a percentage of overall median life span, this difference corresponds to a ~15-year difference for humans. We have replicated this shortened life span in two separate cohorts, studied at two different institutions. Importantly, the better predictor of this shortened life span was stable inhibition in a social (as opposed to nonsocial) setting ($\chi^2 = 12.80$ vs. 3.89, $p < 0.01$ vs. $p = 0.14$, Cavigelli et al., 2009), although nonsocial inhibition was also related to life span (e.g., Cavigelli & McClintock, 2003). The greater predictive value of social vs. nonsocial inhibition presents a consistent theme in other domains of the rodent model and is important because this aspect of human behavioral inhibition also seems to be of greater clinical and physiological significance (e.g., Buss et al., 2004, Kertes et al., 2009; see the chapter "The Neural Mechanisms of Behavioral Inhibition" by Jarcho and Guyer).

To understand underlying physiological processes that are associated with behavioral inhibition and that may predict a shorter life span, we have measured several different physiological responses. Based on human studies, two physiological responses that may predict a shortened life span include consistently elevated glucocorticoid levels and increased autonomic activity (e.g., Gilad & Gilad, 1995; McEwen & Seeman, 1999). For example, in a study of human biomarkers of health and longevity, both elevated cortisol production and systolic and diastolic blood pressure were significant predictors of increased mortality rates in older adults adults (Gruenewald, Seeman, Ryff, Karlamangla, & Singer, 2006). In addition, glucocorticoid production in early life may be an important predictor of later childhood maladaptive behaviors (e.g., Pérez-Edgar, Schmidt, Henderson, Schulkin, & Fox, 2008), and in rodents, individuals with elevated glucocorticoid responses are shorter-lived than lower glucocorticoid-producing individuals (Cavigelli et al., 2006; Gilad & Gilad, 1995, Cavigelli & McClintock, 2003, Pérez-Álvarez et al., 2005).

Glucocorticoid Production and Associated Physiology

Based on these suggestions from the literature, and associated health implications of elevated physiological stress, we documented basal and reactive glucocorticoid production in behaviorally inhibited vs. non-BI rats. Consistently across multiple studies, we have found that behaviorally inhibited rats have elevated basal and novelty-induced glucocorticoid production relative to non-BI rats (Cavigelli et al., 2007; Cavigelli & McClintock, 2003). Behaviorally inhibited rats have 20–30% more glucocorticoids in circulation than non-BI rats, and as was seen with behavior, glucocorticoid production within an individual was linearly consistent over time ($r_{53} = 0.37$–0.66, $p < 0.01$ with a test-retest interval of 2–4 months; Cavigelli et al., 2009). Further, elevated basal GC production was better predicted by social inhibition rather than nonsocial inhibition (Cavigelli et al., 2007). Importantly, in the rat model of behavioral inhibition, the magnitude of difference in GC production between behavioral inhibition and non-BI rats is comparable to the difference between behaviorally inhibited and non-BI children GC levels (Kagan et al., 1987; Nachmias et al., 1996).

Similar GC elevations in low-exploration individuals have been documented by others, although there is variance in these results. Variance in results relates to the behavioral tests used and whether the modeled trait is thought to reflect behavioral inhibition or novelty-seeking, two traits that seem related but that do not necessarily represent two ends of the same spectrum (e.g., Cavigelli, 2005; Dellu, Piazza, Mayo, Le Moal, & Simon, 1996; Gentsch, Lichtsteiner, Driscoll, & Feer, 1982; Kabbaj, Devin, Savage, & Akil, 2000; Pérez-Álvarez et al., 2005; Ray & Hansen, 2004). Specifically, when a simple test arena is used (e.g., without rat-sized objects or partners present), variance in exploratory behavior likely reflects variance in novelty-seeking or escape motivation rather than variance in fear. In these simple testing conditions, higher exploration tends to be associated with higher circulating glucocorticoids (e.g., Dellu et al., 1996). However, in more complex test arenas, variance in exploratory behavior likely reflects variance in fear or behavioral inhibition, and in this context, higher exploration is usually associated with lower circulating glucocorticoids (e.g., Cavigelli et al., 2007; Ray & Hansen, 2004).

To determine the relative association between BI-related glucocorticoid (GC) production and health outcomes, we conducted pilot studies to compare variations in GC production to important health outcomes. In a longitudinal study, we found that basal GC production in young adulthood (4–8 months of age) linearly predicted basal metabolic rate in late adulthood (18 months), with greater basal GC production predicting diminished basal metabolic rate in old age ($r_9 = -0.698$, $p < 0.05$; McCarter & Cavigelli n.d.). Interestingly, young adult GC response to an acute challenge did not strongly predict late adult metabolic rate ($r_7 = 0.354$, $p > 0.35$). Similarly, in another correlational life-span study, basal GC production in young adults (4–8 months) was a better predictor of a shorter life span than was young adult acute GC response to a brief challenge ($\chi^2 = 3.16$ vs. 0.21, $p = 0.076$ vs. 0.65, Cavigelli et al., 2009). In other words, a physiological profile that involves elevated basal (i.e., unstimulated) GC production, rather than elevated peak (stimulated) production, may lead to more chronic biological overexposure to GC throughout the life span. Elevated circulating GC during low-stimulation periods likely persists longer than elevated circulating levels after an acute stressor, and this longer-term, albeit lower-grade, over-exposure to GCs during basal periods may be more detrimental for metabolic function and longevity.

Elevated basal GC production in behavioral inhibition is likely just one of many physiological process that may influence health. When we included both basal GC production and degree of behavioral inhibition (i.e., mean latency to approach two different forms of novelty) in a statistical model of life span, each variable accounted for a unique proportion of life-span variance, and stable behavioral inhibition was a better predictor of life span than was elevated basal GC production (Cavigelli et al., 2009). These results suggest that other variables, beyond elevated basal GC levels, account for a shortened life span in behavioral inhibition. These preliminary results suggest specific experimental follow-up studies that can be uniquely conducted in rodents. For example, manipulations of circulating GC levels could determine if slight but chronic GC elevations are enough to alter basal metabolic rate and life span (discussed in “Future Directions”). In addition, with a rodent model, it is possible to chronically manipulate some of the following physiological processes to test their long-term influence on specific health outcomes.

Cardiovascular Function

In humans, a classic physiological correlate of behavioral inhibition is elevated autonomic nervous system activity in response to novelty compared to non-inhibited children (Heponiemi, Keltikangas-Järvinen, Kettunen, Puttonen, & Ravaja, 2004; Kagan et al., 1987; Kagan & Snidman, 1999; Marshall & Stevenson-Hinde, 1998; Stevenson-Hinde & Marshall, 1999). Interestingly, this physiological trait may be relatively consistent over the life span: older adults that self-identify as shy also have elevated sitting systolic blood pressure compared to less shy individuals (Bell et al., 1993). Follow-up studies specifically point to increased sympathetic activity in behaviorally inhibited children estimated from more refined cardiovascular measures such as heart rate variability and respiratory sinus arrhythmia (Burgess, Marshall, Rubin, & Fox, 2003; Kagan & Snidman, 1991; Stifter & Corey, 2001).

To determine if rodent behavioral inhibition is related to elevated autonomic activity, we documented basal and responsive blood pressure and heart rate in behaviorally inhibited and non-BI rats. This work was conducted with a noninvasive blood pressure cuff similar to that used with humans, although with rats the cardiovascular measures require involuntary restraint to minimize animal movement. Restraint necessarily introduces a significant stressor, and thus cardiovascular measures must be interpreted accordingly. To estimate *basal* cardiovascular function, we measured blood pressure and heart rate immediately after placement into the restrainer affixed with an inflatable tail cuff. We estimated cardiovascular *reactivity* by measuring these variables several minutes after the initial introduction to the restrainer/cuff. At rest (i.e., within the first minute of restraint), behaviorally inhibited rats had heart rates that were 5–10% greater (450 vs. 412 BPM) and blood pressures that were 15–20% greater (systolic mean 164 vs. 138 mmHg; diastolic means 94 vs. 82 mmHg) than non-BI rats. In the longer-term response to restraint, behaviorally inhibited rats maintained elevated heart rates and increased blood pressure, while non-BI rats decreased rate and pressure over time (Fig. 1).

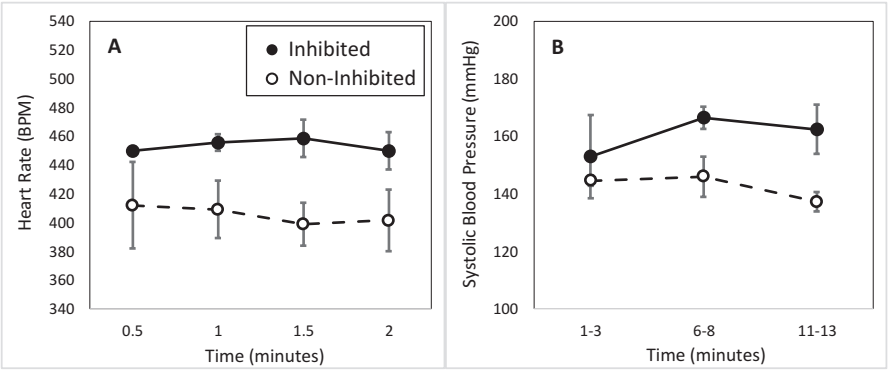

Fig. 1 Mean (**A**) heart rate response, and (**B**) systolic blood pressure response to novelty (restraint) for inhibited (filled circle) and non-inhibited (open circle) adult male Sprague-Dawley rats

Immune Function

Immune function is associated with many of the physiological and health symptoms of BI: altered regulation of cardiovascular function, GC production, life span, allergies, and mental health. We have studied several immune responses in behaviorally inhibited and non-BI rats. Given the low-grade chronic elevation in basal GC production in behaviorally inhibited rats (and potentially in children), we focused on two immune responses that are affected by experimentally induced chronic GC overexposure: innate proinflammatory signaling and localized delayed-type hypersensitivity (DTH) (Dhabhar & McEwen, 1997, 1999; van de Garde et al., 2014).

Given that behaviorally inhibited rats consistently have higher concentration of GC in circulation during basal conditions, we hypothesized that, even in the absence of chronic stress, behaviorally inhibited rat immune cells would experience GC resistance often seen in an individual experiencing chronic stress (i.e., desensitization to the normal anti-inflammatory effects of GC). If this were the case, we would expect an accentuated innate inflammatory response in behaviorally inhibited rats. We also predicted a dampened DTH response as a result of a GC-induced shift toward a T-helper-2-cell-mediated immune bias (Elenkov, 2004). Importantly, this immunological profile could be a risk factor for chronic disorders associated with behavioral inhibition (allergies, asthma, anxiety; Elenkov & Chrousos, 1999; Maggi, 1998).

In support of this hypothesis, in two cohorts of young adult male rats, we found that behaviorally inhibited rats had an elevated acute peripheral interleukin-6 response to a systemic, moderate dose of lipopolysaccharide (an endotoxin) (Michael et al., n.d.). This accentuated response is an index of accentuated innate inflammatory response. Interestingly, in response to this immune challenge, behaviorally inhibited rats also produced more GC than non-BI rats, suggesting that the normal anti-inflammatory action of GC was dampened in behaviorally inhibited rats. This result suggests a testable hypothesis and mechanism for chronic, unregulated peripheral inflammation in behaviorally inhibited children. Behaviorally inhibited rats also had a dampened DTH induration response when re-exposed to a novel non-pyrogenic antigen (keyhole limpet hemocyanin), indicating that not all immune responses are elevated or underregulated. As with GC production, these immune differences between behaviorally inhibited and non-BI rats were more closely associated with a rat's inhibitory response to a novel social rather than nonsocial stimulus (e.g., $r_{25} = 0.40$ vs. 0.23, and $p < 0.05$ vs. ns). In other words, a rat's GC and immune profile were more closely predicted by behavioral response to social novelty as opposed to nonsocial novelty.

Central Neurobiology

Given stable behavioral and physiological differences between behaviorally inhibited and non-BI individuals, we examined evidence of static differences in central neurobiological signaling. Based on prior literature on central mechanisms of stress, anxiety, and fear-related behavior, we focused on GC, corticotropin-releasing hormone, and

serotonergic receptors/transporters in limbic brain areas involved in HPA regulation and stress-related psychopathology (prefrontal cortex, hippocampus, hypothalamus). To examine basal differences in neurotransmitter signaling in behavioral inhibition vs. non-BI (i.e., stable behavioral traits), we focused on static postmortem receptor measures (e.g., receptor mRNA and binding levels), rather than measures of dynamic signaling (e.g., neurotransmitter release, EPSC/IPSC, glucose utilization measures).

Based on receptor gene expression, we found that behaviorally inhibited rats had decreased expression of the glucocorticoid receptor (GR) gene in the hippocampus and serotonin transporter (SERT) gene in the brain stem ($F_{2,26} = 6.33$, $p < 0.01$, $F_{2,21} = 3.37$, $p < 0.01$; Fig. 2). In addition, mean latency to approach both social and nonsocial novelty was a linear predictor of hippocampal and hypothalamic *GR* expression and prefrontal corticotropin-releasing hormone receptor 1 gene (*Crhr1*) expression. Approach latency accounted for 42% and 14% of the variance in *GR* mRNA expression in the hippocampus and hypothalamus, respectively ($\beta = -0.66$, $t_{28} = -4.57$, $p < 0.001$; $\beta = -0.42$, $t_{26} = -2.30$, $p < 0.05$) and 10% of the variance in prefrontal *Crhr1* expression ($\beta = -0.36$, $t_{28} = -2.01$, $p = 0.05$; Caruso, Crouse, & Cavigelli, 2015). In the predator-induced model of rodent behavioral inhibition, hippocampal (CA1) and hypothalamic expression of *homer1a* were linearly and positively associated with a greater behavioral inhibition response (Qi et al. 2010). These differences in gene expression between behaviorally inhibited and non-BI rats are comparable to changes seen in chronically stressed rodents that experience altered HPA axis regulation (Raone et al., 2007; Zhu et al., 2014). Overall, these results suggest that the rat brain in behavioral inhibition functions in a manner that may be comparable to individuals experiencing chronic stress.

In summary, there are several aspects of rat physiology in behavioral inhibition that may suggest important clinical insights about human behavioral inhibition. Briefly, (1) social inhibition, rather than inhibition in nonsocial settings, is a more important predictor of biases in physiological regulation, (2) altered regulation of

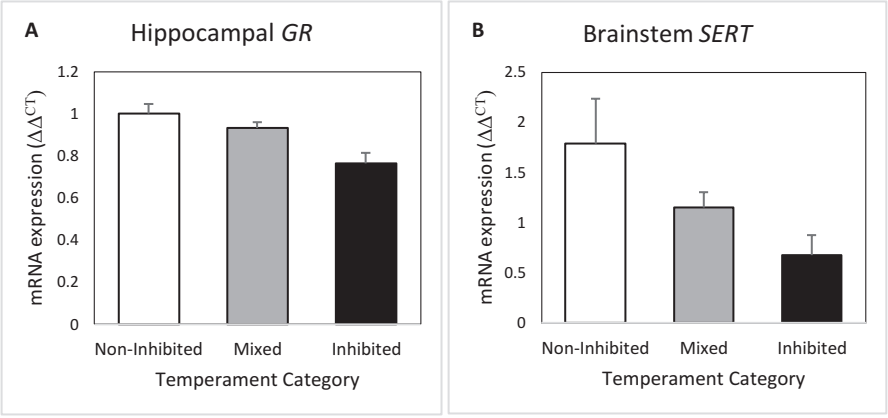

Fig. 2 Central nervous system gene expression. Mean (**A**) hippocampal glucocorticoid receptor and (**B**) brainstem serotonin transporter gene expression in non-inhibited (open square), mixed (gray square), and inhibited (filled square) male Sprague-Dawley rats

basal physiology may be more important than altered regulation of acute physiological responses, and (3) alterations to many physiological processes must be considered when trying to understand underlying mechanisms involved in different health trajectories in behaviorally inhibited vs. non-BI individuals.

Developmental Processes Underlying Rodent Behavioral Inhibition

In humans, a basic trait like behavioral inhibition emerges relatively early in development, but the phenotype can be relatively flexible, with some individuals showing consistent inhibition throughout development and others showing decreased inhibition over time. Clinically, developmental consistency in behavioral inhibition over time appears to be a key predictor of susceptibility to social anxiety (Chronis-Tuscano et al., 2009; Hirshfeld et al., 1992). Given the value of a developmentally predictive behavioral trait that allows for early targeted interventions (Kennedy et al., 2009; Rapee, Kennedy, Ingram, Edwards, & Sweeney, 2005; Rapee, 2013), and greater flexibility of personality traits during childhood/adolescence (e.g. Roberts & Delvecchio, 2000), it is likely that interventions during development rather than adulthood may be more effective (see the chapter "Behavioural Inhibition and the Prevention of Internalising Distress in Early Childhood" by Rapee and Bayer). In addition, attention to early life social contexts (e.g., family dynamics, parenting styles) and their influence on behavioral inhibition physiology and health is key (e.g., Cho & Buss, 2017; Hane & Fox, 2006; Kertes et al., 2009; Kiel & Buss, 2011).

To determine developmental experiences that shape behavioral inhibition in rats, we have examined early and later social predictors of behavioral inhibition (particularly early maternal behavior and later peer social interactions). These studies suggest a certain degree of flexibility in the behavioral inhibition phenotype. Like in humans, there is some evidence that overattentive parenting (in the form of maternal licking/grooming of young pups) is associated with increased behavioral inhibition. In three different studies, we found that differential maternal licking rates among pups in a litter was a good predictor of offspring behavioral inhibition and anxiety-related behavior (Cavigelli, Ragan, Barrett, & Michael, 2010; Ragan, Harding, & Lonstein, 2016; Ragan, Loken, Stifter, & Cavigelli, 2012). Pups that received the most licking were later more inhibited than their littermates and they solicited more maternal responses early in life. That is, they solicited maternal interactions/attention more often than their littermates. These results suggest that increased maternal attention within a litter may not cause increased offspring inhibition but that early life inhibition may be associated with behaviors that solicit increased maternal attention (e.g., Stern, 1997).

These studies are all correlational and thus the causal relation has yet to be determined. In addition, this literature is quite mixed, with abundant historical evidence that mothers that are highly attentive (i.e., maintain high lick/groom rates) produce litters of offspring that are, on the whole, relatively low anxiety (e.g., Caldji et al., 1998; Caldji, Diorio, & Meaney, 2003; Francis, Diorio, Liu, & Meaney, 1999; Meaney, 2001; Pan, Fleming, Lawson, Jenkins, & McGowan, 2014). Thus, in studying early developmental

conditions that enhance or diminish behavioral inhibition, it is important to distinguish variability in maternal behavior among offspring within a family vs. variability among different mothers. In addition, it is important to note whether offspring behavioral and physiological outcomes are more closely related to anxiety or to behavioral inhibition. From the rodent model perspective, there is still much work that could be done to determine the causal role of early offspring-mother interactions in the development of a stable or flexible behavioral inhibition phenotype in offspring. Importantly, with the rodent model, these early developmental questions could be examined experimentally by using creative methods to manipulate maternal licking behavior (e.g., Francis et al., 1999; Lee & Williams, 1974; Lovic & Fleming, 2004).

In addition to early life experiences, we have found that adolescent social experiences can influence adult behavioral inhibition (Caruso et al., 2014). Adolescence represents a final developmental period of behavioral and physiological flexibility, when individuals engage in frequent and diverse extrafamilial social interactions and when both behavior and HPA axis regulation can be shaped by social experiences (Sachser, Kaiser, & Hennessy, 2013). We have found that a lack of novel social experiences during adolescence can cause a transient blunting or shift in behavioral phenotype. Male behaviorally inhibited rats that do not experience novel social partners during adolescence displayed increased exploratory behavior soon after adolescence, compared to those that experienced novel social partners (Caruso et al., 2014).

Importantly, behaviorally inhibited and non-BI rats that showed a transient shift in behavior after exposure to impoverished adolescent social experiences returned to their predictable low or high exploratory phenotypes within a month of their adolescent social experience (Caruso et al., 2014). However, GC production in these animals seemed to be persistently altered into adulthood. Non-BI rats that had been exposed to novel social experiences during adolescence produced expected low-GC production relative to similarly treated behaviorally inhibited rats. However, non-BI rats exposed to impoverished adolescent social experiences had increased GC production in adulthood and no longer showed the expected lower GC production relative to their behaviorally inhibited littermates. These studies suggest that while behaviorally inhibited and non-BI behavior may be transiently altered by adolescent social experiences, physiological processes may be re-regulated in a more permanent fashion by adolescent social experiences. This work carries important significance in terms of understanding how early social interventions may alter underlying physiological biases that may be responsible for health trajectories in behavioral inhibition.

Future Directions and Limitations

Broadly speaking, there are two main areas for future work. The first involves building on the correlational validation studies reviewed here. The major benefits of a preclinical rodent model center on the power provided to conduct experimental and longitudinal studies that are prohibitive with humans. The second area for future work involves increased characterization of sex differences underlying the development, physiology, and health consequences of behavioral inhibition.

Experimental/Longitudinal Studies

Basic studies with outbred rodents, and other species, indicate that behavioral inhibition is a basic trait that can be identified relatively early on in development, is relatively stable in certain individuals, and is associated with predictable physiological response biases, which may also be relatively stable within individuals. Given these similarities between human and rodent behavioral inhibition, future experimental work should test (1) the relative role of different physiological biases in predicting health outcomes and (2) the influence of environmental conditions on the development and health consequences of the trait. In particular, environmental manipulations during later childhood and adolescence may be particularly beneficial since this represents a later period of behavioral and physiological "programming" and an age at which school interventions may be more easily implemented.

In terms of manipulating underlying physiology, experimental rodent studies provide a means to ask whether underlying physiological processes associated with behavioral inhibition are a causal agent in altered health and life-span trajectories in behavioral inhibition. If underlying physiological processes are key mediators of health trajectories associated with behavioral inhibition, then this work would suggest interventions that target physiological processes rather than interventions aimed toward altering behavior per se. A specific example of a possible appropriate physiological manipulation in the rodent model involves chronic manipulation of basal GC production. As a first experimental study, this manipulation would be useful because basal GC production is trait-like and relevant to other physiological processes, such as metabolic and immune function, and is related to life span in the rodent model. Further, basal GC production is relevant to the same health-related processes in humans and other species.

In preliminary tests, we have used a noninvasive method to alter basally circulating GC levels in a physiologically relevant manner by administering corticosterone in drinking water. This method allows for circulating GC manipulations that mimic those seen in behaviorally inhibited rats while also maintaining circadian and pulsatile rhythmicity of normal GC release into circulation (Fig. 3).

This manipulation works elegantly because rats drink more during the active period, which is the time when circulating corticosterone levels are normally highest during the 24-h day. In addition, rats drink in bouts that occur every 60–90 min which mimics the natural frequency of corticosterone pulses in rats (Kakolewski, Deaux, Christensen, & Case, 1971; Lightman et al., 2008; Marwine & Collier, 1979). With this manipulation, we found no evidence of behavioral changes, although this would have to be replicated in a larger study. Other physiological manipulations are also possible, and, like the described GC manipulation, these manipulations can be designed to be minimally invasive so that they can be sustained over time and made to mimic naturally occurring physiological differences between behaviorally inhibited and non-BI individuals. This allows for specific physiological processes to be manipulated while monitoring lifelong health outcomes.

The rodent behavioral inhibition model also provides a means to determine, experimentally, how developmental experiences influence the trajectory of the trait, at both the behavioral and physiological level. Theoretically, it will be of interest to determine if a transient and/or permanent change in behavioral predisposition

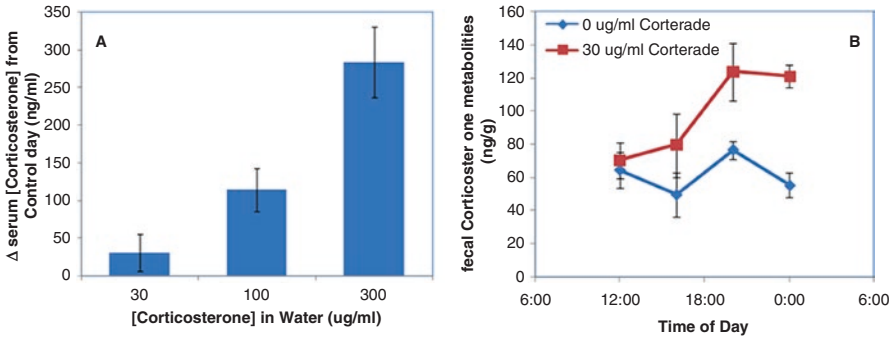

Fig. 3 Experimental manipulation of circulating glucocorticoids. (**A**) Mean relative increase in circulating corticosterone levels in male Sprague-Dawley rats provided one of three corticosterone concentrations in the home cage drinking water. Rats provided with water that had a 30 μg/ml concentration of corticosterone showed a relative increase in circulating concentrations that most closely mimicked the naturally-occurring increase in circulating GCs in BI rats. (**B**) Mean excreted corticosterone metabolite levels across the day in male rats provided *ad lib* home-cage access to pure tap water (blue line: "0 μg/ml Corterade") vs. tap water with low corticosterone concentration (red line: "30 μg/ml Corterade"). Experimentally increased GC levels are most pronounced during the active portion of the day (20:00 and 0:00 h)

induced during development leads to long-term changes in either health outcomes and/or underlying physiological processes that influence health. It is highly likely, as we found previously, that underlying physiological processes may be more open to "permanent reprogramming" during postnatal life than are behavioral processes. Behavioral profiles may involve more complex cognitive/learning processes that are more difficult to shift in a permanent manner. This could be of interest clinically—it may be that behavioral inhibition, defined according to behavioral repertoire, can remain intact while a permanent shift can occur in correlated physiological processes (e.g., basal GC production, innate immune responses, etc.). If we find that the physiology of innate behavioral inhibition presents itself as a major mediator of health, then the ideal goal may be to alter the physiology rather than the behavior of behavioral inhibition. In terms of environmental experimental manipulations, the focus will likely be on early developmental experiences, when behavioral and physiological traits are more flexible, fluid, and less fixed.

Sex Differences

A final area for future study involves a better characterization of the sex differences involved in the development, physiology, and health trajectories of behavioral inhibition. At present, in rodent models, there is strong evidence that behavioral tests to quantify behavioral inhibition are more sensitive or accurate for identifying behavioral inhibition in male rather than female rodents (e.g., Cavigelli et al., 2011; Qi et al., 2010). Some studies suggest that major exploratory motivations in rodents differ for males and females and that these differences may drive differential sensitivity of tests for identifying a reticent exploratory style in males vs. females

(Fernandes, González, Wilson, & File, 1999; Ray & Hansen, 2004). In particular, females are more active and more exploratory than males (Cavigelli et al., 2011; Ray & Hansen, 2004), and based on careful behavioral analyses, Ray and Hansen (2004) concluded that these rodent sex differences reflect a female bias toward more novelty-seeking behaviors vs. a male bias toward more harm-avoidance behaviors. Thus, it is possible that males prefer and need to be tested on a simpler novel environment, while females seek and require more complex stimulation (Pisula & Siegel, 2005).

In prior studies with older male and female Sprague-Dawley rats, we have seen opposite relationships between exploratory behavior and glucocorticoid reactivity for males vs. females. For males, increased locomotion in a novel environment was associated with low glucocorticoid responses to novelty, indicative of low fear (Cavigelli & McClintock, 2003), whereas in females, increased locomotion was associated with increased glucocorticoid production, indicative of elevated sensation-seeking (Cavigelli et al., 2006). These results were documented in relatively old rats where sex steroids in females were declining, and differential aging of the reproductive system among high- and low-active females may have accounted for the differences. Thus, further research is required on the developmental and physiological processes that may underlie sex differences in behavioral inhibition and whether these processes are related between humans and animals.

Conclusions

Studies on rodent behavioral inhibition suggest many parallel links with human behavioral inhibition: behavioral and physiological stability parameters are similar, the trait can be identified early in development and predicts later behavior and physiology, and developmental interventions seem to have some lasting influences on underlying mechanisms associated with behaviorally inhibited health trajectories. These parallels suggest that behavioral inhibition is a fundamental trait that likely can be well-modeled in other species, with the expected limitations of any animal model. The rodent model provides a unique arena to experimentally test causal relationships and to conduct life-span longitudinal studies to understand change in both behavioral and physiological traits, their relative stability over time, and their relationship to health outcomes.

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References

Bell, I. R., Martino, G. M., Meredith, K. E., Schwartz, G. E., Siani, M. M., & Morrow, F. D. (1993). Vascular disease risk factors, urinary free cortisol, and health histories in older adults: Shyness and gender interactions. *Biological Psychology, 35*, 37–49.

Biederman, J., Rosenbaum, J. F., Hirshfeld, D. R., Faraone, S. V., Bolduc, E. A., Gersten, M., … Reznick, J. S. (1990). *Archives of General Psychiatry, Psychiatric correlates of behavioral inhibition in young children of parents with and without psychiatric disorders. 47*, 21–26.

Blanchard, R. J., Flannelly, K. J., & Blanchard, D. C. (1986). Defensive behaviors of laboratory and wild *Rattus norvegicus*. *Journal of Comparative Psychology, 100*, 101–107.

Blanchard, R. J., Nikulina, J. N., Sakai, R. R., McKittrick, C., McEwen, B., & Blanchard, D. C. (1998). Behavioral and endocrine change following chronic predatory stress. *Physiology & Behavior, 63*, 561–569.

Brindley, D. N., & Rolland, Y. (1989). Possible connections between stress, diabetes, obesity, hypertension and altered lipoprotein metabolism that may result in arteriosclerosis. *Clinical Science, 77*, 453–461.

Burgess, K. B., Marshall, P. J., Rubin, K. H., & Fox, N. A. (2003). Infant attachment and temperament as predictors of subsequent externalizing problems and cardiac physiology. *Journal of Child Psychology and Psychiatry, 44*, 819–831.

Buss, A. H., & Plomin, R. (1984). *Temperament: Early developing personality traits*. Hillsdale, NJ: Lawrence Erlbaum Associates.

Buss, K. A., Davidson, R. J., Kalin, N. H., & Goldsmith, H. H. (2004). Context-specific freezing and associated physiological reactivity as a dysregulated fear response. *Developmental Psychology, 40*, 583–594.

Caldji, C., Diorio, J., & Meaney, M. J. (2003). Variations in maternal care alter $GABA_A$ receptor subunit expression in brain regions associated with fear. *Neuropsychopharmacology, 28*, 1950–1959.

Caldji, C., Tannenbaum, B., Sharma, S., Francis, D., Plotsky, P. M., & Meaney, M. J. (1998). Maternal care during infancy regulates the development of neural systems mediating the expression of neural systems mediating the expression of behavioral fearfulness in adulthood in the rat. *Proceedings of the National Academy of Sciences of the United States of America, 95*, 5335–5340.

Campeau, S., Nyhuis, T. J., Sasse, S. K., Day, H. E., & Masini, C. V. (2008). Acute and chronic effects of ferret odor exposure in Sprague-Dawley rats. *Neuroscience and Biobehavioral Reviews, 32*, 1277–1286.

Caruso, M. J., Crouse, R. A., & Cavigelli, S. A. (2015). *Corticosteroid receptor expression is linearly related to individual differences in novelty exploration*. Poster presented International Society for Developmental Psychobiology. *Developmental Psychobiology, 57*, 866.

Caruso, M. J., McClintock, M. K., & Cavigelli, S. A. (2014). Temperament moderates the influence of periadolescent social experience on behavior and adrenocortical activity in adult male rats. *Hormones and Behavior, 66*, 517–524.

Cavigelli, S. A. (2005). Animal personality and health. *Behaviour, 142*, 1223–1244.

Cavigelli, S. A., & McClintock, M. K. (2003). Fear of novelty in infant rats predicts adult corticosterone dynamics and an early death. *Proceedings of the National Academy of Sciences of the United States of America, 100*, 16131–16136.

Cavigelli, S. A., Michael, K. C., & Ragan, C. M. (2013). Behavioral, physiological, and health biases in laboratory rodents: A basis for understanding mechanistic links between human personality and health. In C. Carere & D. Maestripieri (Eds.), *Animal personalities: Behavior, physiology and evolution*. Chicago, IL: University of Chicago Press.

Cavigelli, S. A., Michael, K. C., West, S. G., & Klein, L. C. (2011). Behavioral responses to physical vs. social novelty in male and female laboratory rats. *Behavioural Processes, 88*, 56–59.

Cavigelli, S. A., Ragan, C. M., Barrett, C. E., & Michael, K. C. (2010). Within-litter variance in rat maternal behavior. *Behavioural Processes, 84*, 696–704.

Cavigelli, S. A., Stine, M. M., Kovacsics, C., Jefferson, A., Diep, M. N., & Barrett, C. E. (2007). Behavioral inhibition and glucocorticoid dynamics in a rodent model. *Physiology & Behavior, 92*, 897–905.

Cavigelli, S. A., Yee, J. R., McClintock, M. K. (2006). Infant temperament predicts life span in female rats that develop spontaneous tumors. *Hormones and Behavior, 50*, 454–62.

Cavigelli, S. A., Ragan, C. M., Michael, K. C., Kovacsics, C. E., Bruscke, A. P. (2009). Stable behavioral inhibition and glucocorticoid production as predictors of longevity. *Physiology & Behavior, 98*, 205–14.

Cho, S., & Buss, K. A. (2017). Toddler parasympathetic regulation and fear: Links to maternal appraisal and behavior. *Developmental Psychobiology, 59*, 197–208.

Chronis-Tuscano, A., Degnan, K. A., Pine, D. S., Pérez-Edgar, K., Henderson, H. A., Diaz, Y., … Fox, N. A. (2009). Stable early maternal report of behavioral inhibition predicts lifetime social anxiety disorder in adolescence. *Journal of the American Academy of Child and Adolescent Psychiatry, 48*, 928–935.

Clauss, J. A., & Blackford, J. U. (2012). Behavioral inhibition and risk for developing social anxiety disorder: A meta-analytic study. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*, 1066–1075.

Costa, P. T., & McCrae, R. R. (1992). Four ways five factors are basic. *Personality and Individual Differences, 13*, 653–665.

Dellu, F., Piazza, P. V., Mayo, W., Le Moal, M., & Simon, H. (1996). Novelty-seeking in rats: Biobehavioral characteristics and possible relationship with the sensation-seeking trait in man. *Neuropsychobiology, 34*, 136–145.

Dhabhar, F. S., & McEwen, B. S. (1997). Acute stress enhances while chronic stress suppresses cell-mediated immunity in vivo: A potential role for leukocyte trafficking. *Brain, Behavior, and Immunity, 11*, 286–306.

Dhabhar, F. S., & McEwen, B. S. (1999). Enhancing versus suppressive effects of stress hormones on skin immune function. *Proceedings of the National Academy of Sciences of the United States of America, 96*, 1059–1064.

Einon, D. F., & Morgan, M. (1976). Habituation of object contact in socially-reared and isolated rats (*Rattus norvegicus*). *Animal Behaviour, 24*, 415–420.

Elenkov, I. J. (2004). Glucocorticoids and the Th1/Th2 balance. *Annals of the New York Academy of Sciences, 1024*, 138–146.

Elenkov, I. J., & Chrousos, G. P. (1999). Stress hormones, Th1/Th2 patterns, pro/−anti-inflammatory cytokines and susceptibility to disease. *Trends in Endocrinology and Metabolism, 10*, 359–368.

Ellenbroek, B., & Youn, J. (2016). Rodent models in neuroscience research: is it a rat race? *Disease Models and Mechanisms, 9*, 1079–1087.

Fernandes, C., González, M. I., Wilson, C. A., & File, S. E. (1999). Factor analysis shows that female rat behaviour is characterized primarily by activity, male rats are driven by sex and anxiety. *Pharmacology, Biochemistry, and Behavior, 64*, 731–738.

Forster, S. E., Finn, P. R., & Brown, J. W. (2017). Neural responses to negative outcomes predict success in community-based substance use treatment. *Addiction, 112*, 884–896.

Francis, D. D., Diorio, J., Liu, D., & Meaney, M. J. (1999). Nongenomic transmission across generations of maternal behavior and stress responses in the rat. *Science, 286*, 1155–8.

García-Coll, C., Kagan, J., & Reznick, J. S. (1984). Behavioral inhibition in young children. *Child Development, 55*, 1005–1019.

Gatt, J. M., Clark, C. R., Kemp, A. H., Liddell, B. J., Dobson-Stone, C., Kuan, S. A., … Williams, L. M. (2007). A genotype-endophenotype-phenotype path model of depressed mood: Integrating cognitive and emotional markers. *Journal of Integrative Neuroscience, 6*, 75–104.

Gentsch, C., Lichtsteiner, M., Driscoll, P., & Feer, H. (1982). Differential hormonal and physiological response to stress in roman high and low-avoidance rats. *Physiology & Behavior, 28*, 259–263.

Gilad, G. M., & Gilad, V. H. (1995). Strain, stress, neurodegeneration and longevity. *Mechanisms of Ageing and Development, 78*, 75–83.

Gosling, S. D., & John, O. P. (1999). Personality dimensions and non-human animals: A cross-species review. *Current Directions in Psychological Science, 8*, 69–75.

Gruenewald, T. L., Seeman, T. E., Ryff, C. D., Karlamangla, A. S., & Singer, B. H. (2006). Combinations of biomarkers predictive of later life mortality. *Proceedings of the National Academy of Sciences of the United States of America, 103*, 14158–14163.

Gurevitz, M., Geva, R., Varon, M., & Leitner, Y. (2014). Early markers in infants and toddlers for development of ADHD. *Journal of Attention Disorders, 18*, 14–22.

Hane, A. A., & Fox, N. A. (2006). Ordinary variations in maternal caregiving influence human infants' stress reactivity. *Psychological Science, 17*, 550–556.

Heponiemi, T., Keltikangas-Järvinen, L., Kettunen, J., Puttonen, S., & Ravaja, N. (2004). BIS-BAS sensitivity and cardiac autonomic stress profiles. *Psychophysiology, 41*, 37–45.

Hirshfeld, D. R., Rosenbaum, J. F., Biederman, J., Bolduc, E. A., Faraone, S. V., Snidman, N., … Kagan, J. (1992). Stable behavioral inhibition and its association with anxiety disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 31*, 103–111.

Hirshfeld-Becker, D. R., Biederman, J., Henin, A., Faraone, S., Davis, S., Harrington, K., & Rosenbaum, J. F. (2007). Behavioral inhibition in preschool children at risk is a specific predictor of middle childhood social anxiety: A five-year follow-up. *Journal of Developmental and Behavioral Pediatrics, 28*, 225–233.

Kabbaj, M., Devin, D. P., Savage, V. R., & Akil, H. (2000). Neurobiological correlates of individual differences in novelty-seeking behavior in the rat: Differential expression of stress-related molecules. *The Journal of Neuroscience, 20*, 6983–6988.

Kagan, J., Reznick, J. S., Clarke, C., Snidman, N., & García-Coll, C. (1984). Behavioral inhibition to the unfamiliar. *Child Development, 55*, 2212–2225.

Kagan, J., Reznick, J. S., & Snidman, N. (1987). The physiology and psychology of behavioral inhibition in children. *Child Development, 58*, 1459–1473.

Kagan, J., & Snidman, N. (1991). Infant predictors of inhibited and uninhibited profiles. *Psychological Science, 2*, 40–44.

Kagan, J., & Snidman, N. (1999). Early childhood predictors of adult anxiety disorders. *Biological Psychiatry, 46*, 1536–1541.

Kagan, J., Snidman, N., McManis, M., Woodward, S., & Hardway, C. (2002). One measure, one meaning: Multiple measures, clear meaning. *Development and Psychopathology, 14*, 463–475.

Kakolewski, J. W., Deaux, E., Christensen, J., & Case, B. (1971). Diurnal patterns of water and food intake and body weight changes in rats with hypothalamic lesions. *The American Journal of Physiology, 221*, 711–718.

Kennedy, S. J., Rapee, R. M., Edwards, S. L. (2009). A selective intervention program for inhibited preschool-aged children of parents with an anxiety disorder: effects on current anxiety disorders and temperament. *Journal of the American Academy of Child and Adolescent Psychiatry, 48*, 602–9.

Kertes, D. A., Donzella, B., Talge, N. M., Garvin, M. C., Van Ryzin, M. J., & Gunnar, M. R. (2009). Inhibited temperament and parent emotional availability differentially predict young children's cortisol responses to novel social and nonsocial events. *Developmental Psychobiology, 51*, 521–532.

Kiel, E. J., & Buss, K. A. (2011). Prospective relations among fearful temperament, protective parenting, and social withdrawal: The role of maternal accuracy in a moderated mediation framework. *Journal of Abnormal Child Psychology, 39*, 953–966.

Lee, M., & Williams, D. (1974). Changes in licking behavior of rat mother following handling of young. *Animal Behaviour, 22*, 679–681.

Lightman, S. L., Wiles, C. C., Atkinson, H. C., Henley, D. E., Russell, G. M., Leendertz, J. A., … Conway-Campbell, B. L. (2008). The significance of glucocorticoid pulsatility. *European Journal of Pharmacology, 583*, 255–262.

Lovic, V., & Fleming, A. S. (2004). Artificially-reared female rats show reduced prepulse inhibition and deficits in the attentional shifting task – reversal of effects with maternal-licking stimulation. *Behavioural Brain Research, 148*, 209–219.

Maggi, E. (1998). The Th1/Th2 paradigm in allergy. *Immunotechnology, 3*, 233–44.
Marshall, P. J., & Stevenson-Hinde, J. (1998). Behavioral inhibition, heart period, and respiratory sinus arrhythmia in young children. *Developmental Psychobiology, 33*, 283–292.
Marwine, A., & Collier, G. (1979). The rat at the waterhole. *Journal of Comparative and Physiological Psychology, 93*, 391–402.
McCarter R. J., & Cavigelli S. A. Behavior and glucocorticoid production in young adulthood predicts metabolic rate in late adulthood. Manuscript.
McEwen, B. S., & Seeman, T. (1999). Protective and damaging effects of mediators of stress: Elaborating and testing the concepts of allostasis and allostatic load. *Annals of the New York Academy of Sciences, 896*, 30–47.
Meaney, M. J. (2001). Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annual Review of Neuroscience, 24*, 1161–1192.
Michael, K., Bonneau, R. H., Crouse, R. A., Godbolt, L., Caruso, M. J., Hohmann, C., & Cavigelli, S. A. in press Divergent immune responses in high- vs low-exploration rats. Under revision.
Morales, S., Pérez-Edgar, K. E., & Buss, K. A. (2015). Attention biases towards and away from threat mark the relation between early dysregulated fear and the later emergence of social withdrawal. *Journal of Abnormal Child Psychology, 43*, 1067–1078.
Nachmias, M., Gunnar, M., Mangelsdorf, S., Parritz, R. H., & Buss, K. (1996). Behavioral inhibition and stress reactivity: The moderating role of attachment security. *Child Development, 67*, 508–522.
Nanda, S. A., Qi, C., Roseboom, P. H., & Kalin, N. H. (2008). Predator stress induces behavioral inhibition and amygdala somatostatin receptor 2 gene expression. *Genes, Brain, and Behavior, 7*, 639–648.
O'Leary-Barrett, M. Mâsse, B. Pihl, R., Stewart, S., Séguin, J. R., & Conrod, P. (2017). A cluster-randomised controlled trial evaluating the effects of delaying onset of adolescent substance abuse on cognitive development and addiction following a selective, personality-targeted intervention program: The co-venture trial. Addiction*,* Epub ahead of print. *112*, 1871–81
Pan, P., Fleming, A. S., Lawson, D., Jenkins, J. M., & McGowan, P. O. (2014). Within- and between-litter maternal care alter behavior and gene regulation in female offspring. *Behavioral Neuroscience, 128*, 736–748.
Pérez-Álvarez, L., Baeza, I., Arranz, L., Marco, E. M., Borcel, E., Guaza, C., … De la Fuente, M. (2005). Behavioral, endocrine and immunological characteristics of a murine model of premature aging. *Developmental and Comparative Immunology, 29*, 965–976.
Pérez-Edgar, K., & Fox, N. A. (2005). Temperament and anxiety disorders. *Child & Adolescent Psychiatric Clinics of North America, 14*, 681–706.
Pérez-Edgar, K., Reeb-Sutherland, B. C., McDermott, J. M., White, L. K., Henderson, H. A., Degnan, K. A., … Fox, N. A. (2011). Attention biases to threat link behavioral inhibition to social withdrawal over time in very young children. *Journal of Abnormal Child Psychology, 39*, 885–895.
Pérez-Edgar, K., Schmidt, L. A., Henderson, H. A., Schulkin, J., & Fox, N. A. (2008). Salivary cortisol levels and infant temperament shape developmental trajectories in boys at risk for behavioral maladjustment. *Psychoneuroendocrinology, 33*, 916–925.
Pisula, W., & Siegel, J. (2005). Exploratory behavior as a function of environmental novelty and complexity in male and female rats. *Psychological Reports, 97*, 631–638.
Qi, C., Roseboom, P. H., Nanda, S. A., Lane, J. C., Speers, J. M., Kalin, N. H. (2010). Anxiety-related behavioral inhibition in rats: a model to examine mechanisms underlying the risk to develop stress-related psychopathology. *Genes, Brain and Behavior, 9*, 974–84.
Ragan, C. M., Harding, K. M., & Lonstein, J. S. (2016). Associations among within-litter differences in early mothering received and later emotional behaviors, mothering, and cortical tryptophan hydroxylase-2 expression in female laboratory rats. *Hormones and Behavior, 77*, 62–71.
Ragan, C. M., Loken, E., Stifter, C. A., & Cavigelli, S. A. (2012). Within-litter variance in early rat pup-mother interactions and adult offspring responses to novelty. *Developmental Psychobiology, 54*, 199–206.

Raone, A., Cassanelli, A., Scheggi, S., Rauggi, R., Danielli, B., & De Montis, M. G. (2007). Hypothalamus-pituitary-adrenal modifications consequent to chronic stress exposure in an experimental model of depression in rats. *Journal of Neuroscience, 146*, 1734–1742.

Rapee, R. M. (2013). The preventative effects of a brief, early intervention for preschool-aged children at risk for internalizing: Follow-up into middle adolescence. *Journal of Child Psychology and Psychiatry, 54*, 780–788.

Rapee, R. M., Kennedy, S., Ingram, M., Edwards, S., & Sweeney, L. (2005). Prevention and early intervention of anxiety disorders in inhibited preschool children. *Journal of Consulting and Clinical Psychology, 73*, 488–497.

Ray, J., & Hansen, S. (2004). Temperament in the rat: Sex differences and hormonal influences on harm avoidance and novelty seeking. *Behavioral Neuroscience, 118*, 488–497.

Réale, D., Reader, S. M., Sol, D., McDougall, P. T., & Dingemanse, N. J. (2007). Integrating animal temperament within ecology and evolution. *Biological Reviews, 82*, 291–318.

Reeb-Sutherland, B. C., Helfinstein, S. M., Degnan, K. A., Pérez-Edgar, K., Henderson, H. A., Lissek, S., … Fox, N. A. (2009). Startle response in behaviorally inhibited adolescents with a lifetime occurrence of anxiety disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 48*, 610–617.

Reeb-Sutherland, B. C., Vanderwert, R. E., Degnan, K. A., Marshall, P. J., Pérez-Edgar, K., Chronis-Tuscano, A., … Fox, N. A. (2009). Attention to novelty in behaviorally inhibited adolescents moderates risk for anxiety. *Journal of Child Psychology and Psychiatry, 50*, 1365–1372.

Reznick, J. S., Kagan, J., Snidman, N., Gersten, M., Baak, K., & Rosenberg, A. (1986). Inhibited and uninhibited children: A follow-up study. *Child Development, 57*, 660–680.

Roberts, B. W., & Delvecchio, W. F. (2000). The rank-order consistency of personality traits from childhood to old age: A quantitative review of longitudinal studies. *Psychological Bulletin, 126*, 3–25.

Rothbart, M. K., Ahadi, S. A., Hershey, K. L., & Fisher, P. (2001). Investigations of temperament at three to seven years: The children's behavior questionnaire. *Child Development, 72*, 1394–1408.

Sachser, N., Kaiser, S., & Hennessy, M. B. (2013). Behavioural profiles are shaped by social experience: When, how and why. *Philosophical Transactions of the Royal Society B, 368*, 20120344

Schneirla, T. C. (1965). Aspects of stimulation and organization in approach/withdrawal processes underlying vertebrate behavioral development. *Advances in the Study of Behaviour, 1*, 1–74.

Schwartz, C. E., Snidman, N., & Kagan, J. (1999). *Journal of the American Academy of Child and Adolescent Psychiatry, 38*, 1008–1015.

Schwartz, C. E., Wright, C. I., Shin, L. M., Kagan, J., & Rauch, S. L. (2003). Inhibited and uninhibited infants "grown up": Adult amygdalar response to novelty. *Science, 300*, 1952–1953.

Stern, J. M. (1997). Offspring-induced nurturance: Animal-human parallels. *Developmental Psychobiology, 31*, 19–37.

Stevenson-Hinde, J., & Marshall, P. J. (1999). Behavioral inhibition, heart period, and respiratory sinus arrhythmia: An attachment perspective. *Child Development, 70*, 805–816.

Stevenson-Hinde, J., Stillwell-Barnes, R., & Zunz, M. (1980). Subjective assessment of rhesus monkeys over four successive years. *Primates, 21*, 66–82.

Stifter, C. A., & Corey, J. M. (2001). Vagal regulation and observed social behavior in infancy. *Social Development, 10*, 189–201.

Suomi, S. J. (1987). Genetic and maternal contributions to individual differences in rhesus monkey behavioral development. In N. A. Krasnegor, E. M. Blass, & M. A. Hofer (Eds.), *Perinatal development: A psychobiological perspective* (pp. 397–419). San Diego, CA: Academic Press.

Swan, G. E., & Carmelli, D. (1996). Curiosity and mortality in aging adults: A 5-year follow-up of the western collaborative group study. *Psychology and Aging, 11*, 449–453.

Takahashi, L. K., & Kim, H. (1994). Intracranial action of corticosterone facilitates the development of behavioral inhibition in the adrenalectomized preweanling rat. *Neuroscience Letters, 176*, 272–276.

Thomas, A., & Chess, S. (1977). *Temperament and development*. New York, NY: Brunner/Mazel.

Turner, S. M., Beidel, D. C., & Wolff, P. L. (1996). Is behavioral inhibition related to the anxiety disorders? *Clinical Psychology Review, 16*, 157–172.

van de Garde, M. D. B., Martinez, F. O., Melgert, B. N., Hylkema, M. N., Jonkers, R. E., & Hamann, J. (2014). Chronic exposure to glucocorticoids shapes gene expression and modulates innate and adaptive activation pathways in macrophages with distinct changes in leukocyte attraction. *Journal of Immunology, 192*, 1196–1208.

Wilckens, T., & De Rijk, R. (1997). Glucocorticoids and immune function: Unknown dimensions and new frontiers. *Immunology Today, 18*, 418–424.

Wilson, D. S., Clark, A. B., Coleman, K., & Dearstyne, T. (1994). Shyness and boldness in humans and other animals. *Trends in Ecology & Evolution, 9*, 442–446.

Zhu, L., Liu, M., Li, H., Chen, C., Han, Z., Wu, H., . . . Zhou, QG. (2014). The different roles of glucocorticoids in the hippocampus and hypothalamus in chronic stress-induced HPA axis hyperactivity. *PLoS One 9:* e97689.

The Neural Mechanisms of Behavioral Inhibition

Johanna M. Jarcho and Amanda E. Guyer

Abstract Unfamiliar people, places, and objects often elicit wariness and distress in behaviorally inhibited infants. As behaviorally inhibited infants mature through childhood and become adolescents, peer-based social situations become the driving source of this wariness. The conflict between a desire for positive social interactions and fear of negative evaluation interferes with one of the primary "jobs" of adolescence: learning to successfully navigate an increasingly complex social world. Neural networks involved in social information processing, social learning, and social competence contribute to the maladaptive approach and avoidance response patterns and tendencies associated with behavioral inhibition. In the present chapter, we review the neural networks involved in social competence and social cognition, discuss key links between altered neural function and social cognition associated with behavioral inhibition, and highlight gaps in the field. Finally, we propose future directions to advance our understanding of the neural mechanisms that underlie behaviors and cognition elicited in novel social contexts for behaviorally inhibited youth.

The Neural Mechanisms of Behavioral Inhibition

Parents are often surprised, and at times dismayed, when they discover that their week-old infant already exhibits distinct characteristics. Yet, few bleary-eyed moms and dads suspect what the last three decades of research have led us to understand: these early emerging temperamental traits have an enduring fingerprint on their child's brain and behavior. Behavioral inhibition (BI) is one such temperamental

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trait, manifesting as the expression of distress, negative affect, or withdrawal in response to novel stimuli that are thought of as potential threats (Fox, Henderson, Marshall, Nichols, & Ghera, 2005; Kagan & Snidman, 1991). During infancy, a wide range of stimuli elicits this response pattern from infants likely to later show behavioral inhibition. However, as infants mature, unfamiliar social stimuli become primary elicitors of wariness. In novel social contexts, these children are often easy to detect—they tend to hover at the periphery of peer-based activities, anxiously observing the other children at play, perhaps partially desiring to be part of the fray, but never actually joining in (Coplan, Rubin, Fox, Calkins, & Stewart, 1994; Henderson, Marshall, Fox, & Rubin, 2004). Such behavior may reflect a conflict between a developmentally normative desire for positive peer-based interaction and an innate fear of social threat or rejection conferred by behavioral inhibition.

What happens when a child's temperamental tendency, starting in very early life, biases them away from the very experiences that promote social interactions and learning that are typically considered adaptive? One consequence may be a failure to receive reinforcement for behavior that would otherwise promote social competence and adaptation to social situations and minimize social mishaps. The absence of such peer-based social cues and feedback may disrupt a critical developmental milestone of late childhood and early adolescence: learning to navigate an increasingly complex social world successfully (Rubin, Coplan, & Bowker, 2009). Because this disruption in positive social reinforcement occurs during a critical phase of brain development, it may have lasting detrimental consequences for social learning and adaptation. This may be in part due to neural network fine-tuning that contributes to elevated rates of psychopathology and negative peer-based relations in individuals with childhood behavioral inhibition.

For example, childhood behavioral inhibition predicts a four- to seven-fold increased risk for developing social anxiety disorder in adolescence (Chronis-Tuscano et al., 2009; Clauss & Blackford, 2012). Children with behavioral inhibition are also more likely to develop substance use disorders, potentially reflecting the use of maladaptive strategies to cope with social distress (Lahat et al., 2012; Williams et al., 2010). Coping strategies may need to be implemented more often by children with behavioral inhibition (Rubin et al., 2009), as they experience heightened rates of peer victimization and ostracism (Affrunti, Geronimi, & Woodruff-Borden, 2014; Deater-Deckard, 2001; Hanish & Guerra, 2004; Kochenderfer-Ladd, 2003; Newcomb, Bukowski, & Pattee, 1993; Sugimura & Rudolph, 2012) and high rates of problems with peers (Hasenfratz, Benish-Weisman, Steinberg, & Knafo-Noam, 2015). Yet, other children seemingly overcome the negative effects of childhood behavioral inhibition and transition into adolescence and adulthood without social deficits or psychological disorders. Thus, the answer to our initial question, while potentially unsatisfying to parents yet intriguing to researchers, is a familiar one: it depends. It depends on neurobiology and environmental inputs.

In this chapter, we explore the neural mechanisms that promote or prevent poor psychosocial outcomes associated with childhood behavioral inhibition. Many environmental, genetic, and contextual factors likely influence variability in outcomes

for children with behavioral inhibition. We suggest that isolating neural mechanisms implicated in behavioral inhibition may shed light on the conditions, stimuli, and contexts that bolster or compromise the neural connections needed to support social competence.

First, we summarize several broad neural networks implicated in social competence. Next, we describe eight distinct yet interrelated processes of social cognition necessary for peer-based interactions through the experience of Ben, an adolescent with early childhood behavioral inhibition, when faced with a birthday party invitation. When applicable, we present evidence that demonstrates that childhood behavioral inhibition is associated with alterations in the neural networks that support these processes. We point out gaps in the literature and at times suggest methods to go about filling those gaps. Third, we discuss potential future directions for research linking behavioral inhibition and brain function, with a focus on work needed to isolate neural mechanisms that facilitate approach-related behavior in novel social contexts. We also discuss various methodological and conceptual issues that emerge from existing work. We then consider whether neural alterations reflect causes or consequences of behavioral inhibition and suggest that some of these alterations may reflect compensatory rather than disrupted processing. Finally, we conclude with some major implications emerging from what has been learned from work on the neural mechanisms of behavioral inhibition.

Neural Networks Implicated in Social Competence

Social relationships play a critical role in human behavior. Having meaningful and supportive social relationships promotes physical and mental health (Narr, Allen, Tan, & Loeb, 2017), whereas loneliness and isolation are associated with morbidity and mortality (Holt-Lunstad, Smith, & Layton, 2010). Achieving a meaningful and supportive relationship requires complex yet coordinated behavior that is often motivated by trust, empathy, and reciprocity, which in turn are influenced by relationship schemas, memory, and the capacity to forecast future events. The complexity of social relationships may have played a role in the evolution of the large human brain (Dunbar & Shultz, 2007). This hypothesis is supported by neuroimaging studies that demonstrate the size and diversity of social networks are associated with the volume and degree of functional connectivity between various structures in the brain (Bickart, Hollenbeck, Barrett, & Dickerson, 2012; Powell, Lewis, Roberts, Garcia-Finana, & Dunbar, 2012). Creating and maintaining complex social relationships builds on a foundation of successful social interactions. Such interactions are likely facilitated by functional engagement within and between neural networks that integrate lower-level stimulus properties via attention, perception, and memory within broader social contexts and social goals (Alcala-Lopez et al., 2017; Barrett & Satpute, 2013; Kennedy & Adolphs, 2012; Nelson, Jarcho, & Guyer, 2016). Thus, social competence is unlikely the result of a unified “social brain network”

but reflects the interface of several neural networks that support social and nonsocial information processing. These four networks are broadly defined as:

- *The salience network*, which includes the dorsal anterior cingulate cortex (dACC) and insula and is implicated in salience detection and generating visceral and affective feelings that guide attention, the need for cognitive control, and motor responses.
- *The limbic network*, which includes the amygdala, striatum (nucleus accumbens, caudate, putamen), orbitofrontal cortex (OFC), medial temporal lobe, and rostral anterior cingulate cortex (rACC) and is implicated in threat detection, attention processes, goal maintenance, affect evaluation, and affect regulation.
- *The mentalizing network*, which includes the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC)/precuneus, hippocampus, superior temporal sulcus, and temporoparietal junction and is implicated in knowledge of prior experience, automatic attributions of self and others' mental states, and first-person experiences.
- *The executive control network*, which includes the dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortex (vlPFC), inferior parietal lobe, precuneus, and middle cingulate cortex (mCC) and is implicated in inhibiting prepotent responses to irrelevant stimuli in the service of achieving current goals.

While the basic structure of these neural networks is established in early life, they undergo a great deal of organizational fine-tuning with maturation. Connections are strengthened or weakened depending on experience and exposure. During sensitive periods of development, particular types of stimuli play a key role in determining the trajectory of the brain's structural and functional maturation (Knudsen, 2004). The most compelling evidence of this relation comes from the animal literature. For example, in male zebra finch, learning a song is associated with changes in forebrain architecture, and learning only occurs during a specific developmental window if another male bird provides an example of the song (Morrison & Nottebohm, 1993).

Similar evidence is beginning to emerge in humans. For example, children raised in impoverished institutional environments suffer from alterations in brain structure and function (Bick et al., 2015; McLaughlin et al., 2014; Sheridan, Fox, Zeanah, McLaughlin, & Nelson, 2012; Stamoulis, Vanderwert, Zeanah, Fox, & Nelson, 2017). These alterations are coupled with deficits in fundamental cognitive processes typically facilitated by caregiver support, adequate nutrition, sensory and cognitive stimulation, and linguistic input (Nelson et al., 2007; Nelson, Westerlund, McDermott, Zeanah, & Fox, 2013; Troller-Renfree, McDermott, Nelson, Zeanah, & Fox, 2015; Troller-Renfree, Nelson, Zeanah, & Fox, 2016).

In late childhood and early adolescence, there is a developmentally normative shift away from parents and caregivers toward peers. This shift manifests socially but also physiologically (Braams & Crone, 2017; Gunnar & Hostinar, 2015; Saxbe, Del Piero, Immordino-Yang, Kaplan, & Margolin, 2015; Steinberg & Morris, 2001). For example, as adolescents spend more time with peers and less time with parents, peers begin to differentially engage the adolescent's brain (Braams & Crone, 2017; Guyer & Jarcho, 2018) and gain the capacity to buffer the adolescent from the psychological and physiological effects of stress (Gunnar & Hostinar, 2015). This shift

is coupled with a normative increase in exposure to unfamiliar social contexts (e.g., shifting from a small elementary school to larger middle school; attending school dances and events), the need to take risks (e.g., asking someone out on a date; running for school government; trusting a friend with a secret), and the need for perspective-taking (e.g., getting negative feedback that behavior change is necessary to retain a friendship; recognizing that not all peers in your cohort will like you).

Thus, from a cultural (Smetana, Campione-Barr, & Metzger, 2006) and evolutionary (Ellis et al., 2012) perspective, adolescents are expected to "put themselves out there." Risk taking is necessary to learn and become independent, including in the social sphere. This expectation conflicts with the wariness that novel social interactions elicit in children with a history of behavioral inhibition. Failure to go out on a social limb during this sensitive period for children with behavioral inhibition may therefore have lasting implications for how their neural networks process and react to a range of social information (see the chapter "The Social World of Behaviorally Inhibited Children: A Transactional Account" by Henderson et al.). Moreover, because peer groups tend to evaluate withdrawn behavior negatively (Rubin et al., 2009), we speculate that it may be possible that when children with behavioral inhibition do hazard to venture out on a social limb, they will be at higher risk for rejection. This may further bias children with behavioral inhibition away from approaching novel social contexts. Such a bias may have two consequences: (1) diminish already tenuous social relationships and (2) weaken already tenuous connections in neural networks which if were used more frequently may have otherwise reinforced social engagement. This may create a vicious cycle that promotes maladaptive social behavior that contributes to heightened risk for poor psychosocial outcomes.

Although the primary focus of this chapter is on brain function, we touch briefly on recent evidence from studies using structural magnetic resonance imaging (sMRI). These data suggest that lasting effects of childhood behavioral inhibition can be seen decades later in the architecture of brain regions within several neural networks. For instance, adults with a history of childhood behavioral inhibition or negative reactivity in infancy have larger amygdala (Clauss et al., 2014), caudate (Clauss et al., 2014), and ventral mPFC (vmPFC) volume (Schwartz et al., 2010), but smaller OFC (Schwartz et al., 2010), hippocampus (Schwartz et al., 2015), and dACC volume (Sylvester et al., 2016). What these data cannot tell us, however, is *when* structural abnormalities emerge: prenatally, in early infancy before behavioral characteristics of behavioral inhibition emerge, in early childhood after behavioral characteristics of behavioral inhibition manifest, or if they are the result of a cascade of social experiences children face as they mature through adolescence and young adulthood. To determine timing, studies that include longitudinally acquired sMRI assessments are needed. Furthermore, a lack of consistency across studies (e.g., Sylvester et al. (2016) failed to find relations between behavioral inhibition and amygdala or hippocampus volume, whereas Clauss et al. (2014) failed to find relations between behavioral inhibition and volume of any PFC regions, dorsal ACC, or hippocampus) indicates more work is needed to confirm the existing findings.

As with studies of brain structure, studies of the brain's function at rest, when not performing an explicit task, have begun to reveal differences in intrinsic functional connectivity within and between brain regions that comprise each of the four networks described above. Intrinsic functional connectivity measures synchronous fluctuations in brain function between a brain region of interest (i.e., a seed region) and one or more other regions during wakeful rest. The correlation in functional activity between regions may reflect underlying structural connectivity between brain regions (Sporns, Chialvo, Kaiser, & Hilgetag, 2004), predispose neural networks toward or away from engagement during goal-directed behavior, and/or shape the outcome of that behavior (Damoiseaux & Greicius, 2009). In adults, evidence shows that behavioral inhibition is linked with weaker connectivity between the amygdala (seed region) and dACC, rACC, insula, striatum, hippocampus, and precuneus (Blackford et al., 2014). Other studies report negative functional connectivity between these regions as well as with dlPFC for young adults with a childhood history of behavioral inhibition (Roy et al., 2014). In children with behavioral inhibition, alterations in intrinsic functional connectivity occur within and between numerous central hubs in the salience, limbic, and executive control networks (Taber-Thomas, Morales, Hillary, & Perez-Edgar, 2016a). Thus, a small but growing literature suggests that even in the absence of specific stimuli or explicit tasks, behavioral inhibition is associated with fundamental patterns of brain function that differ from individuals without childhood behavioral inhibition. Mounting evidence suggests that these patterns extend to alterations in neural mechanisms engaged during goal-directed behavior and provide clues about the specific processes that may impede social competence among individuals with childhood behavioral inhibition (see the chapter "The Neurobiology of Behavioral Inhibition as a Developmental Mechanism" by Blackford et al.).

Ingredients for Successful Social Interactions

If successful social interactions are needed to establish adaptive, effective, and healthy social relationships, then it is important to consider the constituent parts of an interaction that can influence its outcome. Social interactions are the culmination of a series of distinct yet interrelated processes that unfold across time. These processes are supported by equally distinct yet interrelated neural networks that shape current and future behavior. In addition, if connections are disrupted repeatedly in one context, such as a social event, they may then spill over or be generalized to another context, including a nonsocial one. Although we are far from definitively mapping the orchestration of neural communication needed for even the most simplistic of real-world social interactions, research with functional MRI (fMRI) has shed light on the neural mechanisms that support some of its constituent parts.

Recent fMRI studies of behavioral inhibition have begun to isolate alterations in brain function that may contribute to poor outcomes related to distress elicited by social novelty or to compensatory reactions used to adapt to social challenges. To

illustrate the constituent parts of a social interaction, the neural networks supported by these processes, and their corresponding alterations in behavioral inhibition, we consider eight steps in the experience of Ben, an adolescent with childhood behavioral inhibition, who is invited to attend the party of a classmate at a new school (see Table 1). This table describes existing research and highlights areas of investigation to be explored in future studies. We focus on adolescence extending into young adulthood because it is a pivotal time when youth are increasingly exposed to novel social interactions given their developmentally appropriate greater need for autonomy and independence (Nelson, Leibenluft, McClure, & Pine, 2005). However, we also focus on this developmental period because risk for many forms of psychopathology and maladaptive behavior increase during this time (Beesdo, Pine, Lieb, & Wittchen, 2010; Ormel et al., 2015). These risks are even greater for youth with a history of behavioral inhibition, who are up to three times more likely to develop anxiety disorders (Chronis-Tuscano et al., 2009; Clauss & Blackford, 2012) and have a higher likelihood of engage in substance abuse, than their non-BI peers (Caspi, Moffitt, Newman, & Silva, 1996; Williams et al., 2010).

The Invitation

Step one in this social interaction occurs well before a face-to-face encounter. Here, and at most steps along the way, several processes occur in parallel or in temporally close succession. Thus, although we describe these processes sequentially, we do not necessarily imply a clear distinction in time.

When confronted with an invitation to attend the party, Ben must first decide whether or not to attend. Such considerations require predictions about the outcome of attending. These predictions are informed by prior experiences (e.g., "At the last party I went to everyone made fun of me." vs. "I had lots of fun!"), which shape the expectation of future outcomes (e.g., "Everyone *will* make fun of me." vs. "I *will* have fun!"). Ben has only just begun the social process and yet has already encountered a great deal of complexity. Basic neuroscience research has demonstrated that functional interactions between the amygdala and the vmPFC (including OFC and other areas of mPFC) are engaged to guide behavior based on expected outcomes (Baxter, Parker, Lindner, Izquierdo, & Murray, 2000) and are evident across contexts related to expectancy, choice, and judgment (Hampton, Adolphs, Tyszka, & O'Doherty, 2007; Shenhav & Greene, 2014). The same brain regions are related to anxiety induced by exposure to threatening stimuli (Feng, Zheng, & Feng, 2016; Gold, Morey, & McCarthy, 2015).

At the same time, Ben must determine what value to ascribe to the invitation based on his expected outcome of attending. This may generate a conflict between the mismatch in desired outcomes (e.g., "I really want the cool kids to like me.") and the expected outcome (e.g., "When I try to talk to the cool kids, they will make fun of me."). The conflict between these simultaneously held beliefs may engage important hubs in the salience network (Botvinick, Cohen, & Carter, 2004; Etkin, Egner, & Kalisch, 2011; Zaki, Hennigan, Weber, & Ochsner, 2010). The executive control

Table 1 Stages of a social interaction, neural circuits that support those stages, and fMRI studies of behavioral inhibition that test neural response to corresponding constructs

Step	Psychological process	Neural systems engaged	fMRI studies of BI
1.	The invitation		
	Expected outcome	*L, M*	–
	Value of expected outcome	*L*	–
	Desired outcome	*L*	–
	Conflict between expected and desired outcome	*L, S, EC*	–
2.	The decision		
	Opt into or out of a social interaction	*L*	–
3.	Old face, new face		
	Faces of familiar and unfamiliar strangers	L	Blackford et al. (2013)
		L	Blackford et al. (2011)
		L	Blackford et al. (2009)
		L	Schwartz et al. (2012)
		L	Schwartz et al. (2003)
	Faces of known and unknown peers	*L, M*	–
	Pictures of known and unknown places	*L, M*	–
4.	Friend or foe		
	Disengaging from negative facial expressions	EC	Fu et al. (2017)
	Attending to negative facial expressions	L, S, EC	Hardee et al. (2013)
	Facilitate or modulate response to negative expressions	*EC*	–
	Maintaining goal-directed behavior in the presence of negative expressions	L, S, EC	Jarcho et al. (2014)
		S	Jarcho et al. (2013)
	Reflecting on fear elicited by emotional expression	L	Perez-Edgar et al. (2007)
5.	I know what you're thinking		
	Predicting peer response	*M*	–
6.	You never get a second chance to make a first impression		
	Initiating a peer interaction	*S, L, M, EC*	–
7.	Will they like me?		
	Anticipating positive/negative feedback	L	Bar-Haim et al. (2009)
		L	Guyer et al. (2006)
		L	Guyer et al. (2014)
		S	Jarcho et al. (2016)
		L	Perez-Edgar et al. (2014)
8.	You can't always get what you want		
	Receipt of positive/negative feedback	L	Jarcho et al. (2016)
		L	Guyer et al. (2014)
		L	Guyer et al. (2015)
		L	Helfinstein et al. (2011)
		L	Lahat et al. (2016)

S salience, *L* limbic, *M* mentalizing, *EC* executive control
Italics indicate hypothesized involvement of neural networks

network (Nelson et al., 2005; Rilling & Sanfey, 2011) is needed to resolve these conflicts in the service of making a final decision to accept or decline the invitation. Calculating the expected value of an outcome relies on vmPFC (Howard, Gottfried, Tobler, & Kahnt, 2015; Metereau & Dreher, 2015), whereas ventral striatum encodes the magnitude of that value (Knutson, Adams, Fong, & Hommer, 2001; Yacubian et al., 2007), and the limbic network calculates the costs and benefits that shape social decision-making behavior (Ruff & Fehr, 2014). Indeed, the value placed on potential outcomes (e.g., "When the cool kids make fun of me it will be the worst thing ever!" vs. "When the cool kids make fun of me, it won't be such a big deal.") parametrically varies with ventral striatal engagement (Becker, Nitsch, Hewig, Miltner, & Straube, 2016; Rodriguez, Aron, & Poldrack, 2006).

Observational, self-, parent-, and teacher-report data suggest that during this first step of social interactions, children with behavioral inhibition may exhibit biases similar to those described in socially anxious individuals. This includes a bias for recollecting past social outcomes as more negative than they actually were (Mathews & MacLeod, 2005), and predicting future social outcomes will be worse than they actually are (Cabeleira et al., 2014; Heimberg, Brozovich, & Rapee, 2010; Miranda & Mennin, 2007). Anxious observation of peers, a behavior that typifies childhood behavioral inhibition, is thought to reflect the conflict between the desire for positive social interactions and the expectation that the interaction will go poorly (Degnan et al., 2014; Fox, Henderson, Rubin, Calkins, & Schmidt, 2001). Also, like anxious youth (Rapee & Spence, 2004), childhood behavioral inhibition may be associated with a bias toward valuing peer feedback more than typically seen in non-anxious youth. Surprisingly little neuroimaging work has been done in behavioral inhibition to disentangle these important first steps of a social interaction.

The Decision

The second step in this social interaction occurs once a decision has been made to accept or decline the invitation to the party. Opting out of the party may elicit relief, thereby conferring appetitive reinforcement for avoiding the social event. In other words, Ben may find the decision to avoid the social event quite rewarding. Reward is closely linked with the release of dopamine (Schultz, Dayan, & Montague, 1997; Tobler, Fiorillo, & Schultz, 2005) and engagement of the striatum within the limbic network (Schultz, 2004; Silverman, Jedd, & Luciana, 2015). The decision to avoid the social interaction could strengthen the connection between hubs within the limbic network, thereby biasing children with behavioral inhibition toward making similarly avoidant decisions in the future. Opting to attend the party may elicit anticipatory anxiety, which, at least in the short term, would be decidedly less rewarding for Ben. Behaviorally inhibited children may be particularly prone to symptoms of social anxiety because the conflict between their desire to interact with peers and their fear of social rejection provokes feelings of inadequacy (Rubin & Burgess, 2001). Such states may differentially prime the brain and corresponding behavioral responses when face-to-face interactions are finally initiated.

Old Face, New Face

Let's assume that Ben decides to go to the party. Upon arrival, when face-to-face interactions are immediately forthcoming, Ben is likely to scan the room to determine whether potential interaction partners are unfamiliar or familiar peers. Recognition of familiar faces based on visual appearance is associated with activity in posterior superior temporal sulcus, inferior occipital, and fusiform gyri (Gobbini & Haxby, 2007), while recall of peer-based biographical information and past interactions are associated with activity in aspects of the mentalizing network (Gobbini & Haxby, 2007; Meyer & Lieberman, 2012).

Given the well-characterized sensitivity to novelty and social threat that typifies behavioral inhibition, the earliest studies testing the neural mechanisms implicated in behavioral inhibition focused on processing novel, unfamiliar faces. These studies suggest that alterations in brain function associated with behavioral inhibition are due less to basic mechanisms implicated in recognition of unfamiliar vs. familiar faces per se and more to do with affective responding to those novel faces, thus implicating the limbic network. Two studies have demonstrated that young adults with a history of childhood behavioral inhibition, or high reactivity to novel stimuli in infancy, exhibit heightened amygdala engagement when viewing novel relative to familiar faces (Schwartz et al., 2003; Schwartz et al., 2012). This response pattern corresponds well with findings from animal models of behavioral inhibition, which suggest that novelty elicits a threat response encoded by a hyper-responsive or sensitized threat detection system situated in the limbic network (Fox & Kalin, 2014) (see the chapter "Behavioral Inhibition in Nonhuman Primates: The Elephant in the Room" by Capitanio and the chapter "Behavioral Inhibition in Rodents: A Model to Study Causes and Health Consequences of Temperament" by Cavigelli).

Further support for this hypothesis came from a separate set of studies that showed alterations in the temporal dynamics of amygdala engagement in response to both familiar and novel faces. Specifically, young adults with a history of behavioral inhibition exhibited a more rapid response to novel (Blackford et al., 2009; Blackford et al., 2011) but also familiar (Blackford et al., 2011) faces and failed to habituate in their response to these faces across time (Blackford et al., 2011; Blackford et al., 2013). Together, as hypothesized, these data suggest a mechanism linked to the limbic network by which individuals with behavioral inhibition tend to be slow to warm up to new people—they remain "new" much longer than would be expected in non-inhibited individuals.

However, this is only half of the story—no study of behavioral inhibition has contrasted novel faces with those of peers who are personally known to the individual. Thus, it is unclear whether behavioral inhibition is also associated with alterations in aspects of the mentalizing network implicated in processing biographical information about familiar peers or other regions within the limbic network implicated in ascribing valence to the experience of specific positive and negative prior interactions with peers. Moreover, studies of neural response to novelty in behavioral inhibition have been limited to faces. While there is an implicit assumption

that alterations in amygdala response associated with behavioral inhibition are unique to faces, particularly given the eventual social wariness and social reticence that unfolds after infancy, no study has directly contrasted neural response to novel and familiar faces with neural response to other novel and familiar objects or images. Would a history of behavioral inhibition be associated with differential amygdala response to novel and familiar rooms in a generic building? Or, would these rooms need to have some form of personal meaning (i.e., one's own bedroom vs. a stranger's bedroom; one's own school hallway vs. a stranger's school hallway)? Such studies would help determine whether these patterns of neural response to novelty in adults with a history of behavioral inhibition are specific to faces or to stimuli imbued with more personal meeting, or signify a more generalized response.

Friend or Foe?

A next step in the social interaction is appraising the level of threat posed by potential interaction partners, whether familiar or unfamiliar. One way to glean this information is to attend to a potential partner's facial expression. When Ben scans the faces in the crowd at the party, he must determine who is most likely to be a friend or foe. To do this, cues that signal safety (e.g., a smile) or threat (e.g., angry, frowning, fearful, or disgust face) must first be detected. Viewing neutral faces generally engages occipital cortex and fusiform gyrus (Kanwisher, McDermott, & Chun, 1997). However negative, relative to positive or neutral, faces consistently engage regions of the limbic and salience networks, including the amygdala and insula, respectively (Calvo & Nummenmaa, 2016; Haxby, Hoffman, & Gobbini, 2000; Vuilleumier & Pourtois, 2007). State- and trait-based factors associated with elevated anxiety can bias perceptions toward detecting imagined and feared stimuli, which, in turn, lead to an inaccurate representation of the environment and can alter behavior based on the misrepresentation.

Once threat is detected, the executive network is engaged to facilitate (Wessa, Heissler, Schonfelder, & Kanske, 2013) or modulate (Buhle et al., 2014) affect-motivated behavioral responding via functional connections with limbic and salience network hubs. For example, Ben may interpret a peer's slight frown as a threat that causes him to give up his goal of having a positive social interaction and walk the opposite direction (facilitation). Whereas Ben's classmate without behavioral inhibition may notice the slight frown, the classmate may temper his response to the frown in the service of achieving that same goal (modulation). Biases in attention to threat may therefore reflect a heightened sensitivity of threat detection systems and/or the inability to exert inhibitory control to shift attention away from threat once it is detected (for review see Cisler & Koster, 2010).

Because there are well-established patterns of bias when processing threatening stimuli in behavioral inhibition, the neural correlates of attention bias are one of the most studied features of behavioral inhibition. The primary focus of this research has been on amygdala response. Researchers have used three strategies for studying

neural response to processing threatening faces in behavioral inhibition. Early work systematically manipulated the attention state of adolescents with or without behavioral inhibition as they viewed happy, angry, fearful, and neutral faces (Perez-Edgar et al., 2007). Regardless of the facial expression, adolescents with behavioral inhibition exhibited enhanced amygdala response when contemplating their own fear, but not during other thought processes. Adolescents without behavioral inhibition did not show this pattern. Thus, if Ben is preoccupied by his own fear of negative evaluation, his limbic network will likely process faces at the birthday party differently, regardless of whether his peers exhibit positive or negative expressions. Moreover, because Ben likely began fearing negative evaluation the moment the invitation arrived, alterations in brain function could extend well beyond the specific social context that represents the threat. This may be one way in which fear circuitry involving the amygdala becomes overly sensitized across time and contexts in behavioral inhibition.

Another way to measure biased processing of threatening faces is via dot-probe attention-orientating tasks, which require participants to identify the type or location of a probe that appears after an angry vs. neutral (or happy) face pair. Neural response when attention is biased toward threat is measured on trials where the probe appears in the same location as the angry face, whereas neural response that requires the avoidance of threat is measured on trials when the probe appears in the location of the neutral (or happy) face. Two studies have used these methods to assess neural mechanisms implicated in attention to threat in behavioral inhibition. Children with behavioral inhibition show greater dlPFC activity on trials where attention was directed away from negative faces (Fu et al., 2017). Moreover, greater dlPFC activation is related to more severe symptoms of anxiety. For adults with childhood behavioral inhibition, probes drawing attention toward negative faces resulted in more negative functional connectivity between the amygdala and the insula, as well as dlPFC (Hardee et al., 2013).

These data highlight the fact that threat-related attention bias is the result of alterations across multiple neural networks, including the salience, limbic, and executive networks. This is a departure from earlier theories that hypothesized behavioral inhibition and associated attention to threat were the result of alterations solely within the limbic network, namely, implicating the amygdala (Caouette & Guyer, 2014). Because multiple neural networks are involved, there are likely several different risk or compensatory neural pathways that would lead Ben to form biased perceptions of those around him or to muster through the situation.

A third method for assessing the neural mechanisms implicated in attention bias toward threat in behavioral inhibition is to measure brain function as participants complete a goal requiring high levels of attention control in the presence or absence of threatening stimuli. To the extent that threat captures attention, neural engagement during the goal-directed task should vary. In other words, can Ben stay intensely focused on walking up to someone he knows at the party while having to walk by many threatening (or not) looking peers with whom he has never before interacted?

In a study of adults with and without a history of childhood behavioral inhibition, participants completed a Stroop task that required high or low attention control when indicating the gender of the face, in the context of threatening and nonthreatening emotional faces (Jarcho et al., 2014). When fearful faces were present, adults with childhood behavioral inhibition exhibited more activity in brain regions from the salience, limbic, and executive control networks than adults without behavioral inhibition. Specifically for individuals with behavioral inhibition, cingulate, striatum, and dlPFC were engaged to a greater degree during high compared with low attention control trials. Engagement of high attention control in the context of threat may have elicited greater arousal and conflict among individuals with behavioral inhibition and required greater engagement of the executive network to deploy regulatory mechanisms to compensate for this distraction.

Thus, sensitivity to conflict may contribute to the distress children experience when their desire to interact with their peers competes with their fears of the negative consequences of doing so (Degnan et al., 2014; Fox et al., 2001). Indeed, in a second study, we demonstrated that regardless of the emotion being expressed, when processing conflict during an emotional Stroop, adults with versus without behavioral inhibition exhibited heightened engagement in the dmPFC, a brain region that indexes conflict (Jarcho, Fox, et al., 2013). This activation pattern suggests that some adults with childhood behavioral inhibition may need to engage compensatory processes to effectively regulate their attention to threatening stimuli around them.

These data provide compelling evidence that behavioral inhibition is associated with alterations in the engagement of salience, limbic, and executive networks while processing threatening faces. However, like research linking behavioral inhibition to altered neural response to novelty, it is unclear whether these alterations are specific to the social domain or extend to other stimulus classes as well. For instance, would individuals with a history of childhood behavioral inhibition also show alterations in neural response to images of nonsocial threats, such as snakes or snarling dogs? Again, new studies would help tease apart whether the altered neural response to threat in behavioral inhibition is specific to threat faces or is more generalized.

I Know What You're Thinking

As Ben imagines how a peer is likely to respond to him before he makes a social bid, he is actively engaged in mentalizing. In this case, mentalizing involves Ben imagining what his peers think about him (i.e., "That guy thinks I'm such a loser."). Mentalizing requires theory of mind, or the ability to infer the intentions or beliefs of another person based on perceptions of their current state (Frith & Frith, 2003; Frith & Frith, 2006). Unsurprisingly, this process is known to engage key hubs in the mentalizing network (Blakemore, 2008; Lombardo et al., 2010). The neural mechanisms implicated in mentalizing are often studied with tasks that require participants to identify the false beliefs of characters in a story. A commonly studied

simple example: David puts his toy on a shelf and leaves the room. His mother puts the toy back in its box. The experimenter will then ask the participant, "Where will David look for the toy when he comes back?". A participant who is successfully able to mentalize will understand that the boy now has the false belief that the toy remains on the shelf. Less frequently, participants are asked to engage in the type of mentalizing that Ben is performing, namely, imagining what a peer thinks about him.

Some data suggest that poor social competence in children with behavioral inhibition is associated with deficits in theory of mind (Suway, Degnan, Sussman, & Fox, 2012). However, it is unclear the extent to which these deficits translate to altered engagement of the mentalizing network. We are not aware of any study that tests the neural mechanisms of mentalizing or theory of mind in behavioral inhibition. Thus, this possibility remains to be empirically tested. In addition, tests in the context of social scenarios, much like the one Ben is experiencing, and nonsocial scenarios, much like the one David experienced, could again help determine the contextual specificity of alterations in brain function in behavioral inhibition.

You Never Get a Second Chance to Make a First Impression

Ben sees Cindy laughing with a group of her friends. Cindy sits a few seats away from Ben in his new homeroom class. Even though they have never had a real conversation, he has developed a crush on her. Ben is scared that she will reject him but finally works up the courage to say hello. His heart is beating rapidly and his hands are sweating (see the chapter "Psychobiological Processes in the Development of Behavioral Inhibition" by Buss and Qu), and he is imagining the worst possible outcome: everyone will start laughing at him and Cindy will tell him to get lost. He walks over to where Cindy and her friends are and stands nearby. When Cindy happens to see him, Ben mumbles, "Hi. I'm Ben, and we're in homeroom together."

A great deal of information is conveyed to a potential interaction partner in even the first few seconds of that interaction (Goffman, 2009; Murphy et al., 2015). Since socially withdrawn behavior is often perceived as atypical, many children with behavioral inhibition experience peer rejection (Gazelle & Rudolph, 2004; Pedersen, Vitaro, Barker, & Borge, 2007; Rubin et al., 2009). These experiences may exacerbate the natural tendency toward social withdrawal, which further minimizes opportunities to gain social competence.

Successful social bids are likely the culmination of a cascade of neural, emotional, and cognitive processes that lead up to this point in the social interaction. They also likely require appropriately matching one of a number of well-learned behaviors to the situation at hand. Because youth with behavioral inhibition tend to avoid social encounters, they may have fewer options in their repertoire. Few neuroimaging studies have investigated the neural mechanisms associated with successful and unsuccessful initiation of social contact. Despite being such a critical facet of social competence, methodological constraints in neuroimaging have hindered progress toward this goal.

Will They Like Me?

Ben begins to anticipate how Cindy will respond to his bid for social engagement. Given that the salience of peer evaluation generally increases during adolescence (Albert, Chein, & Steinberg, 2013; Brown, Bakken, Ameringer, & Mahon, 2008; Brown & Larson, 2009), this phase of the social interaction may be particularly anxiety provoking for adolescents like Ben, who have a history of behavioral inhibition. Additionally, since rejection is common among behaviorally inhibited youth (Rubin et al., 2009), memories of prior experience and fear of negative evaluation are likely quite salient during the moments leading up to receiving social evaluation from peers. For instance, Ben may be thinking back to the last time he was snubbed after approaching a girl. Moreover, if he is contemplating his own fear, Ben's limbic network is likely already engaged. This may influence his interpretation of subtle nonverbal cues or bias his impression of social feedback once it is received.

We developed a "Chatroom" paradigm to test the neural response during the anticipation and receipt of social evaluation in a range of studies (Guyer et al., 2008; Guyer et al., 2014; Guyer et al., 2015; Guyer, Choate, Pine, & Nelson, 2012; Guyer, McClure-Tone, Shiffrin, Pine, & Nelson, 2009; Spielberg et al., 2015). Participants review pictures of age-matched peers and select the peers they want to have a subsequent online chat with (high-value peers) and the peers they do not want to have a subsequent online chat with (low-value peers). Participants believe these purported peers make the same evaluation about them. To measure anticipation of peer feedback, participants see photographs of their peers while undergoing fMRI, are reminded of whether they are of high or low value, and predict how likely the peer is to want to chat with them.

When anticipating whether a high-value peer would like them, greater activity in the striatum, hypothalamus, hippocampus, and insula was found in girls (but not boys) and was most heightened among older girls (Guyer et al., 2009). Given the relevance of social anxiety to behavioral inhibition, we have also found heightened amygdala activation among socially anxious versus healthy adolescents when anticipating how interested high-value peers would be in chatting with them (Guyer et al., 2008; Spielberg et al., 2015). The amygdala and vlPFC were also strongly co-activated during the anticipation of peer evaluation in socially anxious versus healthy adolescents (Guyer et al., 2008). This pattern was specific to when youth had previously judged the peers negatively, possibly signifying a fear of subsequent negative outcomes such as retaliation.

Two studies have assessed neural response during the anticipation of social evaluation in behavioral inhibition. First, using the chatroom paradigm, we showed that the normative pattern of responding is potentiated in late adolescents with behavioral inhibition. Specifically, striatal engagement is enhanced in behaviorally inhibited relative to non-BI adolescents while anticipating feedback from high- but not low-value peers (Guyer et al., 2014). That is, these adolescents are thinking about what peers they ascribed high value to will think of them. Because the striatum aids in processing rewarding stimuli and generating motivated behavior, this may signify

an alarm, so to speak, to prepare to approach this social feedback that has been given high value. Heightened engagement in a key hub of the limbic network may therefore reflect greater sensitivity in adolescents with behavioral inhibition when they put themselves out on that proverbial social limb: these are the peers participants said they most wanted to talk to, and now they are waiting to find out if the feeling is mutual. Thus, as Ben awaits Cindy's response following his initial social bid, he may experience elevated striatal engagement in a way that he would not have when making a social bid toward Lisa, someone to whom he did not assign high value.

In most social evaluation neuroimaging studies, purported peers are unknown to the participant. This maps on well to the experience of meeting a new peer for the first time—something that becomes increasingly common during adolescence as social networks expand. Such an experience may be particularly anxiety provoking because there is no way to predict if an unfamiliar peer will provide positive or negative feedback. However, given that all peers in the existing chatroom studies have been unfamiliar, the extent to which predictability from familiarity with others plays a role in these patterns of brain function of adolescents with behavioral inhibition could not be determined. Moreover, many social interactions occur between peers who have some knowledge of one another based on their reputation or prior interactions. Thus, we built on this work to develop the "Virtual School" paradigm (Jarcho et al., 2013).

Using the virtual school, we tested whether neural response in adolescents with and without early childhood social reticence, a common symptom of behavioral inhibition, varied during anticipated social interactions. Notably, we were able to do so depending on whether the peers had a reputation for being predictably nice, predictably mean (i.e., a bully), or unpredictable (Jarcho et al., 2016). Here, a cue signals when one of the purported peers begins typing a socially evaluative comment to the participant. Among socially reticent youth, anticipating unpredictable, relative to predictably nice or mean, feedback based on reputation elicited heightened engagement in dACC and bilateral insula, key regions of the salience network. This pattern supported the idea that unpredictable social contexts are particularly salient for socially reticent youth. Moreover, high social reticence was also associated with negative functional connectivity between the insula and vmPFC, a region often implicated in self-reflection, valuation, and inhibitory control (Jenkins & Mitchell, 2011; Nelson & Guyer, 2011). Interplay between the insula and interconnected brain regions may help guide subsequent responses to socially distressing or salient stimuli (Uddin, 2015). However, further work is needed to test relations between brain function during the anticipation of social evaluation and brain and behavioral response to its eventual receipt.

Unlike other processes discussed thus far, neural networks engaged while anticipating potentially positive or negative outcomes have been tested in both social and nonsocial domains. This is because the anticipatory period is so relevant to the phenotype of individuals with social anxiety and behavioral inhibition. That is, both groups show heightened concern about what will happen, intolerance to uncertainty, and fear of negative outcomes. In the nonsocial domain, three studies have assessed

neural engagement, while adolescents anticipate the receipt of positive and negative monetary outcomes. Behaviorally inhibited, relative to non-BI, adolescents showed heightened striatal engagement while anticipating monetary gains (Guyer et al., 2006), essentially exhibiting greater activation as the size of the gain increased (i.e., the stakes were higher). This effect may be limited to contexts in which rewards are contingent on their own performance (Bar-Haim et al., 2009).

Thus, heightened engagement in a key hub of the limbic network may also reflect greater neural sensitivity in adolescents with behavioral inhibition when they put themselves out on a *nonsocial* limb as well: these are trials in which participants performed an action in order to receive a monetary reward, and now they are waiting to find out if that action was acceptable. Interestingly, individual differences in a DRD4 genetic polymorphism, which is associated with weaker dopamine transmission and greater functional striatal response to reward, influences these relations. Specifically, among carriers of the polymorphism, higher behavioral inhibition was associated with a striatal response that varied based on anticipated incentive value, again indicating greater neural engagement as the stake of the outcome increased (Perez-Edgar et al., 2014). Among non-carriers, behavioral inhibition did not differentially influence neural response to varying incentive values.

Together, these data provide initial evidence for generalized alterations in neural networks engaged during the anticipation of potentially rewarding social and nonsocial outcomes in behavioral inhibition. Some similarities and differences emerged with regard to the networks engaged. When all anticipated outcomes were unpredictable, and adolescents were asked to put themselves out on a limb through some sort of performance or behavior, social or otherwise, behavioral inhibition was associated with heightened limbic network. When anticipating predictable relative to unpredictable outcomes in a social context, a different pattern of results emerged, such that adolescents with behavioral inhibition exhibited enhanced salience network engagement. We are aware of no studies that directly contrast brain function during the anticipation of social and nonsocial outcomes in individuals with or without behavioral inhibition. One challenge to doing so is the discrepancy in methods used in tasks across each domain. Thus, a critical next step in this work is to design and implement social and nonsocial reward-based tasks that use identical methods and vary along only a single dimension: modality of outcome.

You Can't Always Get What You Want

One of the final phases of the social interaction involves the receipt of social evaluation. When we left Ben, he was waiting for Cindy to respond. In one scenario, Cindy might smile warmly at Ben, shake his hand, and introduce him to her friends. Positive social feedback engages brain regions in the limbic network implicated in reward processing, including the striatum and vmPFC. Adolescents are happier after being accepted versus rejected by high-value peers, which is corroborated by acceptance vs. rejection feedback eliciting greater activity in the striatum (Guyer

et al., 2012). The vmPFC encodes reward values (Grabenhorst & Rolls, 2011) and shows greater activation following the receipt of positive relative to negative feedback (Knutson, Fong, Bennett, Adams, & Hommer, 2003; O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001). In another scenario, Cindy may stare blankly at Ben, roll her eyes, and scold him for interrupting her conversation. Negative social feedback, such as rejection and ostracism, engages brain regions implicated in threat and distress-based processes that include limbic and salience networks, including the amygdala, dACC, and insula (Masten, Telzer, Fuligni, Lieberman, & Eisenberger, 2012).

Once Ben receives Cindy's feedback, he evaluates it to determine whether it is better or worse than expected. Recall that Ben went into this situation with fairly negative expectations. Thus, negative feedback would be consistent with Ben's predicted outcome (e.g., "She thinks I'm a loser—I knew this was going to happen."). Positive feedback would be inconsistent with his predicted outcome (e.g., "She likes me? What a surprise!"). A mismatch between expectations and outcomes, also known as a prediction error, prompts learning, whereby current experience modifies future expectations.

Regardless of whether the outcome is social or monetary, this form of learning depends on signals from the brain's dopamine system and functional engagement of important hubs in the limbic, salience, and executive networks, including the striatum, ACC, and dlPFC (Lin, Adolphs, & Rangel, 2012; Tremblay, Sharika, & Platt, 2017). Moreover, functional connectivity between the striatum and vmPFC appears to play a key role in reward-based learning and shaping behavior toward obtaining positive outcomes (O'Doherty et al., 2004). In the social domain, youth with behavioral inhibition may both expect and experience more negative social encounters than typical youth and therefore have relatively few opportunities to engage in this form of learning.

Two lines of evidence suggest alterations in neural mechanisms that support neural processes engaged during the receipt of positive and negative outcomes in behavioral inhibition. The first comes from work in the social domain. Using the chatroom paradigm, we found that among young adults *without* a history of behavioral inhibition, the striatum was differentially engaged by acceptance and rejection from high-value peers (Guyer et al., 2014). Specifically, non-BI youth exhibited greater activity when receiving positive versus negative feedback from high-value peers. This is similar to the brain function observed in response to social acceptance in typically developing adolescents (Guyer et al., 2012; Moor, van Leijenhorst, Rombouts, Crone, & Van der Molen, 2010).

A different pattern emerged among adolescents with behavioral inhibition. Their striatum was relatively unresponsive and failed to discriminate between social outcomes from high- or low-value peers, regardless of whether their feedback was positive or negative. This blunted response suggests that neural circuits typically engaged in reward responding and learning from social experiences may be impaired in behavioral inhibition, despite strong social motivation in the context of negative social interactions (Fox et al., 2005; Rubin et al., 2009), as indicated by heightened striatal response when anticipating high-value peers' opinions. Although some

inroads have been made into isolating neural circuits implicated in prediction-error learning in pediatric social anxiety (Jarcho et al., 2015), these specific relations have yet to be tested in behavioral inhibition.

Another intriguing possibility is that learning that you are liked may not be a particularly positive experience for adolescents with behavioral inhibition. As we have seen with Ben, being invited to attend a party of a peer he did not know well resulted in a cascade of thoughts and emotions—not all of which were positive. In the chatroom studies, participants believed they would be matched with a highly valued but unfamiliar peer who expressed a mutual interest in having a subsequent online chat. For adolescents with behavioral inhibition, this may not be an entirely positive outcome given their conflict between wanting peer acceptance, and being fearful of the social uncertainty that goes along with it. Further work is needed to determine the extent to which this conflict influences affective responding to positive peer feedback. Neuroimaging studies that utilize functional connectivity techniques could shed light on whether striatal engagement is dampened by nodes in the executive network when participants report greater conflict with positive social outcomes. Finally, as with studies discussed in previous sections, it is unclear whether the same results would emerge were adolescents with behavioral inhibition to receive positive and negative feedback from peers they know well.

While striatal activity did not vary based on the receipt of different types of social feedback or from differently valued peers in behavioral inhibition, the amygdala was differentially engaged based on contextual aspects of social rejection. Specifically, in a chatroom study, we demonstrated that greater distress elicited by negative peer feedback was associated with heightened amygdala engagement in adolescents with behavioral inhibition, but not their non-BI peers (Guyer et al., 2015). Using the virtual school paradigm, we found that predictable relative to unpredictable negative peer feedback was associated with greater amygdala activity in behavioral inhibition, whereas typical adolescents showed the opposite pattern (Jarcho et al., 2016).

This was a somewhat surprising result given the greater engagement of the salience network during the anticipation of unpredictable social feedback. Although further work is needed to clarify these relations, our data suggest that, unlike earlier conceptualizations of social threat in adolescent behavioral inhibition, amygdala response is not consistently elevated to negative peer feedback. Rather, the amygdala response is greater than in typical adolescents given the correct conditions. Factors driving these differences (i.e., experience of distress, uncertainty of outcome) are therefore important to consider from both methodological and theoretical perspectives.

The second line of evidence suggesting alterations in neural networks that process positive and negative outcomes in behavioral inhibition comes from the nonsocial domain. These relations have been tested with tasks in which monetary outcomes are gained or withheld. In one study, among adolescents *without* a history of behavioral inhibition, the striatum was engaged by gain relative to withhold outcomes (Helfinstein et al., 2011). As in the social domain, this is similar to the brain function observed in response to monetary gains in typically developing adolescents

(Galvan et al., 2006). The opposite effect emerged among adolescents with behavioral inhibition such that greater striatal response was observed on trials with withhold outcomes compared to trials with gain outcomes. However, these results are inconsistent with a second study that showed the receipt of higher-value incentives was associated with greater striatal engagement in behaviorally inhibited relative to non-BI youth (Lahat et al., 2016). Despite the inconsistencies, taken together, these results suggest alterations in the limbic network via reward processing systems that may generalize across social and nonsocial modalities.

Only the Tip of the Social Iceberg

Despite its complexity, what we have described thus far is merely a glimpse through a pinhole camera into the remarkably broad and rich landscape of a social interaction. We have described only the beginning of a social interaction; Ben now needs to determine how to respond to Cindy's feedback. A critical feature of social competence is the capacity to respond flexibly to changes in social contexts (Nelson et al., 2016; Nelson & Guyer, 2011). Yet, it is unclear if the neural circuits that support this flexibility are impaired in behavioral inhibition.

Additionally, we have not considered the fact that other facets of Ben's early life experience may have affected how his brain processes social information. For instance, there is some evidence that parenting style influences neural response during the anticipation and receipt of peer feedback in adolescents with behavioral inhibition (Guyer et al., 2015). Nor have we considered whether a different cascade of cognitions and neural engagement may have occurred had Ben found himself in a slightly different social context. For instance, would we expect the same set of thoughts and corresponding alterations in brain function were he at a small gathering, attending the party with one well-known friend, or participating his own party, where he invited all of the people in attendance? These and other person- and situation-based factors need further consideration to obtain a clearer picture of the association between behavioral inhibition and how the brain responds to its surroundings.

Future Directions

Although much progress has been made to identify neural mechanisms related to behavioral inhibition, numerous relations remain untested. In this section, we raise questions about the operationalization and definition of behavioral inhibition and then about conceptual issues to consider when interpreting the current literature and when designing future studies.

Operationalization of Behavioral Inhibition

The majority of imaging studies described here dichotomized participants into two groups based on self-report, parent-report, and/or observational data: BI and non-BI. While this approach facilitates the interpretability of neuroimaging data by using the extreme ends of a continuum of early behavior, it assumes that the behaviorally inhibited group deviates from some standard or norm, which is represented by the non-BI group. Groups are often determined based on a median split such that participants in the behaviorally inhibited group have high scores on a measure or composite of measures, while participants in the non-BI group have low scores on those same measures. While individuals with high levels of behavioral inhibition have been fairly well-characterized, it is less clear what it means to have low levels of behavioral inhibition. Is that indeed the norm? Some evidence indicates that low levels of behavioral inhibition are associated with increased risk for externalizing disorders (Lahat et al., 2012; Williams et al., 2010). Thus, participants in a "non-BI" group may not represent a normative population. This complicates the interpretation of existing neuroimaging data, particularly in cases where the non-BI group drives significant interactions.

Another methodological issue is the way in which behavioral inhibition is defined. The standard definition relies on behavioral and maternal report data that is collected beginning in the first several months of life and continues with the addition of self-report across the first several years of childhood (Kagan, 2012; Rothbart, 2012). Most of the neuroimaging studies of behavioral inhibition described here use such methods. However, other studies use a single data point from infancy, data collected beginning after the first 2 years of life, or current/retrospective self-reports on childhood behavioral inhibition symptoms from adolescents and young adults (e.g., Buss, 2011; Buss et al., 2013; Fu et al., 2017; Morales, Fu, & Perez-Edgar, 2016; Morales, Taber-Thomas, & Perez-Edgar, 2017; Kenneth H Rubin, Hymel, Mills, & Rose-Krasnor, 1991; Schwartz, Snidman, & Kagan, 1999; Schwartz et al., 2003; Taber-Thomas, Morales, Hillary, & Perez-Edgar, 2016b). Thus, some variability in results may be due to variability in the operational definition of behavioral inhibition and its associated constructs.

Conceptual Issues of Behavioral Inhibition

The first issue is teasing apart whether the effects of early childhood behavioral inhibition on brain function reflect mechanisms that promote risk and resilience. One of the primary interests in studying alterations in the neural circuits associated with childhood behavioral inhibition is to understand the mechanisms by which temperament increases risk for psychopathology. However, rates of psychopathology in the small sample of participants included in many of the imaging studies are not elevated in the behaviorally inhibited group, as they typically are in large

samples of longitudinally followed participants. Indeed, use of psychotropic medication is an exclusionary criterion for most of the neuroimaging studies described in this chapter. This suggests that instead of studying the behaviorally inhibited youth and young adults at greatest risk for psychopathology, we may have studied those who are most resilient to psychopathology. This may help explain why virtually none of the studies reviewed here show relations between behavioral inhibition and task-based or symptom-relevant behaviors, and few show relations between brain function and symptoms of psychopathology.

The only way to gain traction on this issue is to image larger longitudinally studied cohorts with and without behavioral inhibition who have and have not gone on to develop internalizing disorders. In doing so, we need to establish criterion that indicate how the brain has compensated for socially reticent behavior around novel or feared social events. This may be done by what we measure in the brain, such as the enlistment of neural networks such as the executive control network to override heightened activation of the limbic and/or salience networks; in all likelihood, this may operate as a balancing act of weighted neural input for generating approach or avoidance behaviors. Or this goal may be accomplished by the types of probes we design and deploy to test for compensatory responses or mechanisms.

A second, and somewhat related, issue is identifying how compensatory behaviors influence neural networks to promote resilience in behavioral inhibition, perhaps defined as achieving a level of comfort in social situations so they are tolerable or the absence of social anxiety disorder. The behavioral literature suggests that, in general, having at least one close friend can help promote positive outcomes for adolescents (Narr et al., 2017) and thus may hold true for youth with childhood behavioral inhibition. However, no neuroimaging studies have tested the effects of friendship on brain function in behavioral inhibition. Other compensatory behaviors may be best identified through teacher or peer report. For instance, a youth with behavioral inhibition may not have noticed that they developed greater social competence over the course of a school year, whereas a teacher may have seen substantial improvement in the capacity to flexibly respond to conflict or navigating new social contexts or expanding existing social groups to include unfamiliar others.

A third issue raises broader questions about the implications of social isolation in childhood. Youth with behavioral inhibition exhibit social reticence, or conflicted shyness, that keeps them from interacting with their peers. Other youth exhibit social disinterest, which also keeps them from interacting with their peers. The objective outcome of each experience is the same: minimized social contact with peers. However, the psychological consequences, and corresponding effects on brain function, of this distinction may be quite different. Few studies have explored this distinction, which could be the key to determining mechanisms by which social isolation becomes problematic.

Conclusion

Ben's sleep-deprived parents were unlikely to have realized that his behavioral characteristics in the first months of life would predict patterns of brain function years and even decades later. Neuroimaging studies have taught us that childhood behavioral inhibition has effects on not just a single neural network but on multiple interconnected networks that support different facets of social cognition and behavior. What they have yet to teach us is how to parlay what we have learned into the development and refinement of parent- and child-based training that will help children like Ben overcome their natural tendency to avoid otherwise adaptive behavior that promotes social interaction and competence (see the chapter "Behavioural Inhibition and the Prevention of Internalising Distress in Early Childhood" by Rapee). Thus, we hope that the next generation of developmental cognitive neuroscience research will include scientific approaches that can be used to inform the design of effective strategies to support children with behavioral inhibition in their social-emotional development.

References

Affrunti, N. W., Geronimi, E. M., & Woodruff-Borden, J. (2014). Temperament, peer victimization, and nurturing parenting in child anxiety: A moderated mediation model. *Child Psychiatry and Human Development, 45*(4), 483–492. https://doi.org/10.1007/s10578-013-0418-2

Albert, D., Chein, J., & Steinberg, L. (2013). Peer influences on adolescent decision making. *Current Directions in Psychological Science, 22*(2), 114–120. https://doi.org/10.1177/0963721412471347

Alcala-Lopez, D., Smallwood, J., Jefferies, E., Van Overwalle, F., Vogeley, K., Mars, R. B., … Bzdok, D. (2017). Computing the social brain Connectome across systems and states. *Cerebral Cortex*, 1–26. https://doi.org/10.1093/cercor/bhx121

Bar-Haim, Y., Fox, N. A., Benson, B., Guyer, A. E., Williams, A., Nelson, E. E., … Ernst, M. (2009). Neural correlates of reward processing in adolescents with a history of inhibited temperament. *Psychological Science, 20*(8), 1009–1018. https://doi.org/10.1111/j.1467-9280.2009.02401.x

Barrett, L. F., & Satpute, A. B. (2013). Large-scale brain networks in affective and social neuroscience: Towards an integrative functional architecture of the brain. *Current Opinion in Neurobiology, 23*(3), 361–372. https://doi.org/10.1016/j.conb.2012.12.012

Baxter, M. G., Parker, A., Lindner, C. C. C., Izquierdo, A. D., & Murray, E. A. (2000). Control of response selection by reinforcer value requires interaction of amygdala and orbital prefrontal cortex. *Journal of Neuroscience, 20*(11), 4311–4319.

Becker, M. P., Nitsch, A. M., Hewig, J., Miltner, W. H., & Straube, T. (2016). Parametric modulation of reward sequences during a reversal task in ACC and VMPFC but not amygdala and striatum. *NeuroImage, 143*, 50–57. https://doi.org/10.1016/j.neuroimage.2016.09.022

Beesdo, K., Pine, D. S., Lieb, R., & Wittchen, H. U. (2010). Incidence and risk patterns of anxiety and depressive disorders and categorization of generalized anxiety disorder. *Archives of General Psychiatry, 67*(1), 47–57. https://doi.org/10.1001/archgenpsychiatry.2009.177

Bick, J., Zhu, T., Stamoulis, C., Fox, N. A., Zeanah, C., & Nelson, C. A. (2015). Effect of early institutionalization and foster care on long-term white matter development: A randomized clinical trial. *JAMA Pediatrics, 169*(3), 211–219. https://doi.org/10.1001/jamapediatrics.2014.3212

Bickart, K. C., Hollenbeck, M. C., Barrett, L. F., & Dickerson, B. C. (2012). Intrinsic amygdala-cortical functional connectivity predicts social network size in humans. *Journal of Neuroscience, 32*(42), 14729–14741. https://doi.org/10.1523/JNEUROSCI.1599-12.2012

Blackford, J. U., Allen, A. H., Cowan, R. L., & Avery, S. N. (2013). Amygdala and hippocampus fail to habituate to faces in individuals with an inhibited temperament. *Social Cognitive and Affective Neuroscience, 8*(2), 143–150. https://doi.org/10.1093/scan/nsr078

Blackford, J. U., Avery, S. N., Cowan, R. L., Shelton, R. C., & Zald, D. H. (2011). Sustained amygdala response to both novel and newly familiar faces characterizes inhibited temperament. *Social Cognitive and Affective Neuroscience, 6*(5), 621–629. https://doi.org/10.1093/scan/nsq073

Blackford, J. U., Avery, S. N., Shelton, R. C., & Zald, D. H. (2009). Amygdala temporal dynamics: Temperamental differences in the timing of amygdala response to familiar and novel faces. *BMC Neuroscience, 10*, 145. https://doi.org/10.1186/1471-2202-10-145

Blackford, J. U., Clauss, J. A., Avery, S. N., Cowan, R. L., Benningfield, M. M., & VanDerKlok, R. M. (2014). Amygdala-cingulate intrinsic connectivity is associated with degree of social inhibition. *Biological Psychology, 99*, 15–25. https://doi.org/10.1016/j.biopsycho.2014.02.003

Blakemore, S. J. (2008). The social brain in adolescence. *Nature Reviews Neuroscience, 9*(4), 267–277. https://doi.org/10.1038/nrn2353

Botvinick, M. M., Cohen, J. D., & Carter, C. S. (2004). Conflict monitoring and anterior cingulate cortex: An update. *Trends in Cognitive Sciences, 8*(12), 539–546. https://doi.org/10.1016/j.tics.2004.10.003

Braams, B. R., & Crone, E. A. (2017). Peers and parents: A comparison between neural activation when winning for friends and mothers in adolescence. *Social Cognitive and Affective Neuroscience, 12*(3), 417–426. https://doi.org/10.1093/scan/nsw136

Brown, B. B., Bakken, J. P., Ameringer, S. W., & Mahon, S. D. (2008). A comprehensive conceptualization of the peer influence process in adolescence. *Understanding Peer Influence in Children and Adolescents*, 17–44.

Brown, B. B., & Larson, J. (2009). Peer relationships in adolescence. In L. Steinberg & R. M. Lerner (Eds.), *Handbook of adolescent psychology, Volume 2: Contextual influences on adolescent development* (Vol. 2, p. 74). Hoboken, NJ: John Wiley & Sons.

Buhle, J. T., Silvers, J. A., Wager, T. D., Lopez, R., Onyemekwu, C., Kober, H., … Ochsner, K. N. (2014). Cognitive reappraisal of emotion: A meta-analysis of human neuroimaging studies. *Cerebral Cortex, 24*(11), 2981–2990. https://doi.org/10.1093/cercor/bht154

Buss, K. A. (2011). Which fearful toddlers should we worry about? Context, fear regulation, and anxiety risk. *Developmental Psychology, 47*(3), 804–819. https://doi.org/10.1037/a0023227

Buss, K. A., Davis, E. L., Kiel, E. J., Brooker, R. J., Beekman, C., & Early, M. C. (2013). Dysregulated fear predicts social wariness and social anxiety symptoms during kindergarten. *Journal of Clinical Child and Adolescent Psychology, 42*(5), 603–616. https://doi.org/10.1080/15374416.2013.769170

Cabeleira, C. M., Steinman, S. A., Burgess, M. M., Bucks, R. S., MacLeod, C., Melo, W., & Teachman, B. A. (2014). Expectancy bias in anxious samples. *Emotion, 14*(3), 588.

Calvo, M. G., & Nummenmaa, L. (2016). Perceptual and affective mechanisms in facial expression recognition: An integrative review. *Cognition & Emotion, 30*(6), 1081–1106. https://doi.org/10.1080/02699931.2015.1049124

Caouette, J. D., & Guyer, A. E. (2014). Gaining insight into adolescent vulnerability for social anxiety from developmental cognitive neuroscience. *Developmental Cognitive Neuroscience, 8*, 65–76.

Caspi, A., Moffitt, T. E., Newman, D. L., & Silva, P. A. (1996). Behavioral observations at age 3 years predict adult psychiatric disorders – longitudinal evidence from a birth cohort. *Archives of General Psychiatry, 53*(11), 1033–1039.

Chronis-Tuscano, A., Degnan, K. A., Pine, D. S., Perez-Edgar, K., Henderson, H. A., Diaz, Y., … Fox, N. A. (2009). Stable early maternal report of behavioral inhibition predicts lifetime social anxiety disorder in adolescence. *Journal of the American Academy of Child and Adolescent Psychiatry, 48*(9), 928–935. https://doi.org/10.1097/CHI.0b013e3181ae09df

Cisler, J. M., & Koster, E. H. (2010). Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. *Clinical Psychology Review, 30*(2), 203–216. https://doi.org/10.1016/j.cpr.2009.11.003

Clauss, J. A., Avery, S. N., VanDerKlok, R. M., Rogers, B. P., Cowan, R. L., Benningfield, M. M., & Blackford, J. U. (2014). Neurocircuitry underlying risk and resilience to social anxiety disorder. *Depression and Anxiety, 31*(10), 822–833. https://doi.org/10.1002/da.22265

Clauss, J. A., & Blackford, J. U. (2012). Behavioral inhibition and risk for developing social anxiety disorder: A meta-analytic study. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*(10), 1066–1075 e1061. https://doi.org/10.1016/j.jaac.2012.08.002

Coplan, R. J., Rubin, K. H., Fox, N. A., Calkins, S. D., & Stewart, S. L. (1994). Being alone, playing alone, and acting alone – distinguishing among reticence and passive and active solitude in young-children. *Child Development, 65*(1), 129–137. https://doi.org/10.1111/j.1467-8624.1994.tb00739.x

Damoiseaux, J. S., & Greicius, M. D. (2009). Greater than the sum of its parts: A review of studies combining structural connectivity and resting-state functional connectivity. *Brain Structure & Function, 213*(6), 525–533. https://doi.org/10.1007/s00429-009-0208-6

Deater-Deckard, K. (2001). Annotation: Recent research examining the role of peer relationships in the development of psychopathology. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 42*(5), 565–579. https://doi.org/10.1111/1469-7610.00753

Degnan, K. A., Almas, A. N., Henderson, H. A., Hane, A. A., Walker, O. L., & Fox, N. A. (2014). Longitudinal trajectories of social reticence with unfamiliar peers across early childhood. *Developmental Psychology, 50*(10), 2311–2323. https://doi.org/10.1037/a0037751

Dunbar, R. I., & Shultz, S. (2007). Understanding primate brain evolution. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 362*(1480), 649–658. https://doi.org/10.1098/rstb.2006.2001

Ellis, B. J., Del Giudice, M., Dishion, T. J., Figueredo, A. J., Gray, P., Griskevicius, V., … Wilson, D. S. (2012). The evolutionary basis of risky adolescent behavior: Implications for science, policy, and practice. *Developmental Psychology, 48*(3), 598–623. https://doi.org/10.1037/a0026220

Etkin, A., Egner, T., & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in Cognitive Sciences, 15*(2), 85–93. https://doi.org/10.1016/j.tics.2010.11.004

Feng, P., Zheng, Y., & Feng, T. Y. (2016). Resting-state functional connectivity between amygdala and the ventromedial prefrontal cortex following fear reminder predicts fear extinction. *Social Cognitive and Affective Neuroscience, 11*(6), 991–1001. https://doi.org/10.1093/scan/nsw031

Fox, A. S., & Kalin, N. H. (2014). A translational neuroscience approach to understanding the development of social anxiety disorder and its pathophysiology. *The American Journal of Psychiatry, 171*(11), 1162–1173. https://doi.org/10.1176/appi.ajp.2014.14040449

Fox, N. A., Henderson, H. A., Marshall, P. J., Nichols, K. E., & Ghera, M. M. (2005). Behavioral inhibition: Linking biology and behavior within a developmental framework. *Annual Review of Psychology, 56*, 235–262.

Fox, N. A., Henderson, H. A., Rubin, K. H., Calkins, S. D., & Schmidt, L. A. (2001). Continuity and discontinuity of behavioral inhibition and exuberance: Psychophysiological and behavioral influences across the first four years of life. *Child Development, 72*(1), 1–21.

Frith, C. D., & Frith, U. (2006). The neural basis of mentalizing. *Neuron, 50*(4), 531–534. https://doi.org/10.1016/j.neuron.2006.05.001

Frith, U., & Frith, C. D. (2003). Development and neurophysiology of mentalizing. *Philosophical Transactions of the Royal Society B-Biological Sciences, 358*(1431), 459–473. https://doi.org/10.1098/rstb.2002.1218

Fu, X., Taber-Thomas, B. C., & Perez-Edgar, K. (2017). Frontolimbic functioning during threat-related attention: Relations to early behavioral inhibition and anxiety in children. *Biological Psychology, 122*, 98–109. https://doi.org/10.1016/j.biopsycho.2015.08.010

Galvan, A., Hare, T. A., Parra, C. E., Penn, J., Voss, H., Glover, G., & Casey, B. J. (2006). Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. *Journal of Neuroscience, 26*(25), 6885–6892. https://doi.org/10.1523/Jneurosci.1062-06.2006

Gazelle, H., & Rudolph, K. D. (2004). Moving toward and away from the world: Social approach and avoidance trajectories in anxious solitary youth. *Child Development, 75*(3), 829–849. https://doi.org/10.1111/j.1467-8624.2004.00709.x

Gobbini, M. I., & Haxby, J. V. (2007). Neural systems for recognition of familiar faces. *Neuropsychologia, 45*(1), 32–41. https://doi.org/10.1016/j.neuropsychologia.2006.04.015

Goffman, E. (2009). *Stigma: Notes on the management of spoiled identity*. Simon and Schuster. New York

Gold, A. L., Morey, R. A., & McCarthy, G. (2015). Amygdala-prefrontal cortex functional connectivity during threat-induced anxiety and goal distraction. *Biological Psychiatry, 77*(4), 394–403. https://doi.org/10.1016/j.biopsych.2014.03.030

Grabenhorst, F., & Rolls, E. T. (2011). Value, pleasure and choice in the ventral prefrontal cortex. *Trends in Cognitive Sciences, 15*(2), 56–67. https://doi.org/10.1016/j.tics.2010.12.004

Gunnar, M. R., & Hostinar, C. E. (2015). The social buffering of the hypothalamic-pituitary-adrenocortical axis in humans: Developmental and experiential determinants. *Social Neuroscience, 10*(5), 479–488. https://doi.org/10.1080/17470919.2015.1070747

Guyer, A. E., Benson, B., Choate, V. R., Bar-Haim, Y., Perez-Edgar, K., Jarcho, J. M., … Nelson, E. E. (2014). Lasting associations between early-childhood temperament and late-adolescent reward-circuitry response to peer feedback. *Development and Psychopathology, 26*(1), 229–243. https://doi.org/10.1017/S0954579413000941

Guyer, A. E., Choate, V. R., Pine, D. S., & Nelson, E. E. (2012). Neural circuitry underlying affective response to peer feedback in adolescence. *Social Cognitive and Affective Neuroscience, 7*(1), 81–92. https://doi.org/10.1093/scan/nsr043

Guyer, A. E., & Jarcho, J. M. (2018). Neuroscience and peer relations. In W. Bukowski, B. Laursen, & K. H. Rubin (Eds.), *Handbook of peer interactions, relationships, and groups* (2nd ed.). New York, NY: Guilford Press.

Guyer, A. E., Jarcho, J. M., Perez-Edgar, K., Degnan, K. A., Pine, D. S., Fox, N. A., & Nelson, E. E. (2015). Temperament and parenting styles in early childhood differentially influence neural response to peer evaluation in adolescence. *Journal of Abnormal Child Psychology, 43*(5), 863–874. https://doi.org/10.1007/s10802-015-9973-2

Guyer, A. E., Lau, J. Y., McClure-Tone, E. B., Parrish, J., Shiffrin, N. D., Reynolds, R. C., … Nelson, E. E. (2008). Amygdala and ventrolateral prefrontal cortex function during anticipated peer evaluation in pediatric social anxiety. *Archives of General Psychiatry, 65*(11), 1303–1312. https://doi.org/10.1001/archpsyc.65.11.1303

Guyer, A. E., McClure-Tone, E. B., Shiffrin, N. D., Pine, D. S., & Nelson, E. E. (2009). Probing the neural correlates of anticipated peer evaluation in adolescence. *Child Development, 80*(4), 1000–1015.

Guyer, A. E., Nelson, E. E., Perez-Edgar, K., Hardin, M. G., Roberson-Nay, R., Monk, C. S., … Ernst, M. (2006). Striatal functional alteration in adolescents characterized by early childhood behavioral inhibition. *Journal of Neuroscience, 26*(24), 6399–6405.

Hampton, A. N., Adolphs, R., Tyszka, M. J., & O'Doherty, J. P. (2007). Contributions of the amygdala to reward expectancy and choice signals in human prefrontal cortex. *Neuron, 55*(4), 545–555. https://doi.org/10.1016/j.neuron.2007.07.022

Hanish, L. D., & Guerra, N. G. (2004). Aggressive victims, passive victims, and bullies: Developmental continuity or developmental change? *Merrill-Palmer Quarterly-Journal of Developmental Psychology, 50*(1), 17–38. https://doi.org/10.1353/mpq.2004.0003

Hardee, J. E., Benson, B. E., Bar-Haim, Y., Mogg, K., Bradley, B. P., Chen, G., … Perez-Edgar, K. (2013). Patterns of neural connectivity during an attention Bias task moderate associations between early childhood temperament and internalizing symptoms in young adulthood. *Biological Psychiatry, 74*(4), 273–279. https://doi.org/10.1016/j.biopsych.2013.01.036

Hasenfratz, L., Benish-Weisman, M., Steinberg, T., & Knafo-Noam, A. (2015). Temperament and peer problems from early to middle childhood: Gene-environment correlations with nega-

tive emotionality and sociability. *Development and Psychopathology, 27*(4 Pt 1), 1089–1109. https://doi.org/10.1017/S095457941500070X

Haxby, J. V., Hoffman, E. A., & Gobbini, M. I. (2000). The distributed human neural system for face perception. *Trends in Cognitive Sciences, 4*(6), 223–233. https://doi.org/10.1016/S1364-6613(00)01482-0

Heimberg, R. G., Brozovich, F. A., & Rapee, R. M. (2010). A cognitive behavioral model of social anxiety disorder: Update and extension. In *Social anxiety* (2nd ed., pp. 395–422). San Diego, CA: Academic Press.

Helfinstein, S. M., Benson, B., Perez-Edgar, K., Bar-Haim, Y., Detloff, A., Pine, D. S., … Ernst, M. (2011). Striatal responses to negative monetary outcomes differ between temperamentally inhibited and non-inhibited adolescents. *Neuropsychologia, 49*(3), 479–485. https://doi.org/10.1016/j.neuropsychologia.2010.12.015

Henderson, H. A., Marshall, P. J., Fox, N. A., & Rubin, K. H. (2004). Psychophysiological and behavioral evidence for varying forms and functions of nonsocial behavior in preschoolers. *Child Development, 75*(1), 251–263. https://doi.org/10.1111/j.1467-8624.2004.00667.x

Holt-Lunstad, J., Smith, T. B., & Layton, J. B. (2010). Social relationships and mortality risk: A meta-analytic review. *PLoS Medicine, 7*(7), e1000316. https://doi.org/10.1371/journal.pmed.1000316

Howard, J. D., Gottfried, J. A., Tobler, P. N., & Kahnt, T. (2015). Identity-specific coding of future rewards in the human orbitofrontal cortex. *Proceedings of the National Academy of Sciences of the United States of America, 112*(16), 5195–5200. https://doi.org/10.1073/pnas.1503550112

Jarcho, J. M., Davis, M. M., Shechner, T., Degnan, K. A., Henderson, H. A., Stoddard, J., … Nelson, E. E. (2016). Early-childhood social reticence predicts brain function in preadolescent youths during distinct forms of peer evaluation. *Psychological Science, 27*(6), 821–835. https://doi.org/10.1177/0956797616638319

Jarcho, J. M., Fox, N. A., Pine, D. S., Etkin, A., Leibenluft, E., Shechner, T., & Ernst, M. (2013). The neural correlates of emotion-based cognitive control in adults with early childhood behavioral inhibition. *Biological Psychology, 92*(2), 306–314. https://doi.org/10.1016/j.biopsycho.2012.09.008

Jarcho, J. M., Fox, N. A., Pine, D. S., Leibenluft, E., Shechner, T., Degnan, K. A., … Ernst, M. (2014). Enduring influence of early temperament on neural mechanisms mediating attention-emotion conflict in adults. *Depression and Anxiety, 31*(1), 53–62. https://doi.org/10.1002/da.22140

Jarcho, J. M., Leibenluft, E., Walker, O. L., Fox, N. A., Pine, D. S., & Nelson, E. E. (2013). Neuroimaging studies of pediatric social anxiety: Paradigms, pitfalls and a new direction for investigating the neural mechanisms. *Biol Mood Anxiety Disord, 3*, 14. https://doi.org/10.1186/2045-5380-3-14

Jarcho, J. M., Romer, A. L., Shechner, T., Galvan, A., Guyer, A. E., Leibenluft, E., … Nelson, E. E. (2015). Forgetting the best when predicting the worst: Preliminary observations on neural circuit function in adolescent social anxiety. *Developmental Cognitive Neuroscience, 13*, 21–31. https://doi.org/10.1016/j.dcn.2015.03.002

Jenkins, A. C., & Mitchell, J. P. (2011). Medial prefrontal cortex subserves diverse forms of self-reflection. *Social Neuroscience, 6*(3), 211–218. https://doi.org/10.1080/17470919.2010.507948

Kagan, J. (2012). The biography of behavioral inhibition. In M. Zentner & R. L. Shiner (Eds.), *Handbook of temperament* (pp. 69–82). New York, NY: Guilford Press.

Kagan, J., & Snidman, N. (1991). Infant predictors of inhibited and uninhibited profiles. *Psychological Science, 2*(1), 40–44. https://doi.org/10.1111/j.1467-9280.1991.tb00094.x

Kanwisher, N., McDermott, J., & Chun, M. M. (1997). The fusiform face area: A module in human extrastriate cortex specialized for face perception. *Journal of Neuroscience, 17*(11), 4302–4311.

Kennedy, D. P., & Adolphs, R. (2012). The social brain in psychiatric and neurological disorders. *Trends in Cognitive Sciences, 16*(11), 559–572. https://doi.org/10.1016/j.tics.2012.09.006

Knudsen, E. I. (2004). Sensitive periods in the development of the brain and behavior. *Journal of Cognitive Neuroscience, 16*(8), 1412–1425. https://doi.org/10.1162/0898929042304796

Knutson, B., Adams, C. M., Fong, G. W., & Hommer, D. (2001). Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *Journal of Neuroscience, 21*(16), RC159.

Knutson, B., Fong, G. W., Bennett, S. M., Adams, C. M., & Hommer, D. (2003). A region of mesial prefrontal cortex tracks monetarily rewarding outcomes: Characterization with rapid event-related fMRI. *NeuroImage, 18*(2), 263–272.

Kochenderfer-Ladd, B. (2003). Identification of aggressive and asocial victims and the stability of their peer victimization. *Merrill-Palmer Quarterly-Journal of Developmental Psychology, 49*(4), 401–425. https://doi.org/10.1353/mpq.2003.0022

Lahat, A., Benson, B. E., Pine, D. S., Fox, N. A., & Ernst, M. (2016). Neural responses to reward in childhood: Relations to early behavioral inhibition and social anxiety. *Social Cognitive and Affective Neuroscience*. https://doi.org/10.1093/scan/nsw122

Lahat, A., Perez-Edgar, K., Degnan, K. A., Guyer, A. E., Lejuez, C. W., Ernst, M., … Fox, N. A. (2012). Early childhood temperament predicts substance use in young adults. *Translational Psychiatry, 2*, e157. https://doi.org/10.1038/tp.2012.87

Lin, A., Adolphs, R., & Rangel, A. (2012). Social and monetary reward learning engage overlapping neural substrates. *Social Cognitive and Affective Neuroscience, 7*(3), 274–281. https://doi.org/10.1093/scan/nsr006

Lombardo, M. V., Chakrabarti, B., Bullmore, E. T., Wheelwright, S. J., Sadek, S. A., Suckling, J., … Consortium, M. A. (2010). Shared neural circuits for mentalizing about the self and others. *Journal of Cognitive Neuroscience, 22*(7), 1623–1635. https://doi.org/10.1162/jocn.2009.21287

Masten, C. L., Telzer, E. H., Fuligni, A. J., Lieberman, M. D., & Eisenberger, N. I. (2012). Time spent with friends in adolescence relates to less neural sensitivity to later peer rejection. *Social Cognitive and Affective Neuroscience, 7*(1), 106–114. https://doi.org/10.1093/scan/nsq098

Mathews, A., & MacLeod, C. (2005). Cognitive vulnerability to emotional disorders. *Annual Review of Clinical Psychology, 1*, 167–195. https://doi.org/10.1146/annurev.clinpsy.1.102803.143916

McLaughlin, K. A., Sheridan, M. A., Winter, W., Fox, N. A., Zeanah, C. H., & Nelson, C. A. (2014). Widespread reductions in cortical thickness following severe early-life deprivation: A neurodevelopmental pathway to attention-deficit/hyperactivity disorder. *Biological Psychiatry, 76*(8), 629–638. https://doi.org/10.1016/j.biopsych.2013.08.016

Metereau, E., & Dreher, J. C. (2015). The medial orbitofrontal cortex encodes a general unsigned value signal during anticipation of both appetitive and aversive events. *Cortex, 63*, 42–54. https://doi.org/10.1016/j.cortex.2014.08.012

Meyer, M. L., & Lieberman, M. D. (2012). Social working memory: Neurocognitive networks and directions for future research. *Frontiers in Psychology, 3*, 571. https://doi.org/10.3389/fpsyg.2012.00571

Miranda, R., & Mennin, D. S. (2007). Depression, generalized anxiety disorder, and certainty in pessimistic predictions about the future. *Cognitive Therapy and Research, 31*(1), 71–82.

Moor, B. G., van Leijenhorst, L., Rombouts, S. A. R. B., Crone, E. A., & Van der Molen, M. W. (2010). Do you like me? Neural correlates of social evaluation and developmental trajectories. *Social Neuroscience, 5*(5-6), 461–482.

Morales, S., Fu, X., & Perez-Edgar, K. E. (2016). A developmental neuroscience perspective on affect-biased attention. *Developmental Cognitive Neuroscience, 21*, 26–41. https://doi.org/10.1016/j.dcn.2016.08.001

Morales, S., Taber-Thomas, B. C., & Perez-Edgar, K. E. (2017). Patterns of attention to threat across tasks in behaviorally inhibited children at risk for anxiety. *Developmental Science, 20*(2). https://doi.org/10.1111/desc.12391

Morrison, R. G., & Nottebohm, F. (1993). Role of a telencephalic nucleus in the delayed song learning of socially isolated zebra finches. *Journal of Neurobiology, 24*(8), 1045–1064. https://doi.org/10.1002/neu.480240805

Murphy, N. A., Hall, J. A., Schmid Mast, M., Ruben, M. A., Frauendorfer, D., Blanch-Hartigan, D., … Nguyen, L. (2015). Reliability and validity of nonverbal thin slices in social interactions. *Personality and Social Psychology Bulletin, 41*(2), 199–213. https://doi.org/10.1177/0146167214559902

Narr, R. K., Allen, J. P., Tan, J. S., & Loeb, E. L. (2017). Close friendship strength and broader peer group desirability as differential predictors of adult mental health. *Child Development*. https://doi.org/10.1111/cdev.12905

Nelson, C. A., Zeanah, C. H., Fox, N. A., Marshall, P. J., Smyke, A. T., & Guthrie, D. (2007). Cognitive recovery in socially deprived young children: The Bucharest early intervention project. *Science, 318*(5858), 1937–1940. https://doi.org/10.1126/science.1143921

Nelson, C. A., Westerlund, A., McDermott, J. M., Zeanah, C. H., & Fox, N. A. (2013). Emotion recognition following early psychosocial deprivation. *Development and Psychopathology, 25*(2), 517–525. https://doi.org/10.1017/S0954579412001216

Nelson, E. E., & Guyer, A. E. (2011). The development of the ventral prefrontal cortex and social flexibility. *Developmental Cognitive Neuroscience, 1*(3), 233–245. https://doi.org/10.1016/j.dcn.2011.01.002

Nelson, E. E., Jarcho, J. M., & Guyer, A. E. (2016). Social re-orientation and brain development: An expanded and updated view. *Developmental Cognitive Neuroscience, 17*, 118–127. https://doi.org/10.1016/j.dcn.2015.12.008

Nelson, E. E., Leibenluft, E., McClure, E. B., & Pine, D. S. (2005). The social re-orientation of adolescence: A neuroscience perspective on the process and its relation to psychopathology. *Psychological Medicine, 35*(2), 163–174.

Newcomb, A. F., Bukowski, W. M., & Pattee, L. (1993). Children's peer relations: A meta-analytic review of popular, rejected, neglected, controversial, and average sociometric status. *Psychological Bulletin, 113*(1), 99–128.

O'Doherty, J., Dayan, P., Schultz, J., Deichmann, R., Friston, K. J., & Dolan, R. J. (2004). Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science, 304*(5669), 452–454. https://doi.org/10.1126/science.1094285

O'Doherty, J., Kringelbach, M. L., Rolls, E. T., Hornak, J., & Andrews, C. (2001). Abstract reward and punishment representations in the human orbitofrontal cortex. *Nature Neuroscience, 4*(1), 95–102. https://doi.org/10.1038/82959

Ormel, J., Raven, D., van Oort, F., Hartman, C. A., Reijneveld, S. A., Veenstra, R., … Oldehinkel, A. J. (2015). Mental health in Dutch adolescents: A TRAILS report on prevalence, severity, age of onset, continuity and co-morbidity of DSM disorders. *Psychological Medicine, 45*(2), 345–360. https://doi.org/10.1017/S0033291714001469

Pedersen, S., Vitaro, F., Barker, E. D., & Borge, A. I. (2007). The timing of middle-childhood peer rejection and friendship: Linking early behavior to early-adolescent adjustment. *Child Development, 78*(4), 1037–1051. https://doi.org/10.1111/j.1467-8624.2007.01051.x

Perez-Edgar, K., Hardee, J. E., Guyer, A. E., Benson, B. E., Nelson, E. E., Gorodetsky, E., … Ernst, M. (2014). DRD4 and striatal modulation of the link between childhood behavioral inhibition and adolescent anxiety. *Social Cognitive and Affective Neuroscience, 9*(4), 445–453. https://doi.org/10.1093/scan/nst001

Perez-Edgar, K., Roberson-Nay, R., Hardin, M. G., Poeth, K., Guyer, A. E., Nelson, E. E., … Ernst, M. (2007). Attention alters neural responses to evocative faces in behaviorally inhibited adolescents. *NeuroImage, 35*(4), 1538–1546. https://doi.org/10.1016/j.neuroimage.2007.02.006

Powell, J., Lewis, P. A., Roberts, N., Garcia-Finana, M., & Dunbar, R. I. (2012). Orbital prefrontal cortex volume predicts social network size: An imaging study of individual differences in humans. *Proceedings of the Biological Sciences, 279*(1736), 2157–2162. https://doi.org/10.1098/rspb.2011.2574

Rapee, R. M., & Spence, S. H. (2004). The etiology of social phobia: Empirical evidence and an initial model. *Clinical Psychology Review, 24*(7), 737–767. https://doi.org/10.1016/j.cpr.2004.06.004

Rilling, J. K., & Sanfey, A. G. (2011). The neuroscience of social decision-making. *Annual Review of Psychology, 62*, 23–48. https://doi.org/10.1146/annurev.psych.121208.131647

Rodriguez, P. F., Aron, A. R., & Poldrack, R. A. (2006). Ventral-striatal/nucleus-accumbens sensitivity to prediction errors during classification learning. *Human Brain Mapping, 27*(4), 306–313. https://doi.org/10.1002/hbm.20186

Rothbart, M. K. (2012). Advances in temperament: History, concepts, and measures. In M. Zentner & R. L. Shiner (Eds.), *Handbook of temperament* (pp. 3–20). New York, NY: Guilford Press.

Roy, A. K., Benson, B. E., Degnan, K. A., Perez-Edgar, K., Pine, D. S., Fox, N. A., & Ernst, M. (2014). Alterations in amygdala functional connectivity reflect early temperament. *Biological Psychology, 103*, 248–254. https://doi.org/10.1016/j.biopsycho.2014.09.007

Rubin, K. H., & Burgess, K. B. (2001). Social withdrawal and anxiety. *The Developmental Psychopathology of Anxiety*, 407–434, New York, NY: Oxford University Press.

Rubin, K. H., Coplan, R. J., & Bowker, J. C. (2009). Social withdrawal in childhood. *Annual Review of Psychology, 60*, 141–171. https://doi.org/10.1146/annurev.psych.60.110707.163642

Rubin, K. H., Hymel, S., Mills, R. S., & Rose-Krasnor, L. (1991). Conceptualizing different developmental pathways to and from social isolation in childhood. In D. Cicchetti & S. L. Toth (Eds.), *Internalizing and externalizing expressions of dysfunction* (Vol. 2, pp. 91–122) New York, NY: Psychology Press.

Ruff, C. C., & Fehr, E. (2014). The neurobiology of rewards and values in social decision making. *Nature Reviews Neuroscience, 15*(8), 549–562. https://doi.org/10.1038/nrn3776

Saxbe, D., Del Piero, L., Immordino-Yang, M. H., Kaplan, J., & Margolin, G. (2015). Neural correlates of adolescents' viewing of parents' and peers' emotions: Associations with risk-taking behavior and risky peer affiliations. *Social Neuroscience, 10*(6), 592–604. https://doi.org/10.1080/17470919.2015.1022216

Schultz, W. (2004). Neural coding of basic reward terms of animal learning theory, game theory, microeconomics and behavioural ecology. *Current Opinion in Neurobiology, 14*(2), 139–147. https://doi.org/10.1016/j.conb.2004.03.017

Schultz, W., Dayan, P., & Montague, P. R. (1997). A neural substrate of prediction and reward. *Science, 275*(5306), 1593–1599. https://doi.org/10.1126/science.275.5306.1593

Schwartz, C. E., Kunwar, P. S., Greve, D. N., Kagan, J., Snidman, N. C., & Bloch, R. B. (2012). A phenotype of early infancy predicts reactivity of the amygdala in male adults. *Molecular Psychiatry, 17*(10), 1042–1050. https://doi.org/10.1038/mp.2011.96

Schwartz, C. E., Kunwar, P. S., Greve, D. N., Moran, L. R., Viner, J. C., Covino, J. M., … Wallace, S. R. (2010). Structural differences in adult orbital and ventromedial prefrontal cortex predicted by infant temperament at 4 months of age. *Archives of General Psychiatry, 67*(1), 78–84. https://doi.org/10.1001/archgenpsychiatry.2009.171

Schwartz, C. E., Kunwar, P. S., Hirshfeld-Becker, D. R., Henin, A., Vangel, M. G., Rauch, S. L., … Rosenbaum, J. F. (2015). Behavioral inhibition in childhood predicts smaller hippocampal volume in adolescent offspring of parents with panic disorder. *Translational Psychiatry, 5*, e605. https://doi.org/10.1038/tp.2015.95

Schwartz, C. E., Snidman, N., & Kagan, J. (1999). Adolescent social anxiety as an outcome of inhibited temperament in childhood. *Journal of the American Academy of Child and Adolescent Psychiatry, 38*(8), 1008–1015. https://doi.org/10.1097/00004583-199908000-00017

Schwartz, C. E., Wright, C. I., Shin, L. M., Kagan, J., & Rauch, S. L. (2003). Inhibited and uninhibited infants "grown up": Adult amygdalar response to novelty. *Science, 300*(5627), 1952–1953. https://doi.org/10.1126/science.1083703

Shenhav, A., & Greene, J. D. (2014). Integrative moral judgment: Dissociating the roles of the amygdala and ventromedial prefrontal cortex. *Journal of Neuroscience, 34*(13), 4741–4749. https://doi.org/10.1523/Jneurosci.3390-13.2014

Sheridan, M. A., Fox, N. A., Zeanah, C. H., McLaughlin, K. A., & Nelson, C. A. (2012). Variation in neural development as a result of exposure to institutionalization early in childhood. *Proceedings of the National Academy of Sciences of the United States of America, 109*(32), 12927–12932. https://doi.org/10.1073/pnas.1200041109

Silverman, M. H., Jedd, K., & Luciana, M. (2015). Neural networks involved in adolescent reward processing: An activation likelihood estimation meta-analysis of functional neuroimaging studies. *NeuroImage, 122*, 427–439. https://doi.org/10.1016/j.neuroimage.2015.07.083

Smetana, J. G., Campione-Barr, N., & Metzger, A. (2006). Adolescent development in interpersonal and societal contexts. *Annual Review of Psychology, 57*, 255–284. https://doi.org/10.1146/annurev.psych.57.102904.190124

Spielberg, J. M., Jarcho, J. M., Dahl, R. E., Pine, D. S., Ernst, M., & Nelson, E. E. (2015). Anticipation of peer evaluation in anxious adolescents: Divergence in neural activation and maturation. *Social Cognitive and Affective Neuroscience, 10*(8), 1084–1091. https://doi.org/10.1093/scan/nsu165

Sporns, O., Chialvo, D. R., Kaiser, M., & Hilgetag, C. C. (2004). Organization, development and function of complex brain networks. *Trends in Cognitive Sciences, 8*(9), 418–425. https://doi.org/10.1016/j.tics.2004.07.008

Stamoulis, C., Vanderwert, R. E., Zeanah, C. H., Fox, N. A., & Nelson, C. A. (2017). Neuronal networks in the developing brain are adversely modulated by early psychosocial neglect. *Journal of Neurophysiology, 118*(4), 2275–2288. https://doi.org/10.1152/jn.00014.2017

Steinberg, L., & Morris, A. S. (2001). Adolescent development. *Annual Review of Psychology, 52*, 83–110. https://doi.org/10.1146/annurev.psych.52.1.83

Sugimura, N., & Rudolph, K. D. (2012). Temperamental differences in Children's reactions to peer victimization. *Journal of Clinical Child and Adolescent Psychology, 41*(3), 314–328. https://doi.org/10.1080/15374416.2012.656555

Suway, J. G., Degnan, K. A., Sussman, A. L., & Fox, N. A. (2012). The relations among theory of mind, Behavioral inhibition, and peer interactions in early childhood. *Social Development, 21*(2), 331–342. https://doi.org/10.1111/j.1467-9507.2011.00634.x

Sylvester, C. M., Barch, D. M., Harms, M. P., Belden, A. C., Oakberg, T. J., Gold, A. L., … Pine, D. S. (2016). Early childhood Behavioral inhibition predicts cortical thickness in adulthood. *Journal of the American Academy of Child and Adolescent Psychiatry, 55*(2), 122–129. https://doi.org/10.1016/j.jaac.2015.11.007

Taber-Thomas, B. C., Morales, S., Hillary, F. G., & Perez-Edgar, K. E. (2016a). Altered topography of intrinsic functional connectivity in childhood risk for social anxiety. *Depression and Anxiety, 33*(11), 995–1004. https://doi.org/10.1002/da.22508

Taber-Thomas, B. C., Morales, S., Hillary, F. G., & Perez-Edgar, K. E. (2016b). Altered topography of intrinsic functional connectivity in childhood risk for social anxiety. *Depression and Anxiety*. https://doi.org/10.1002/da.22508

Tobler, P. N., Fiorillo, C. D., & Schultz, W. (2005). Adaptive coding of reward value by dopamine neurons. *Science, 307*(5715), 1642–1645. https://doi.org/10.1126/science.1105370

Tremblay, S., Sharika, K. M., & Platt, M. L. (2017). Social decision-making and the brain: A comparative perspective. *Trends in Cognitive Sciences, 21*(4), 265–276. https://doi.org/10.1016/j.tics.2017.01.007

Troller-Renfree, S., McDermott, J. M., Nelson, C. A., Zeanah, C. H., & Fox, N. A. (2015). The effects of early foster care intervention on attention biases in previously institutionalized children in Romania. *Developmental Science, 18*(5), 713–722. https://doi.org/10.1111/desc.12261

Troller-Renfree, S., Nelson, C. A., Zeanah, C. H., & Fox, N. A. (2016). Deficits in error monitoring are associated with externalizing but not internalizing behaviors among children with a history of institutionalization. *Journal of Child Psychology and Psychiatry, 57*(10), 1145–1153. https://doi.org/10.1111/jcpp.12604

Uddin, L. Q. (2015). Salience processing and insular cortical function and dysfunction. *Nature Reviews. Neuroscience, 16*(1), 55–61. https://doi.org/10.1038/nrn3857

Vuilleumier, P., & Pourtois, G. (2007). Distributed and interactive brain mechanisms during emotion face perception: Evidence from functional neuroimaging. *Neuropsychologia, 45*(1), 174–194. https://doi.org/10.1016/j.neuropsychologia.2006.06.003

Wessa, M., Heissler, J., Schonfelder, S., & Kanske, P. (2013). Goal-directed behavior under emotional distraction is preserved by enhanced task-specific activation. *Social Cognitive and Affective Neuroscience, 8*(3), 305–312. https://doi.org/10.1093/scan/nsr098

Williams, L. R., Fox, N. A., Lejuez, C. W., Reynolds, E. K., Henderson, H. A., Perez-Edgar, K. E., … Pine, D. S. (2010). Early temperament, propensity for risk-taking and adolescent substance-related problems: A prospective multi-method investigation. *Addictive Behaviors, 35*(12), 1148–1151. https://doi.org/10.1016/j.addbeh.2010.07.005

Yacubian, J., Sommer, T., Schroeder, K., Glascher, J., Braus, D. F., & Buchel, C. (2007). Subregions of the ventral striatum show preferential coding of reward magnitude and probability. *NeuroImage, 38*(3), 557–563. https://doi.org/10.1016/j.neuroimage.2007.08.007

Zaki, J., Hennigan, K., Weber, J., & Ochsner, K. N. (2010). Social cognitive conflict resolution: Contributions of domain-general and domain-specific neural systems. *Journal of Neuroscience, 30*(25), 8481–8488. https://doi.org/10.1523/JNEUROSCI.0382-10.2010

Psychobiological Processes in the Development of Behavioral Inhibition

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Abstract Despite robust prediction from early behavioral inhibition to anxiety development, evidence is accumulating for heterogeneity among children identified as behaviorally inhibited. In this chapter, we examine how behavioral inhibition is associated with a range of psychophysiological markers to better understand this heterogeneity. We suggest that these measures are not just correlated with behavioral inhibition but are markers of underlying processes that help to characterize which children are at highest risk for anxiety, thereby reducing heterogeneity. We organize the literature by discussing physiological markers as indexing reactivity and regulation, consistent with a temperament framework, and cover a wide range of physiological measures linked to behavioral inhibition and risk for anxiety, including electrodermal activity, cortisol, and EEG asymmetry, respiratory sinus arrhythmia, EEG delta-beta coupling, and event-related potentials. The findings presented herein support the notion that these physiological markers index mechanisms that contribute to children's behavioral manifestation of behavioral inhibition and may exacerbate the risk for inhibited children to remain on the trajectory of developing anxiety symptoms.

Psychobiological Processes in the Development of Behavioral Inhibition

Behavioral inhibition—or extreme fearful temperament more broadly defined—is the tendency to avoid and withdraw to novel situations, often while showing fearful reactions (García Coll, Kagan, & Reznick, 1984; Kagan & Fox, 2006). Behavioral inhibition is among the strongest early predictors of anxiety symptom development, specifically social anxiety (Beesdo, Knappe, & Pine, 2009). When inhibition is stable throughout the childhood (Chronis-Tuscano et al., 2009; Essex, Klein, Slattery, Goldsmith, & Kalin, 2010), and when inhibition is displayed more prominently in

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certain contexts (Buss, 2011; Buss et al., 2013), this increases the risk for social anxiety symptoms.

Perhaps due to the robust and consistent nature of the findings in the literature, there is an implicit assumption that temperamentally fearful children are a homogeneous group. However, most inhibited toddlers, despite being at increased risk for anxiety development, ultimately mature to become healthy children (Pine, Helfinstein, Bar-Haim, Nelson, & Fox, 2009). Two related questions emerge in attempts to explain these findings: (1) Which children are the ones that we should worry about? That is, what are the unique *characteristics* that are associated with risk for social anxiety development in inhibited children? (2) What *factors or processes* are associated with increased risk for social anxiety? Differences in outcome may have roots in early heterogeneity among temperamentally fearful children.

As the first question suggests, not all fearful/inhibited children are the same, and perhaps only a certain type of inhibited child develops social anxiety. This has been the focus of our work as well as others using human and nonhuman models (see the chapter "Behavioral Inhibition in Nonhuman Primates: The Elephant in the Room" by Capitanio and the chapter "Behavioral Inhibition in Rodents: A Model to Study Causes and Health Consequences of Temperament" by Cavigelli). In addressing the issue of heterogeneity, we argue that fearful temperament needs to be measured dynamically across situations and development because children's reactions to or interpretations of situations (as threatening or not) will determine more precisely whether behavior is, or will be, maladaptive. We characterized extreme fearful behavior in toddlers across a series of novel laboratory situations ranging from low to high threat (Buss, 2011) as an index of fear sensitivity (Buss, Davis, Ram, & Coccia, 2018). By examining how fear changes across these situations, we have been able to quantify a dimension of fear regulation ranging from *well-regulated fear* (fear increases in expected ways with increases in putative threat) to *dysregulated fear* (fear is higher than expected to putatively lower threat situations because these situations are reacted to or interpreted as potential threats). Had we not assessed fear across a range of situations (especially those low in putative threat), we would have missed identification of these children altogether—they are indistinguishable from other inhibited children in higher threat contexts. Importantly, dysregulated fear (DF) pattern at age 2 predicts reported and observed social withdrawal behavior at 3, 4, and 5 years (Buss, 2011) and social anxiety disorder symptoms at age 6 and in early adolescence (Buss et al., 2013; Buss et al., 2018).

What accounts for this heterogeneity? Other factors or characteristics could differentiate which fearful children are at highest risk, reflecting the underlying processes that account for the fearful, inhibited, and anxious behavior. From a temperament perspective, the processes that account for behavioral differences include both reactive and regulatory processes (Rothbart, 2011). We, and others, argue that examining physiological processes may help in elucidating the underlying processes that link behavioral inhibition to social anxiety symptom development (see the chapter "The Neurobiology of Behavioral Inhibition as a Developmental Mechanism" by Blackford et al.) and may help tease apart inhibited behavior that

does not confer risk for social anxiety (i.e., the false-positive cases of inhibition) from the at-risk cases.

Numerous studies, some of which will be summarized in this chapter, have documented dysregulated physiological measures and systems associated with fearful and anxious behavior (Davidson, Jackson, & Kalin, 2000; Fox, Henderson, Marshall, Nichols, & Ghera, 2005; Rothbart, 2011). Moreover, greater attention has been paid to integrating across biological and psychological domains in explicating the development of anxiety across development (Bauer, Quas, & Boyce, 2002). In the sections that follow, we review the evidence for the links between different physiological measures and behavioral inhibition. This review is not exhaustive but rather will highlight the underlying processes and mechanisms we believe are associated with the behavior pattern of inhibited children at highest risk for difficulties with social anxiety. In our read of the literature over the past 25 years, we believe there are a few key processes that are highlighted in the work examining links among physiology, inhibited behavior, and risk for anxiety development. These include, but are not limited to, the role of (stress) reactivity, regulation or dysregulation in context, and executive processes. We will conclude with our view of what these findings to date mean and recommendations for future directions.

Behavioral Inhibition and Increased Reactivity

Kagan (1994) suggested that behaviorally inhibited children have lower threshold of sensitivity in the amygdala that give rise to the inhibition, fear, and withdrawal (see the chapter "The History and Theory of Behavioral Inhibition" by Kagan). Decades of work has examined physiological markers of this hypothesis including increases in heart rate (Degnan & Fox, 2007) and other SNS-mediated markers, stress physiology such as cortisol, and examination of neural mechanisms that may be markers of fear and withdrawal behavior (see the chapter "The Neural Mechanisms of Behavioral Inhibition" by Jarcho and Guyer). We review some of this work by focusing on three measures: electrodermal activity (EDA), cortisol, and EEG asymmetry and coherence.

Electrodermal Activity

Electrodermal activity (EDA) is caused by activity in sweat glands when activated by the sympathetic nervous system (SNS) during times of physical or psychological stress (El-Sheikh et al., 2009). This electrodermal activity is accompanied by increased oxygenation in the body and increased heart rate to prepare the body for action (Boucsein, 2012). However, there are individual differences in terms of how easily the SNS system can be activated and the length and intensity of SNS activation (Fowles, Kochanka, & Murray, 2000). Generally, elevation in SNS can be

considered adaptive as the body mobilizes its resources to cope with environmental challenges (El-Sheikh et al., 2009). However, prolonged SNS reactivity is maladaptive and can produce negative health consequences in the body (McEwen, 1998; see the chapter "Behavioral Inhibition in Rodents: A Model to Study Causes and Health Consequences of Temperament" by Cavigelli). Skin conductance has been used to examine the relation between children's stress reactivity and internalizing symptoms, setting the foundation for studies specifically focused on anxiety risk and behavioral inhibition.

Most of the skin-conductance literature has focused on adult samples. However, there are a few notable studies examining skin-conductance levels in relation to behavioral inhibition in children. Toddlers who were high on behavioral inhibition showed higher skin-conductance levels while at rest compared to children who were low on behavioral inhibition (Scarpa, Raine, Venables, & Mednick, 1997). Additionally, a handful of studies also examined EDA with additional moderators such as parenting quality or other physiological measures.

Temperamentally fearful preschoolers showed higher EDA to the fearful-eliciting stimulus when they had lower parent-child relationship quality (Gilissen, Koolstra, van Ijzendoorn, Bakermans-Kranenburg, & van Veer, 2007). Thus, poor parent-child relationship quality is one context in which we see evidence for a link between stress reactivity and fearful temperament, because not all fearful children showed higher EDA. EDA has also been examined together with RSA to form parasympathetic nervous system (PNS)-SNS activation profiles in predicting anxiety symptoms (El-Sheikh, Keiley, Erath, & Dyer, 2013). In contrast to the findings with behavioral inhibition, children who exhibited lower EDA reactivity and lower RSA reactivity were at highest risk of developing anxiety symptoms, whereas children who showed higher RSA and lower EDA at baseline demonstrated decreased anxiety over time.

Furthermore, these general findings also differed based on child gender and levels of family conflict (El-Sheikh et al., 2013). Specifically, girls from higher conflict homes who had both low baseline RSA and EDA had higher and increasing levels of anxiety over time, whereas boys showed the opposite pattern such that their anxiety started out high at age 8 but declined over time. Behavioral inhibition has been shown to correlate with higher EDA levels, although other work examining anxiety symptoms demonstrates the opposite pattern. One consistent component across these studies is evidence of environmental factors, such as parenting, and other physiological markers that may moderate these effects.

In sum, children with higher behavioral inhibition and/or anxious traits also demonstrate higher EDA consistent with the stress-response hypothesis that EDA will be elevated in stressful situations, but only under certain environmental contexts such as parenting. These findings are consistent with our previous work on context effects (Buss, 2011). Moreover, the interactions with other physiological markers suggest heterogeneity, such that not all fearful children will display an elevated stress response. In this case, it may be that the response is potentiated only when coupled with difficulty regulating—as marked by poorer physiological regulation (see RSA section later in this chapter).

Cortisol

Cortisol is the main glucocorticoid of the hypothalamic-pituitary-adrenocortical (HPA) system and it reflects elevated activity in the limbic system (amygdala and bed nucleus of the stria terminalis) (Kalin, Shelton, Fox, Oakes, & Davidson, 2005; Schwartz, Wright, Shin, Kagan, & Rauch, 2003). This neuroendocrine response system is regulated by the central nucleus of the amygdala (Fox et al., 2005). Elevations in cortisol are part of the cascade of physiological changes that occur under stress, increasing glucose available to the muscles for "fight or flight" response (Doom & Gunnar, 2013).

Like other physiological processes, activation of the HPA axis is sensitive to a variety of psychological and social stressors. Moreover, prolonged elevation of cortisol may pose cardiovascular-related health risks such as elevation of blood pressure, insulin resistance, and truncal obesity (Whitworth, Williamson, Mangos, & Kelly, 2005). In addition, the persistent elevation of cortisol may be associated with smaller volume in the hippocampus, a brain region implicated in memory, motivation, and emotion (Pagliaccio et al., 2014). Prolonged elevations of cortisol levels may lower the threshold to trigger children's next cortisol activation and also interfere with recovery from with stress (Buss, Davis, & Kiel, 2011). Therefore, it is important to examine for whom elevations in cortisol are most likely and under what circumstances elevations occur.

Children with high baseline cortisol levels displayed social withdrawal and social reticence, a marker of behavioral inhibition, at age 4 (Pérez-Edgar, Schmidt, Henderson, Schulkin, & Fox, 2008). This finding was the strongest for boys who also displayed higher levels of negative affect as infants. These data may suggest a pathway supporting the larger finding that boys high in behavioral inhibition go on to display more anxiety than their equally inhibited female peers (Fox, Snidman, Haas, Degnan, & Kagan, 2015). Furthermore, there seems to be a bidirectional effect between behavioral inhibition and cortisol levels across development.

Higher cortisol levels at 4.5 years predicted mother and teacher reports of social wariness in kindergarten (Smider et al., 2002). In a follow-up study with the same longitudinal sample, cortisol levels at 4.5 years were positively associated with chronic behavioral inhibition assessed from grade 1 through grade 9 (Essex et al., 2010). In another study examining change in cortisol levels across the Trier Social Stress test for Children (TSST-C), behavioral inhibition at age 7 was positively associated with higher baseline cortisol (measured as AUC_g, area under the curve ground) and cortisol reactivity (indexed by AUC_i, area under the curve increase) at age 9 (Mackrell et al., 2014). Thus, stability in behavioral inhibition may be, in part, accounted for by consistency of the HPA stress response, suggesting that stress reactivity may also contribute to identification of the most vulnerable inhibited children.

The associations between elevated cortisol levels and fear behaviors have been well documented in the nonhuman primate literature (Dettmer, Novak, Suomi, & Meyer, 2012; Shackman et al., 2013). Using a rhesus macaque model, monkeys

who exhibited higher baseline cortisol exhibited more freezing behavior compared to those who exhibited lower baseline cortisol levels (Kalin, 1993). Moreover, Shackman et al. (2013) distinguished the brain regions that predicted elevated cortisol levels, freezing behavior, and vocalization indicating that there are heterogeneous dimensions of anxious temperament in the animal model. This is consistent with our model (Buss & Kiel, 2013) and data with toddlers demonstrating heterogeneity across fearful temperament profiles and emerging evidence for an accompanying unique pattern of physiology (Buss, 2011; Buss et al., 2013; Buss, Davis, et al., 2018).

Variation in environmental contexts and transitions may highlight the association between temperament and stress reactivity. For instance, some children may experience elevated stress during the transition to school (Russ et al., 2012; Tarullo, Mliner, & Gunnar, 2011). Specifically, Tarullo et al. (2011) found that cortisol levels for highly inhibited children remained elevated across the school year, compared to cortisol levels in highly exuberant children, that is, children who are high on positive reactivity and approach (Fox, 1991). Consistent with the findings, children who were classified as "inhibited" at 14 months and whose mothers were diagnosed with social phobia displayed higher afternoon cortisol collected 1 month before starting school, the first week at school, and near the end of the first term (Russ et al., 2012).

Other environmental factors may also contribute to the pattern of stress reactivity observed. For instance, for behaviorally inhibited children, having more friends and being more dominant and popular were actually associated with increasing cortisol levels over the school years (Tarullo et al., 2011). Therefore, children with behavioral inhibition are more likely to show prolonged cortisol elevation during the transition to school and to experience elevated stress associated with social interactions. These findings illustrate the importance of examining the interactions among children's inhibited temperament and the social environment to predict their physiological reactivity. The positive peer context for exuberant children may not be the equivalent positive peer context for children with behavioral inhibition.

In addition to the cortisol stress response, cortisol "regulation," or stress recovery, has also been examined in relation to behavioral inhibition. Cortisol regulation, indexed by the extent and speed of recovery after a social stressor, may buffer children who are high on shyness from demonstrating high solitary/reticent behaviors (Davis & Buss, 2012). In a sample of 6-year-olds, parent-reported shyness was positively associated with shyness/reticence and solitary passive play behavior only when children had low levels of cortisol recovery (Davis & Buss, 2012). Thus, the ability to regulate cortisol levels may be adaptive such that recovery from a cortisol stress response for inhibited children may support social competence.

In addition, parenting behaviors play an important role for inhibited children's elevation in cortisol. Specifically, maternal overprotection may prevent the opportunities for children to be more autonomous, which in turn exacerbates children's behavioral inhibition behaviors (Hutt, Buss, & Kiel, 2013). Higher levels of caregiver protective behaviors predicted higher levels of cortisol reactivity (indexed by an increase of cortisol levels from the baseline) above and beyond toddler's observed fear and sadness (Hutt et al., 2013). Caregivers' activity also mediated toddlers' fear

and sadness and their cortisol reactivity, such that mothers who not only were able to predict their children's fear, but also protected their children from getting exposed to the external stimulus, had children with higher behavioral inhibition (Hutt et al., 2013). Similarly, mothers who have an insecure attachment with their children may be overly intrusive and encourage their children to try fearful tasks without paying attention to children's needs. Having a secure attachment may buffer children with fearful temperament from experiencing elevated cortisol (Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996). Together these examples highlight the important role that the caregiving environment plays on stress reactivity for children with behavioral inhibition.

In sum, elevated cortisol level may serve as a stress-reactivity marker for behaviorally inhibited children. The impact of peer, school, and the caregiving contexts suggests that children's levels of stress reactivity are malleable to environmental influences and can be regulated to a certain degree (Davis & Buss, 2012; Hutt et al., 2013). Even though EDA and elevated cortisol have been found to be physiological markers for behavioral inhibition, the findings always need to be considered in specific environmental contexts. Therefore, whether or not individual differences in stress reactivity help address the question of heterogeneity and aid in the identification of which children are at greatest risk is still an open question.

Neural Correlates: EEG Asymmetry

The anterior regions of both hemispheres may be lateralized for the behavioral/motivational systems involved in approach and withdrawal behaviors (Davidson, 1988; Fox, 1991). For example, a recent study of 9- to 12-year-old children (Taber-Thomas, Galinsky, Morales, Thai, & Pérez-Edgar, in prep) suggests that EEG asymmetry patterns reflect functional connectivity patterns in frontolimbic networks. The two sides of the frontal cortex may be associated with approach or withdrawal tendencies. The left frontal area is associated with approach behaviors that can be measured via positive emotions and other motor behaviors (Fox & Davidson, 1984). The right fontal area is associated with behaviors that are characterized by withdrawing from a novel or a stressful stimulus, and this withdrawal tendency is usually assessed via measuring autonomic reactivity and expressions of negative affect (Fox & Davidson, 1984), with the exception of anger, which is considered an approach emotion.

Individuals with behavioral inhibition usually demonstrate right frontal EEG asymmetry (Degnan & Fox, 2007). This pattern is evident as early as infancy (Calkins, Fox, & Marshall, 1996) and among young children (Fox, Henderson, Rubin, Calkins, & Schmidt, 2001). Right fontal asymmetry has also been found in children who demonstrated anxious behaviors during social interactions (Fox et al., 1995; Henderson, Fox, & Rubin, 2001).

In addition, the presence of right frontal EEG asymmetry increases the likelihood that behaviorally inhibited children will demonstrate poor social behavior

(Henderson et al., 2001). Furthermore, frontal EEG asymmetry is also associated with the stability of behavioral inhibition. Stability of behavioral inhibition from age 3 to age 10 was only observed when children also showed stable right frontal asymmetry from age 3 to age 10 (Davidson & Rickman, 1999), suggesting that right frontal EEG asymmetry serves as a physiological marker of behavioral inhibition traits in children.

In the adult literature, right frontal EEG asymmetry has been associated with negative affect, behavioral withdrawal, behavioral inhibition, anxiety, and depression (Harmon-Jones, Gable, & Peterson, 2010). For instance, attention bias to threat—a correlate of behavioral inhibition—has been associated with increased right frontal EEG asymmetry in response to stress (Pérez-Edgar, Kujawa, Nelson, Cole, & Zapp, 2013). In a fear context, decreased alpha power (increased cortical activity) in the right fontal (F4) site was correlated with higher scores on a behavioral inhibition measure (Balconi & Mazza, 2010). Similar patterns were also found in the context of anger and surprise (Balconi & Mazza, 2010). On the other hand, individuals characterized by the behavioral approach system had greater left (vs. right) side frontal cortical activity (Amodio, Master, Yee, & Taylor, 2008). Therefore, findings from the adult literature are consistent with those reported from child literature.

In sum, right frontal EEG asymmetry is generally associated with higher behavioral inhibition and anxious traits across development; thus, it is, at minimum, an important neural correlate of behavioral inhibition behaviors. However, we suggest that the pattern of results is robust enough to suggest that right frontal asymmetry is a marker of behavioral inhibition and could be used as an additional measure to identify these children. Considering that the association is stable in both childhood and adulthood, right frontal EEG asymmetry may also be an underlying mechanism supporting the behavioral manifestation of inhibited behaviors. Thus, the presence of this pattern of neural activity would help to increase homogeneity of children identified as behaviorally inhibited.

Behavioral Inhibition and Self–Regulation

In the previous section, we summarized data across a few physiological systems that suggests behavioral inhibition is associated with, or marked by, an underlying reactivity bias. In particular, children evidence an increase in cortisol, EDA, and right frontal EEG asymmetry. This is consistent with the theoretical explanations of inhibited behavior put forth by Kagan and with underlying neural mechanisms of fear and anxiety. However, reactive processes may not explain all of the differences that are observed at the phenotypic level. Moreover, these reactivity processes do not operate in isolation. In this section, we will briefly discuss physiological systems that demonstrate that regulatory and specific executive processes are also implicated in inhibited and anxious behavior across development.

Parasympathetic Vagal Tone Via Respiratory Sinus Arrhythmia (RSA)

Vagal tone, an index of heart rate variability, is usually measured via respiratory sinus arrhythmia (RSA). RSA refers to the high frequency variability in heart rate that occurs at the frequency of spontaneous respiration (Calkins, Graziano, Berdan, Keane, & Degnan, 2008; Porges, 1996). The vagus nerve is the 10th cranial nerve, has efferent connections to the heart, and mediates the parasympathetic control of the heart, controlling acceleration and deceleration of heart rate (Porges, 1996; Porges, 2007). When facing an external demand to increase metabolic output (e.g., during a novel or challenging situation), withdrawal (i.e., decrease) of parasympathetic input to the heart will result in increased heart rate, allowing individuals to shift from maintaining internal homeostasis to coping with external demands (Porges, 1996).

Thus, vagal withdrawal is considered a physiological regulation process that leads to a greater cardiac output (e.g., HR acceleration) and active coping behaviors in order to adjust to the environmental demands (Calkins et al., 2008; Porges, 1996). In addition, the vagus nerve is connected in humans to muscles in the face, head, and neck. Changes in the activity in the vagal system may manifest in changes in individuals' facial expression, neck tension, and tone of voice (Porges & Furman, 2011). Therefore, it serves an important role during the process of social engagement across multiple levels of functioning.

RSA is used to quantify vagal tone and is believed to be a marker of regulation (Beauchaine, 2001; Calkins, 2011). Individual differences in RSA reflecting regulatory processes have been indexed by both baseline RSA and changes from baseline to task (i.e., RSA withdrawal or suppression), and both of these measures have been examined in the broader socioemotional literature, including studies including behavioral inhibition explicitly. Children with lower baseline RSA have difficulty with self-regulation (Beauchaine, 2001; Porges, 1996). Higher resting baseline RSA is associated with better sustained attention (Suess, Porges, & Plude, 1994), greater behavioral reactivity (Porges, Doussard-Roosevelt, Portales, & Suess, 1994), and more sociable and exploratory behaviors (Fox, 1989).

Mixed findings also exist on the association between shyness and RSA across development. For preschoolers' who were high in shyness, lower RSA was associated with lower effortful control (Sulik, Eisenberg, Silva, Spinrad, & Kupfer, 2013). However, in other samples, shyness and RSA were not linked (Marshall & Stevenson-Hinde, 1998; Dietrich et al., 2009). In an adolescent sample, behaviorally inhibited youth exhibited lower RSA and less variability in heart rate (Balle, Tortella-Feliu, & Bornas, 2013). Generally, lower baseline RSA and less RSA suppression are considered maladaptive and are associated with more social wariness (Hastings, Kahle, & Nuselovici, 2014) and anxiety symptoms (Licht, de Geus, van Dyck, & Penninx, 2009). In general, lower baseline RSA is associated with higher risk of maladaptive social behaviors, but the findings are mixed suggesting more research is needed to pinpoint specific risk across development.

In addition to baseline RSA, the ability to suppress RSA during challenging tasks has been associated with greater self-regulation and adaptive behavioral outcomes for inhibited children across development. In our own work, RSA suppression was associated with less fear in novel situations and lower risk for social anxiety for temperamentally fearful children (Buss, Davis, et al., 2018). Moreover, fear sensitivity (i.e., higher inhibition to low-threat situations) at 24 months predicted social inhibition only for toddlers who exhibited higher averaged RSA, reflecting a failure to suppress RSA across tasks (Buss, Davis, et al., 2018). In another study from our laboratory, toddlers who suppressed RSA during a novel, putatively threatening, task engaged in more approach behaviors (Brooker & Buss, 2009), further demonstrating the link between RSA regulation and adaptive behavior.

These findings extend longitudinally as well. Infants, who showed less RSA suppression during a stranger approach task at 6 months, were more than three times as likely to be characterized in a high/stable social-fear class than in the low/steady social-fear class from 6 to 36 months (Brooker et al., 2013). Moreover, infants in the high/stable social-fear class were more likely to be rated as behaviorally inhibited at 36 months. In contrast, infants who showed greater RSA suppression were also slightly more likely to be in the decreasing social-fear class than in the slow increase class (Brooker et al., 2013). Therefore, across multiple studies the pattern of findings suggest that vagal withdrawal may buffer children who have temperamental risk from developing inhibited social behavior (Brooker et al., 2013; Cho & Buss, 2017) and from developing social inhibition and anxiety problems (Buss, Davis, et al., 2018).

Despite these previous findings supporting RSA withdrawal as an adaptive regulatory process, in other contexts, vagal augmentation or stable RSA levels from baseline to challenge may be more adaptive. For example, in a social context with playmates, preschool children who exhibited higher RSA compared to baseline had lower behavioral problems and better self-regulation (Hastings et al., 2008). In this case, RSA augmentation was considered adaptive as children recruit resources to engage in social situations. In addition, children who exhibited dysregulated fear (i.e., high-fear to low-threat contexts) showed more dynamic RSA changes in a stranger approach context compared to all other children (Brooker & Buss, 2009). Using a time-series analysis, high-fear toddlers demonstrated faster rate of increase in RSA (indexed by steeper linear slope) and a steeper decline (indexed by a quadratic slope) across the episode than non-high-fear toddlers. In contrast, non-high-fear toddlers showed a relative constant level of RSA over time (Brooker & Buss, 2009). In addition, these dynamic changes in RSA were related to less positive affect for high-fear toddlers (Brooker & Buss, 2009). The adaptiveness of RSA withdrawal always needs to be considered within a specific eliciting context (e.g., high fear vs. low fear; social vs. emotionally challenging). What is consistent, however, is that inhibited and fearful children are more likely to show maladaptive patterns of RSA during novel and social challenges.

Vagal withdrawal also plays an important moderating role in the association between parenting and children's behavioral inhibition and anxious behavior. For

example, fathers' high protective overcontrol was associated with inhibition only for preschoolers who showed less RSA suppression (Hastings et al., 2008). In contrast, fathers' supportive parenting reduced inhibition for children with less RSA suppression (Hastings, Sullivan, et al., 2008). In another study examining RSA, attachment, and behavioral inhibition, Paret and colleagues found that insecurely attached (ambivalent attachment), behaviorally inhibited preschoolers were less likely to suppress RSA to a novel situation compared to securely attached children (Paret, Bailey, Roche, Bureau, & Moran, 2015). These differences were not found for children who were low on behavioral inhibition (Paret et al., 2015). This finding is consistent with those presented earlier demonstrating an interaction between behavioral inhibition and insecure attachment in predicting increases in cortisol (Nachmias et al., 1996). In our own work, we have found similar moderating effects with RSA. We found that when mothers predicted high fear in their 24-month-old toddlers during fear-eliciting tasks, they were more likely to engage in overprotective behaviors and rate children as anxious in preschool, when toddlers were lower in baseline RSA and lower RSA suppression (Cho & Buss, 2017). Much like the previous findings with cortisol stress reactivity, these findings demonstrate the importance of the caregiving environment and the quality of parent-child relationship for how inhibited children regulate their distress and engage with their environment.

In sum, although not all studies find a consistent association between RSA (baseline or reactive) and behavioral inhibition, the pattern of findings points to a pattern of dysregulation for inhibited and anxious children across development. Specifically, lower baseline RSA and less RSA suppression to stressful and challenging situations mark a failure to engage with environment, less self and emotion regulation, greater fearful behavior, and risk for anxiety across development. Not only does this pattern of findings suggest difficulty with regulation for inhibited children on average; it suggests that those inhibited children who most consistently have difficulty regulating may be at greatest risk. Thus, RSA as a marker of regulation can be considered an important contributor to the identification of the most at-risk inhibited children.

Delta-Beta Coupling

There is increasing evidence that behavioral inhibition, and other types of extreme fearful traits (e.g., dysregulated fear), may be associated with a propensity to overregulate (Eisenberg et al., 2001; Murray & Kochanska, 2002), putting inhibited children at increased risk for developing anxiety. Although summarizing these behavioral studies is beyond the scope of this review, there is emerging literature suggesting that other processes examined at the neural level that may shed light on this question. For instance, delta-beta coupling has recently emerged as a putative biomarker of regulation (Knyazev & Slobodskaya, 2003; Phelps, Brooker, & Buss, 2016).

The coupling between slow (e.g., delta) and fast (e.g., beta) wave EEG activity is believed to reflect functional interactions between cortical and subcortical circuitry (Knyazev & Slobodskaya, 2003). Greater positive associations between delta and beta power reflect functional coherence between cortical (i.e., cerebral cortex) and subcortical (i.e., limbic) structures, and delta-beta coupling may reflect a form of top-down regulation (Knyazev & Slobodskaya, 2003). Thus, high delta-beta coupling in the context of anxiety risk is believed to reflect overcontrol or overregulation. Emerging work related to behavioral inhibition and anxiety symptoms reveals a robust link between these behavior patterns and greater delta-beta coupling in adults (Miskovic et al., 2011; Putman, 2011) and in children (Miskovic et al., 2011; Phelps et al., 2016).

We have shown that patterns of coupling in toddlers differ based on the context (i.e., high fear and low fear). In a low-fear context, high levels of fear (i.e., dysregulated fear) were associated with significant delta-beta coupling at frontal, central, and parietal electrodes, whereas low levels of fear were associated with significant coupling only at parietal sites (Phelps et al., 2016). In contrast, in a high-fear context, there were no differences in coupling between the high- and low-fear groups (Phelps et al., 2016). Consistent with other work highlighting the role of the eliciting context (Buss, 2011; Buss, Davis, et al., 2018), these findings indicate that children who exhibited dysregulated fear showed higher levels of regulation (i.e., overcontrol) at a neural level.

Event–Related Potentials (ERPs)

Specific executive processes—executive function—have also been examined in the behavioral inhibition literature, particularly as mechanisms that contribute to the development of anxiety. For purposes of this chapter, we focus primarily on the literature wherein the processes of inhibitory control and attentional control have been examined. Intrinsic traits, such as children's attention control, attention shifting, and inhibitory control, are regulated by children's executive functioning and contribute to children's lasting behavioral inhibition (Degnan & Fox, 2007). Children with behavioral inhibition who can flexibly maintain and switch their attention may be less likely to develop anxiety symptoms and more likely to demonstrate adaptive social behavior (Degnan & Fox, 2007). These executive processes can be assessed using event-related potentials (ERP). Event-related potentials measure the brain's electrophysiological response to a specific sensory or a cognitive event or a response to a stimulus. Of particular benefit, ERPs are noninvasive and can record activity at a millisecond level (Luck, 2014). Different components of the ERP wave reflect distinct brain processes.

Among the ERP components, N2 and P2 components have been repeatedly found in association with children's anxiety symptoms. The N2 component has been associated with conflict monitoring, reflecting inhibitory and attention control (Van Veen & Carter, 2002). In work closely aligned with anxiety development, these

components have been associated with affective, attentional, and cognitive processes, such as attention to and away from threat (Dennis & Chen, 2009), and have been linked to anxiety problems (Dennis & Chen, 2009; Ladouceur, Conway, & Dahl, 2010; Pérez-Edgar & Fox, 2005).

The N2 has also been correlated with executive attention and temperamental traits. For example, in 4- to 8-year-old children, increased N2 during a flanker task was associated with less efficient executive attention and lower temperamental effortful control (Buss, Dennis, Brooker, & Sippel, 2011). The P2 component has been associated with early visual perception and attention (Schupp et al., 2004) and has been found to be enhanced to negatively valenced visual stimuli (Foti & Hajcak, 2008; Huang & Luo, 2006).

Turning to the behavioral inhibition literature, there have been a number of studies examining these ERP components. In a sample of 9- to 12-year-old children, attention bias toward threat was marginally positively correlated with N2 amplitude during a concurrent dot-probe task. Furthermore, the positive association between attention bias to threat and behavioral inhibition was only evident for children who had a larger N2 (Thai, Taber-Thomas, & Pérez-Edgar, 2016). In contrast, social anxiety symptoms were negatively correlated with P2 amplitude (Thai et al., 2016). The association between attention bias toward threat and N2 amplitude has also been found in longitudinal studies. For example, behavioral inhibition assessed at age 2 was negatively associated with N2 activation in a go-no-go task at age 7, indicating greater N2 activation as behavioral inhibition increased (Lamm et al., 2014).

Therefore, larger N2 and smaller P2 seem to be risk factors for behaviorally inhibited children who are likely to develop anxiety symptoms. These ERP components have also been found to moderate the association between behavioral inhibition and anxious behavior. When N2 activation was high, toddler behavioral inhibition was positively associated with later social reticence at age 7. However, this association was not significant when N2 activation was low (Lamm et al., 2014). Likewise, the association between behavioral inhibition and social anxiety was stronger with smaller P2 compared to larger P2 amplitudes (Thai et al., 2016).

There has also been a surge of recent studies examining error-related negativity and behavioral inhibition. The error-related negativity (ERN) is an ERP component that peaks at frontocentral midline scalp recording sites and usually occurs 50–100 msec following an incorrect behavioral response (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991). A large ERN has been associated with high fear and behavioral inhibition (Brooker & Buss, 2014a) and anxiety symptoms (Meyer et al., 2013). Specifically, high-fear toddlers showed a larger ERN compared to correct-trial negativity (CRN indicates correct response negativity, used as a comparison condition to ERN) at age 4.5, compared to low-fear toddler (Brooker & Buss, 2014a). In a follow-up study, harsh maternal parenting interacted with toddler fearfulness to predict inhibition and ERN at age 4.5 (Brooker & Buss, 2014b). In other work, children who were diagnosed with an anxiety disorder at age 3 demonstrated a larger difference between the ERN and CRN at age 6 (Meyer et al., 2013). In a follow-up study with the same children, Meyer and colleagues found that punitive

parenting practices predicted ERN and ERN mediated the association between parenting and anxiety symptoms (Meyer et al., 2015).

Similar findings have also been reported in an adolescent sample. Adolescents who were high in childhood behavioral inhibition exhibited greater ERN amplitude compared to adolescents who were low in childhood behavioral inhibition (McDermott et al., 2009). In addition, in the high behavioral inhibition group, smaller ERN responses were related to lower risk for anxiety diagnosis at a trend level. For the low behavioral inhibition group, there was no relation between ERN response and anxiety diagnosis (McDermott et al., 2009). These findings suggest that greater ERN seems to be a correlate of behavioral inhibition traits and greater ERN responses maybe especially maladaptive for children who are high in behavioral inhibition.

The difference between ERN and CRN also serves as a putative risk marker for anxiety for children who demonstrated early behavioral inhibition. Specifically, toddler behavioral inhibition was associated with social phobia at age 9, but only among children who had a larger difference in amplitude between ERN and CRN at age 7 (Lahat et al., 2014). Therefore, larger difference in amplitude between ERN and CRN not only is a correlate of children's behavioral inhibition but also serves as an additional risk factor for children who already demonstrated early behavioral inhibition.

In addition to ERN, the error positivity (Pe) has also been examined in relation to behavioral inhibition. The Pe is a positive-going slow wave that follows the ERN and has a slightly more posterior scale distribution than the ERN (Falkenstein et al., 1991). Pe is believed to reflect more conscious processing of errors relative to the ERN (Falkenstein et al., 1991). In a sample of 5-year-old children, higher Pe was associated with less boldness during conversations with strangers, indicating hypervigilance in these children and a lack of efficiency in cognitive processing (Brooker, Buss, & Dennis, 2011). These findings suggest that children with highly inhibited traits tend to have enhanced performance concerns and increased vigilance (see the chapter "The Neural Mechanisms of Behavioral Inhibition" by Jarcho and Guyer and the chapter "Relations Between Behavioral Inhibition, Cognitive Control, and Anxiety: Novel Insights Provided by Parsing Subdomains of Cognitive Control" by Buzzell et al.), which may reflect a rigid and inflexible pattern of behaviors during social situations (Lahat et al., 2014).

In sum, children's behavioral manifestation of their inhibition may be reflected in the way they process salient information in reflecting higher vigilance, conflict, and error monitoring. The pattern of ERP difference is consistent with findings of children and adolescents with anxiety symptoms and disorders, suggesting that these measures may serve as additional risk markers for behaviorally inhibited children who are already susceptible to developing subsequent anxiety symptoms.

Concluding Thoughts

Despite robust evidence that behavioral inhibition is the best early predictor of anxiety, not all behaviorally inhibited develop anxiety problems. As we have discussed in this chapter, this suggests heterogeneity in behavioral inhibition and developmental trajectories of anxiety for these children. In our work, the primary focus has been on the pattern of behavior across eliciting contexts that differentiates subtypes of fearful children as evidence for the heterogeneity. This approach has enhanced the identification of which of inhibited/fearful children are at greatest risk. However, this work and the identification of behavioral inhibition, more broadly, have exclusively focused on behavioral observations despite both temperament and anxiety theory positing these traits as neurodevelopmental in nature.

Consistent with temperament theories (e.g., Rothbart & Bates, 2006), there is growing evidence that the processes of reactivity and regulation account for these extreme behavioral differences and serve as putative mechanisms by which this temperamental risk is manifest as psychopathology. As we have reviewed in this chapter, multiple physiological markers of these processes have been consistently linked to behavioral inhibition and also provide a more complete picture of anxiety risk for these behaviorally inhibited children. Rather than considering these physiological measures as correlates or moderators, researchers should move to examining physiological processes as additional indicators of behavioral inhibition, as we have suggested previously (Buss, Morales, Cho, & Philbrook, 2015). Thus, focusing on how physiological markers can enhance identification of behaviorally inhibited children thereby decreases heterogeneity in group membership and increases prediction of which fearful children are at risk for anxiety problems.

References

Amodio, D. M., Master, S. L., Yee, C. M., & Taylor, S. E. (2008). Neurocognitive components of the behavioral inhibition and activation systems: Implications for theories of self-regulation. *Psychophysiology, 45*, 11–19. https://doi.org/10.1111/j.1469-8986.2007.00609.x

Balconi, M., & Mazza, G. (2010). Lateralisation effect in comprehension of emotional facial expression: A comparison between EEG alpha band power and behavioural inhibition (BIS) and activation (BAS) systems. Laterality: Asymmetries of body. *Brain and Cognition, 15*, 361–384. https://doi.org/10.1080/13576500902886056

Balle, M., Tortella-Feliu, M., & Bornas, X. (2013). Distinguishing youths at risk for anxiety disorders from self-reported BIS sensitivity and its psychophysiological concomitants. *International Journal of Psychology, 48*, 964–977. https://doi.org/10.1080/00207594.2012.723804

Bauer, A. M., Quas, J. A., & Boyce, W. T. (2002). Associations between physiological reactivity and children's behavior: Advantages of a multisystem approach. *Journal of Developmental and Behavioral Pediatrics, 23*, 102–113. https://doi.org/10.1097/00004703-200204000-00007

Beauchaine, T. (2001). Vagal tone, development, and Gray's motivational theory: Toward an integrated model of autonomic nervous system functioning in psychopathology. *Development and Psychopathology, 13*, 183–214.

Beesdo, K., Knappe, S., & Pine, D. S. (2009). Anxiety and anxiety disorders in children and adolescents: Developmental issues and implications for DSM-V. *Psychiatric Clinics of North America, 32*, 483–524. https://doi.org/10.1016/j.psc.2009.06.002

Boucsein, W. (2012). *Electrodermal activity*. Berlin, Germany: Springer.

Brooker, R. J., & Buss, K. A. (2009). Dynamic measures of RSA predict distress and regulation in toddlers. *Developmental Psychobiology, 52*, 372–382. https://doi.org/10.1002/dev.20432

Brooker, R. J., & Buss, K. A. (2014a). Toddler fearfulness is linked to individual differences in error-related negativity during preschool. *Developmental Neuropsychology, 39*, 1–8. https://doi.org/10.1080/87565641.2013.826661

Brooker, R. J., & Buss, K. A. (2014b). Harsh parenting and fearfulness in toddlerhood interact to predict amplitudes of preschool error-related negativity. *Developmental Cognitive Neuroscience, 9*, 148–159.

Brooker, R. J., Buss, K. A., & Dennis, T. A. (2011). Error-monitoring brain activity is associated with affective behaviors in young children. *Developmental Cognitive Neuroscience, 1*, 141–152. https://doi.org/10.1016/j.dcn.2010.12.002

Brooker, R. J., Buss, K. A., Lemery-Chalfant, K., Aksan, N., Davidson, R. J., & Goldsmith, H. H. (2013). The development of stranger fear in infancy and toddlerhood: Normative development, individual differences, antecedents, and outcomes. *Developmental Science, 16*, 864–878. https://doi.org/10.1037/t06070-000

Buss, K. A. (2011). Which fearful toddlers should we worry about? Context, fear regulation, and anxiety risk. *Developmental Psychology, 47*, 804–819. https://doi.org/10.1037/a0023227

Buss, K. A., Davis, E. L., & Kiel, E. J. (2011). Allostatic and environmental load in toddlers predicts anxiety in preschool and kindergarten. *Development and Psychopathology, 23*, 1069–1087. https://doi.org/10.1017/S0954579411000502

Buss, K. A., Davis, E. L., Kiel, E. J., Brooker, R. J., Beekman, C., & Early, M. C. (2013). Dysregulated fear predicts social wariness and social anxiety symptoms during kindergarten. *Journal of Clinical Child and Adolescent Psychology, 42*, 603–616. https://doi.org/10.1080/15374416.2013.769170

Buss, K. A., Davis, E. L., Ram, N., & Coccia, M. (2018). Dysregulated fear, social inhibition, and respiratory sinus arrhythmia: A replication and extension. *Child Development, 89 (3, e214-e228)*. https://doi.org/10.1111/cdev.12774

Buss, K. A., Dennis, T. A., Brooker, R. J., & Sippel, L. M. (2011). An ERP study of conflict monitoring in 4–8-year old children: Associations with temperament. *Developmental Cognitive Neuroscience, 1*, 131–140. https://doi.org/10.1016/j.dcn.2010.12.003

Buss, K. A., & Kiel, E. J. (2013). Temperamental risk factors for pediatric anxiety disorders. In *Pediatric anxiety disorders* (pp. 47–68). New York, NY: Springer.

Buss, K. A., Morales, S., Cho, S., & Philbrook, L. (2015). A biopsychosocial framework for infant temperament and socioemotional development. In S. D. Calkins (Ed.), *Handbook of infant biopsychosocial development; handbook of infant biopsychosocial development* (pp. 232–258). New York, NY: Guilford Press.

Calkins, S. D. (2011). Caregiving as coregulation: Psychobiological processes and child functioning. In A. Booth, S. M. McHale, & N. S. Landale (Eds.), *Biosocial foundations of family processes; biosocial foundations of family processes* (pp. 49–59). New York, NY: Springer. https://doi.org/10.1007/978-1-4419-7361-0_3

Calkins, S. D., Fox, N. A., & Marshall, T. R. (1996). Behavioral and physiological antecedents of inhibited and uninhibited behavior. *Child Development, 67*, 523–540.

Calkins, S. D., Graziano, P. A., Berdan, L. E., Keane, S. P., & Degnan, K. A. (2008). Predicting cardiac vagal regulation in early childhood from maternal-child relationship quality during toddlerhood. *Developmental Psychobiology, 50*, 751–766. https://doi.org/10.1002/dev.20344

Cho, S., & Buss, K. A. (2017). Toddler parasympathetic regulation and fear: Links to maternal appraisal and behavior. *Developmental Psychobiology, 59*, 197–208. https://doi.org/10.1002/dev.21481

Chronis-Tuscano, A., Degnan, K. A., Pine, D. S., Pérez-Edgar, K., Henderson, H. A., Diaz, Y., … Fox, N. A. (2009). Stable early maternal report of behavioral inhibition predicts lifetime social

anxiety disorder in adolescence. *Journal of the American Academy of Child & Adolescent Psychiatry, 48*, 928–935. https://doi.org/10.1097/CHI.0b013e3181ae09df

Davidson, R. J. (1988). EEG measures and cerebral asymmetry: Conceptual and methodological issues. *International Journal of Neuroscience, 39*, 71–89.

Davidson, R. J., Jackson, D. C., & Kalin, N. H. (2000). Emotion, plasticity, context, and regulation: Perspectives from affective neuroscience. *Psychological Bulletin, 126*, 890–909. https://doi.org/10.1037/0033-2909.126.6.890

Davidson, R. J., & Rickman, M. (1999). Behavioral inhibition and the emotional circuitry of the brain: Stability and plasticity during the early childhood years. In L. A. Schmidt & J. Schulkin (Eds.), *Extreme fear, shyness, and social phobia: Origins, biological mechanisms, and clinical outcomes; extreme fear, shyness, and social phobia: Origins, biological mechanisms, and clinical outcomes* (pp. 67–87). New York, NY: Oxford University Press. https://doi.org/10.1093/acprof:oso/9780195118872.003.0005

Davis, E. L., & Buss, K. A. (2012). Moderators of the relation between shyness and behavior with peers: Cortisol dysregulation and maternal emotion socialization. *Social Development, 21*, 801–820. https://doi.org/10.1111/j.1467-9507.2011.00654.x

Degnan, K. A., & Fox, N. A. (2007). Behavioral inhibition and anxiety disorders: Multiple levels of a resilience process. *Development and Psychopathology, 19*, 729–746. https://doi.org/10.1017/S0954579407000363

Dennis, T. A., & Chen, C. (2009). Trait anxiety and conflict monitoring following threat: An ERP study. *Psychophysiology, 46*, 122–131. https://doi.org/10.1111/j.1469-8986.2008.00758.x

Dettmer, A., Novak, M., Suomi, S., & Meyer, J. (2012). Physiological and behavioral adaptation to relocation stress in differentially reared rhesus monkeys: Hair cortisol as a biomarker for anxiety-related responses. *Psychoneuroendocrinology, 37*, 191–199. https://doi.org/10.1016/j.psyneuen.2011.06.003

Dietrich, A., Riese, H., van Roon, A. M., Minderaa, R. B., Oldehinkel, A. J., Neeleman, J., & Rosmalen, J. G. (2009). Temperamental activation and inhibition associated with autonomic function in preadolescents. The TRAILS study. *Biological Psychology, 81*(1), 67–73.

Doom, J. R., & Gunnar, M. R. (2013). Stress physiology and developmental psychopathology: Past, present, and future. *Development and Psychopathology, 25*, 1359–1373. https://doi.org/10.1017/S0954579413000667

Eisenberg, N., Cumberland, A., Spinrad, T. L., Fabes, R. A., Shepard, S. A., Reiser, M., … Guthrie, I. K. (2001). The relations of regulation and emotionality to children's externalizing and internalizing problem behavior. *Child Development, 72*, 1112–1134. https://doi.org/10.1111/1467-8624.00337

El-Sheikh, M., Keiley, M., Erath, S., & Dyer, W. J. (2013). Marital conflict and growth in children's internalizing symptoms: The role of autonomic nervous system activity. *Developmental Psychology, 49*, 92–108. https://doi.org/10.1037/a0027703

El-Sheikh, M., Kouros, C. D., Erath, S., Cummings, E. M., Keller, P., & Staton, L. (2009). Marital conflict and children's externalizing behavior: Pathways involving interactions between parasympathetic and sympathetic nervous system activity. *Monographs of the Society for Research in Child Development, 74*, vii.

Essex, M. J., Klein, M. H., Slattery, M. J., Goldsmith, H. H., & Kalin, N. H. (2010). Early risk factors and developmental pathways to chronic high inhibition and social anxiety disorder in adolescence. *The American Journal of Psychiatry, 167*, 40–46. https://doi.org/10.1176/appi.ajp.2009.07010051

Falkenstein, M., Hohnsbein, J., Hoormann, J., & Blanke, L. (1991). Effects of crossmodal divided attention on late ERP components: II. Error processing in choice reaction tasks. *Electroencephalography and Clinical Neurophysiology, 78*, 447–455. https://doi.org/10.1016/0013-4694(91)90062-9

Foti, D., & Hajcak, G. (2008). Deconstructing reappraisal: Descriptions preceding arousing pictures modulate the subsequent neural response. *Journal of Cognitive Neuroscience, 20*, 977–988.

Fowles, D., Kochanka, G., & Murray, K. (2000). Electrodermal activity and temperament in preschool children. *Psychophysiology, 37*, 777–787.

Fox, N. A. (1989). Psychophysiological correlates of emotional reactivity during the first year of life. *Developmental Psychology, 25*, 364–372. https://doi.org/10.1037/0012-1649.25.3.364

Fox, N. A. (1991). If it's not left, it's right. *American Psychologist, 46*, 863–872.

Fox, N. A. & Davidson, R. J. (1984). Hemispheric substrates of affect: A developmental model. In N. A. Fox & R. J. Davidson (Eds.), The Psychobiology of Affective Development (pp. 353–381). Hillsdale, NJ: Erlbaum.

Fox, N. A., Henderson, H. A., Marshall, P. J., Nichols, K. E., & Ghera, M. M. (2005). Behavioral inhibition: Linking biology and behavior within a developmental framework. *Annual Review of Psychology, 56*, 235–262. https://doi.org/10.1146/annurev.psych.55.090902.141532

Fox, N. A., Henderson, H. A., Rubin, K. H., Calkins, S. D., & Schmidt, L. A. (2001). Continuity and discontinuity of behavioral inhibition and exuberance: Psychophysiological and behavioral influences across the first four years of life. *Child Development, 72*, 1–21. https://doi.org/10.1111/1467-8624.00262

Fox, N. A., Rubin, K. H., Calkins, S. D., Marshall, T. R., Coplan, R. J., Porges, S. W., … Stewart, S. (1995). Frontal activation asymmetry and social competence at four years of age. *Child Development, 66*, 1770–1784. https://doi.org/10.1111/j.1467-8624.1995.tb00964.x

Fox, N. A., Snidman, N., Haas, S. A., Degnan, K. A., & Kagan, J. (2015). The relations between reactivity at 4 months and behavioral inhibition in the second year: Replication across three independent samples. *Infancy, 20*, 98–114.

García Coll, C., Kagan, J., & Reznick, J. (1984). Behavioral inhibition in young children. *Child Development, 55*, 1005–1019. https://doi.org/10.2307/1130152

Gilissen, R., Koolstra, C. M., van Ijzendoorn, M. H., Bakermans-Kranenburg, M., & van der Veer, R. (2007). Physiological reactions of preschoolers to fear-inducing film clips: Effects of temperamental fearfulness and quality of the parent-child relationship. *Developmental Psychobiology, 49*, 187–195. https://doi.org/10.1002/dev.20188

Harmon-Jones, E., Gable, P. A., & Peterson, C. K. (2010). The role of asymmetric frontal cortical activity in emotion-related phenomena: A review and update. *Biological Psychology, 84*, 451–462.

Hastings, P. D., Kahle, S., & Nuselovici, J. M. (2014). How well socially wary preschoolers fare over time depends on their parasympathetic regulation and socialization. *Child Development, 85*, 1586–1600. https://doi.org/10.1111/cdev.12228

Hastings, P. D., Nuselovici, J. N., Utendale, W. T., Coutya, J., McShane, K. E., & Sullivan, C. (2008). Applying the polyvagal theory to children's emotion regulation: Social context, socialization, and adjustment. *Biological Psychology, 79*, 299–306. https://doi.org/10.1016/j.biopsycho.2008.07.005

Hastings, P. D., Sullivan, C., McShane, K. E., Coplan, R. J., Utendale, W. T., & Vyncke, J. D. (2008). Parental socialization, vagal regulation, and preschoolers' anxious difficulties: Direct mothers and moderated fathers. *Child Development, 79*, 45–64. https://doi.org/10.1111/j.1467-8624.2007.01110.x

Henderson, H. A., Fox, N. A., & Rubin, K. H. (2001). Temperamental contributions to social behavior: The moderating roles of frontal EEG asymmetry and gender. *Journal of the American Academy of Child & Adolescent Psychiatry, 40*, 68–74. https://doi.org/10.1097/00004583-200101000-00018

Huang, Y.-X., & Luo, Y.-J. (2006). Temporal course of emotional negativity bias: An ERP study. *Neuroscience Letters, 398*, 91–96.

Hutt, R. L., Buss, K. A., & Kiel, E. J. (2013). Caregiver protective behavior, toddler fear and sadness, and toddler cortisol reactivity in novel contexts. *Infancy, 18*, 708–728. https://doi.org/10.1111/j.1532-7078.2012.00141.x

Kagan, J. (1994). *The nature of the child*. New York, NY, US: Basic Books.

Kagan, J., & Fox, N. A. (2006). Biology, culture, and temperamental biases. In N. Eisenberg, W. Damon & R. M. Lerner (Eds.), Handbook of child psychology: Social, emotional, and personality development Vol. 3 (6th ed. pp. 167-225) John Wiley & Sons Inc, Hoboken, NJ.

Kalin, N. H. (1993). The neurobiology of fear. *Scientific American, 268*, 94.

Kalin, N. H., Shelton, S. E., Fox, A. S., Oakes, T. R., & Davidson, R. J. (2005). Brain regions associated with the expression and contextual regulation of anxiety in primates. *Biological Psychiatry, 58*, 796–804. https://doi.org/10.1016/j.biopsych.2005.05.021

Knyazev, G. G., & Slobodskaya, H. R. (2003). Personality trait of behavioral inhibition is associated with oscillatory systems reciprocal relationships. *International Journal of Psychophysiology, 48*, 247–261. https://doi.org/10.1016/S0167-8760(03)00072-2

Ladouceur, C. D., Conway, A., & Dahl, R. E. (2010). Attentional control moderates relations between negative affect and neural correlates of action monitoring in adolescence. *Developmental Neuropsychology, 35*, 194–211. https://doi.org/10.1080/87565640903526553

Lahat, A., Lamm, C., Chronis-Tuscano, A., Pine, D. S., Henderson, H. A., & Fox, N. A. (2014). Early behavioral inhibition and increased error monitoring predict later social phobia symptoms in childhood. *Journal of the American Academy of Child & Adolescent Psychiatry, 53*, 447–455. https://doi.org/10.1016/j.jaac.2013.12.019

Lamm, C., Walker, O. L., Degnan, K. A., Henderson, H. A., Pine, D. S., McDermott, J. M., & Fox, N. A. (2014). Cognitive control moderates early childhood temperament in predicting social behavior in 7-year-old children: An ERP study. *Developmental Science, 17*, 667–681. https://doi.org/10.1111/desc.12158

Licht, C. M. M., de Geus, E. J. C., van Dyck, R., & Penninx, B. W. J. H. (2009). Association between anxiety disorders and heart rate variability in the Netherlands study of depression and anxiety (NESDA). *Psychosomatic Medicine, 71*, 508–518. https://doi.org/10.1097/PSY.0b013e3181a292a6

Luck, S. J. (2014). *An introduction to the event-related potential technique*. Cambridge, MA: MIT press.

Mackrell, S. V. M., Sheikh, H. I., Kotelnikova, Y., Kryski, K. R., Jordan, P. L., Singh, S. M., & Hayden, E. P. (2014). Child temperament and parental depression predict cortisol reactivity to stress in middle childhood. *Journal of Abnormal Psychology, 123*, 106–116. https://doi.org/10.1037/a0035612

Marshall, P. J., & Stevenson-Hinde, J. (1998). Behavioral inhibition, heart period, and respiratory sinus arrhythmia in young children. *Developmental Psychobiology, 33*, 283–292. https://doi.org/10.1002/(SICI)1098-2302(199811)33:3<283::AID-DEV8>3.0.CO;2-N

McDermott, J. M., Pérez-Edgar, K., Henderson, H. A., Chronis-Tuscano, A., Pine, D. S., & Fox, N. A. (2009). A history of childhood behavioral inhibition and enhanced response monitoring in adolescence are linked to clinical anxiety. *Biological Psychiatry, 65*, 445–448. https://doi.org/10.1016/j.biopsych.2008.10.043

McEwen, B. S. (1998). Protective and damaging effects of stress mediators. *New England Journal of Medicine, 338*, 171–179.

Meyer, A., Hajcak, G., Torpey, D. C., Kujawa, A., Kim, J., Bufferd, S., … Klein, D. N. (2013). Increased error-related brain activity in six-year-old children with clinical anxiety. *Journal of Abnormal Child Psychology, 41*, 1257–1266. https://doi.org/10.1007/s10802-013-9762-8

Meyer, A., Proudfit, G. H., Bufferd, S. J., Kujawa, A. J., Laptook, R. S., Torpey, D. C., & Klein, D. N. (2015). Self-reported and observed punitive parenting prospectively predicts increased error-related brain activity in six-year-old children. *Journal of Abnormal Child Psychology, 43*, 821–829. https://doi.org/10.1007/s10802-014-9918-1

Miskovic, V., Campbell, M. J., Santesso, D. L., Van Ameringen, M., Mancini, C. L., & Schmidt, L. A. (2011). Frontal brain oscillatory coupling in children of parents with social phobia: A pilot study. *The Journal of Neuropsychiatry and Clinical Neurosciences, 23*, 111–114. https://doi.org/10.1176/appi.neuropsych.23.1

Miskovic, V., Moscovitch, D. A., Santesso, D. L., McCabe, R. E., Antony, M. M., & Schmidt, L. A. (2011). Changes in EEG cross-frequency coupling during cognitive behavioral therapy for social anxiety disorder. *Psychological Science, 22*, 507–516. https://doi.org/10.1177/0956797611400914

Murray, K. T., & Kochanska, G. (2002). Effortful control: Factor structure and relation to externalizing and internalizing behaviors. *Journal of Abnormal Child Psychology, 30*, 503–514. https://doi.org/10.1023/A:1019821031523

Nachmias, M., Gunnar, M., Mangelsdorf, S., Parritz, R. H., & Buss, K. (1996). Behavioral inhibition and stress reactivity: The moderating role of attachment security. *Child Development, 67*, 508–522. https://doi.org/10.2307/1131829

Pagliaccio, D., Luby, J. L., Bogdan, R., Agrawal, A., Gaffrey, M. S., Belden, A. C., … Barch, D. M. (2014). Stress-system genes and life stress predict cortisol levels and amygdala and hippocampal volumes in children. *Neuropsychopharmacology, 39*, 1245–1253. https://doi.org/10.1038/npp.2013.327

Paret, L., Bailey, H. N., Roche, J., Bureau, J., & Moran, G. (2015). Preschool ambivalent attachment associated with a lack of vagal withdrawal in response to stress. *Attachment & Human Development, 17*, 65–82. https://doi.org/10.1080/14616734.2014.967786

Pérez-Edgar, K., & Fox, N. A. (2005). Temperament and anxiety disorders. *Child and Adolescent Psychiatric Clinics of North America, 14*, 681–706. https://doi.org/10.1016/j.chc.2005.05.008

Pérez-Edgar, K., Kujawa, A., Nelson, S. K., Cole, C., & Zapp, D. J. (2013). The relation between electroencephalogram asymmetry and attention biases to threat at baseline and under stress. *Brain and Cognition, 82*, 337–343.

Pérez-Edgar, K., Schmidt, L. A., Henderson, H. A., Schulkin, J., & Fox, N. A. (2008). Salivary cortisol levels and infant temperament shape developmental trajectories in boys at risk for behavioral maladjustment. *Psychoneuroendocrinology, 33*, 916–925. https://doi.org/10.1016/j.psyneuen.2008.03.018

Phelps, R. A., Brooker, R. J., & Buss, K. A. (2016). Toddlers' dysregulated fear predicts delta–beta coupling during preschool. *Developmental Cognitive Neuroscience, 17*, 28–34.

Pine, D., Helfinstein, S., Bar-Haim, Y., Nelson, E., & Fox, N. (2009). Challenges in developing novel treatments for childhood disorders: Lessons from research on anxiety. *Neuropsychopharmacology, 34*, 213–228. https://doi.org/10.1038/npp.2008.113

Porges, S. W. (1996). Physiological regulation in high-risk infants: A model for assessment and potential intervention. *Development and Psychopathology, 8*, 29–42.

Porges, S. W. (2007). The polyvagal perspective. *Biological Psychology, 74*, 116–143. https://doi.org/10.1016/j.biopsycho.2006.06.009

Porges, S. W., Doussard-Roosevelt, J. A., Portales, A. L., & Suess, P. E. (1994). Cardiac vagal tone: Stability and relation to difficultness in infants and 3-year-olds. *Developmental Psychobiology, 27*, 289–300. https://doi.org/10.1002/dev.420270504

Porges, S. W., & Furman, S. A. (2011). The early development of the autonomic nervous system provides a neural platform for social behaviour: A polyvagal perspective. *Infant and Child Development, 20*, 106–118. https://doi.org/10.1002/icd.688

Putman, P. (2011). Resting state EEG delta-beta coherence in relation to anxiety, behavioral inhibition, and selective attentional processing of threatening stimuli. *International Journal of Psychophysiology, 80*, 63–68. https://doi.org/10.1016/j.ijpsycho.2011.01.011

Rothbart, M. K. (2011). *Becoming who we are: Temperament and personality in development*. New York, NY: Guilford Press.

Rothbart, M. K., & Bates, J. E. (2006). Temperament. In N. Eisenberg (Ed.), *Handbook of child psychology: Social, emotional, and personality development* (6th ed., pp. 99–166). Hoboken, NJ: John Wiley and Sons.

Russ, S. J., Herbert, J., Cooper, P., Gunnar, M. R., Goodyer, I., Croudace, T., & Murray, L. (2012). Cortisol levels in response to starting school in children at increased risk for social phobia. *Psychoneuroendocrinology, 37*, 462–474. https://doi.org/10.1016/j.psyneuen.2011.07.014

Scarpa, A., Raine, A., Venables, P. H., & Mednick, S. A. (1997). Heart rate and skin conductance in behaviorally inhibited mauritian children. *Journal of Abnormal Psychology, 106*, 182–190. https://doi.org/10.1037/0021-843X.106.2.182

Schupp, H. T., Öhman, A., Junghöfer, M., Weike, A. I., Stockburger, J., & Hamm, A. O. (2004). The facilitated processing of threatening faces: An ERP analysis. *Emotion, 4*, 189–200. https://doi.org/10.1037/1528-3542.4.2.189

Schwartz, C. E., Wright, C. I., Shin, L. M., Kagan, J., & Rauch, S. (2003). Inhibited and uninhibited infants "grown up": Adult amygdalar response to novelty. *Science, 300*, 1952–1953.

Shackman, A. J., Fox, A. S., Oler, J. A., Shelton, S. E., Davidson, R. J., & Kalin, N. H. (2013). Neural mechanisms underlying heterogeneity in the presentation of anxious temperament. *Proceedings of the National Academy of Sciences of the United States of America, 110*, 6145–6150. https://doi.org/10.1073/pnas.1214364110

Smider, N. A., Essex, M. J., Kalin, N. H., Buss, K. A., Klein, M. H., Davidson, R. J., & Goldsmith, H. H. (2002). Salivary cortisol as a predictor of socio-emotional adjustment during kindergarten: A prospective study. *Child Development, 73*, 75–92.

Suess, P. E., Porges, S. W., & Plude, D. J. (1994). Cardiac vagal tone and sustained attention in school-age children. *Psychophysiology, 31*, 17–22.

Sulik, M. J., Eisenberg, N., Silva, K. M., Spinrad, T. L., & Kupfer, A. (2013). Respiratory sinus arrhythmia, shyness, and effortful control in preschool-age children. *Biological Psychology, 92*, 241–248. https://doi.org/10.1016/j.biopsycho.2012.10.009

Taber-Thomas, B., Galinsky, P., Morales, S., Thai, N., & Pérez-Edgar, K. (in prep). Intrinsic functional correlates of frontal EEG asymmetry in developmental risk for psychopathology.

Tarullo, A. R., Mliner, S., & Gunnar, M. R. (2011). Inhibition and exuberance in preschool classrooms: Associations with peer social experiences and changes in cortisol across the preschool year. *Developmental Psychology, 47*, 1374–1388. https://doi.org/10.1037/a0024093

Thai, N., Taber-Thomas, B., & Pérez-Edgar, K. E. (2016). Neural correlates of attention biases, behavioral inhibition, and social anxiety in children: An ERP study. *Developmental Cognitive Neuroscience, 19*, 200–210. https://doi.org/10.1016/j.dcn.2016.03.008

Van Veen, V., & Carter, C. S. (2002). The anterior cingulate as a conflict monitor: FMRI and ERP studies. *Physiology & Behavior, 77*, 477–482. https://doi.org/10.1016/S0031-9384(02)00930-7

Whitworth, J. A., Williamson, P. M., Mangos, G., & Kelly, J. J. (2005). Cardiovascular consequences of cortisol excess. *Vascular Health and Risk Management, 1*, 291–299.

The Neurobiology of Behavioral Inhibition as a Developmental Mechanism

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Abstract Humans are social creatures and have variable responses to novel social cues that range from cautious avoidance to eager approach. These trait differences in response to novelty have been defined as behavioral inhibition, a temperament that ranges from behaviorally inhibited on one extreme to behaviorally uninhibited at the other. For centuries temperament has been thought to reflect underlying differences in biology. With advances in neuroimaging methods, we now have a unique opportunity to identify the neurobiological basis of behavioral inhibition. In this chapter, we review the evidence that behavioral inhibition is associated with alterations in brain structure, function, and connectivity and present implications for understanding developmental trajectories. The emerging findings point to alterations in "bottom-up" mechanisms—heightened reactivity to novelty and failure to habituate—and "top-down" processes, failure of cognitive control and maladaptive anticipatory processing.

We propose that the bottom-up mechanisms, which are present very early in childhood, contribute to the earliest observations of behavioral inhibition in children and shape early developmental trajectories. In contrast, the top-down mechanisms emerge in early adolescence as the prefrontal cortex begins rapid maturation. Developmental trajectories of behaviorally inhibited children likely diverge in adolescence based on prefrontal cortex development. Adolescents with early maturation or robust prefrontal cortical function will move toward a trajectory of normative development, while adolescents with delayed or deficient prefrontal cortical development will maintain their trajectory of extreme inhibition and risk for anxiety. Future research must systematically study behaviorally inhibited children across development to document developmental differences in brain structure, function, and connectivity and to further clarify the role of neurobiological mechanisms in shaping developmental trajectories.

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Introduction

Humans are inherently social creatures, and our relationships are a crucial component of adaptive functioning. From the earliest relationships between newborn and parent, to the peer groups that support the transition from the nuclear family to the broader community, our social bonds with others form the basis of successful development. Within the framework of social relationships, individuals respond to social cues differently. These responses vary across an approach-avoidance continuum, ranging from eager approach to fearful avoidance. Individuals at these two extremes have been coined "behaviorally uninhibited" and "behaviorally inhibited." These groups are highly conserved across species (for a review see Gosling, 2001) and moderately heritable (Dilalla, Kagan, & Reznick, 1994; Emde et al., 1992; Plomin & Daniels, 1986; Robinson, Reznick, Kagan, & Corley, 1992), suggesting that the extreme groups are maintained by natural selection. Both behaviorally inhibited and behaviorally uninhibited individuals have an evolutionary advantage, with relative strengths in different contexts (Biro & Post, 2008). For example, in contexts of social predator threat, inhibited individuals who avoid new people and stay close to their own group are more likely to survive, whereas the uninhibited individuals are more likely to be captured or killed. However, in contexts of limited resources, the uninhibited individuals are more likely to venture to other social groups and obtain new resources, whereas inhibited individuals are more likely to stay close to their own group and fail to secure the resources necessary for survival.

In modern times of relative safety and plentiful resources, behavioral inhibition may confer an evolutionary disadvantage, most readily observed as an increased risk for developing anxiety or depressive disorders. Data from longitudinal studies shows that behaviorally uninhibited children are more likely to develop anxiety disorders (Biederman et al., 1993, 2001; Chronis-Tuscano et al., 2009; Essex, Klein, Slattery, Goldsmith, & Kalin, 2010; Hirshfeld et al., 1992; Schwartz, Snidman, & Kagan, 1999) and depression (Caspi, Moffitt, Newman, & Silva, 1996). Our meta-analysis of the association between childhood behavioral inhibition and later risk for social anxiety disorder showed a 7.5-fold increase in odds of developing the disorder (Clauss & Blackford, 2012). As shown in Fig. 1, more than 40% of behaviorally inhibited children had a social anxiety disorder by adolescence relative to 12% of their non-inhibited peers (see the chapter "Behavioral Inhibition as a Precursor to Psychopathology" by Klein and the chapter "The Biological Bridge Between Behavioral Inhibition and Psychopathology" by Sylvester and Pine).

Anxiety disorders are a common and often under-recognized source of significant morbidity. Because they often begin in early childhood, anxiety disorders can significantly alter the course of typical development. Furthermore, in addition to the negative consequences of anxiety disorders themselves, anxious youth are also more likely to later suffer from depression and substance use disorders (Beesdo

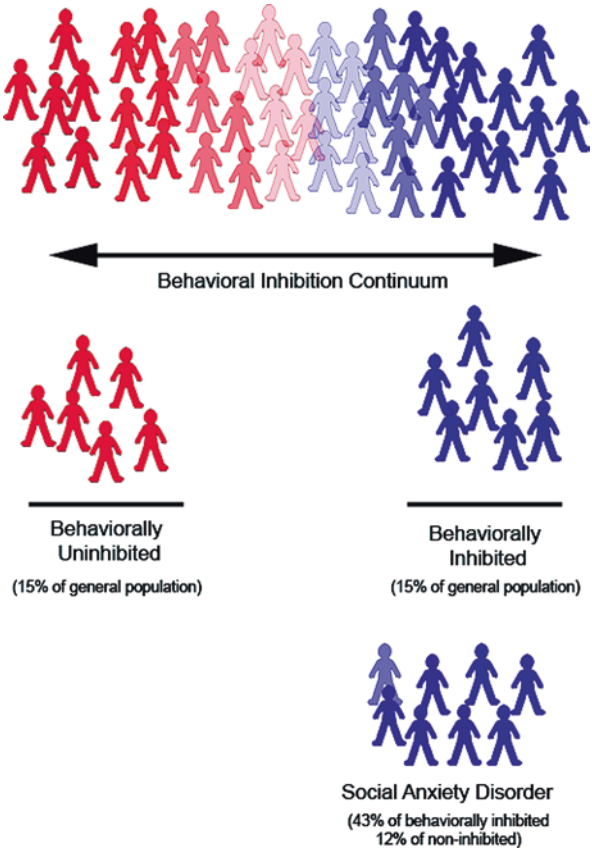

Fig. 1 Pathway from behavioral inhibition to social anxiety disorder. Data based on Clauss and Blackford (2012)

et al., 2007; Buckner et al., 2008; Caspi et al., 1996; Wittchen et al., 2007; Woodward & Fergusson, 2001). Early identification of risk is critical to decreasing the public health impact of anxiety disorders. Analogous to treating hyperlipidemia to prevent the outcome of myocardial infarction, identifying early indicators of risk for psychiatric morbidity has the potential to reduce disease burden and improve the lives of individuals and families who suffer. However, unlike cardiology, where we understand much of the physiologic mechanisms of heart disease, we have yet to identify reliable biomarkers for early identification of risk for psychiatric disease.

Behavioral inhibition has the potential to serve as a biologically linked phenotype for understanding the pathway from risk to manifestation of illness. Importantly, a significant percentage of individuals with early childhood behavioral inhibition do not remain inhibited and do not develop anxiety disorders (Chronis-Tuscano et al., 2009; Clauss & Blackford, 2012; Essex et al., 2010). This fact highlights the need to characterize and understand the different developmental trajectories for inhibited children in order to elucidate neurobiological mechanisms of both risk and resilience. Recent progress in our ability to image the functioning human brain provides an opportunity to investigate the neurobiological underpinnings of temperament with the potential to shed light on new approaches for prevention and treatment.

Biological Mechanisms Underlying Behavioral Inhibition

Structural and Functional Brain Differences

In the search for biological mechanisms that contribute to the etiology and development of behavioral inhibition, we propose that differences in the brain's architecture—the structure, function, and connectivity—provide the foundation for behavioral inhibition and the associated anxiety vulnerability. Growing evidence suggests that behaviorally inhibited individuals have core differences in brain structure, function, and connectivity. In this chapter we will provide an overview of these differences focused on developmental trajectories and pathways to anxiety. For a more comprehensive review of this literature, see this recent review (Clauss, Avery, & Blackford, 2015).

Differences in the brain's structure provide the foundation from which functional differences in brain activation arise. Structural differences found in individuals with behavioral inhibition include: larger amygdala volume (Clauss et al., 2014; Hill, Tessner, Wang, Carter, & Mcdermott, 2010), larger caudate volume (Clauss, Seay, et al., 2014), increased ventromedial prefrontal cortex (vmPFC) thickness (Schwartz et al., 2010), decreased lateral orbitofrontal cortex thickness (Schwartz et al., 2010), larger orbitofrontal cortex volume (Hill et al., 2010), and decreased dorsal anterior cingulate cortex thickness (Sylvester et al., 2015). Unfortunately, most of these findings are unique to a single sample and have not replicated across studies. There are multiple potential explanations for the failure to replicate including differences in image resolution, sample size, structural imaging methods, and sample characteristics.

However, taken together these findings point to differences in the amygdala—involved in novelty detection, salience detection, and fear processing—and multiple regions of the prefrontal cortex, involved in both fear processing and emotion regulation. Similar differences in these regions are also found in patients with anxiety disorders (Bas-Hoogendam et al., 2016; Brühl, Delsignore, Komossa, & Weidt, 2014; Frick et al., 2013), suggesting a possible mechanism for a link between behavioral inhibition and anxiety disorders. Two of the studies referenced above explicitly assessed the role of anxiety with respect to differences in brain structure in behavioral inhibition. In the first of these, Clauss et al. (2014) found that inhibited young adults with an anxiety disorder had larger amygdala volume than inhibited young adults without an anxiety disorder. The other study found that cortical thickness in dorsal anterior cingulate was not moderated by anxiety (Sylvester et al., 2015). Large multi-site studies of brain structure and behavioral inhibition are needed to determine which findings are robust and replicable. In addition, longitudinal studies can investigate the developmental trajectories to identify which structural differences are associated with different developmental trajectories and, thus, may contribute to risk for the development of anxiety disorders.

Temperament differences in brain function have been investigated across a relatively large number of studies. A recent meta-analysis investigated functional

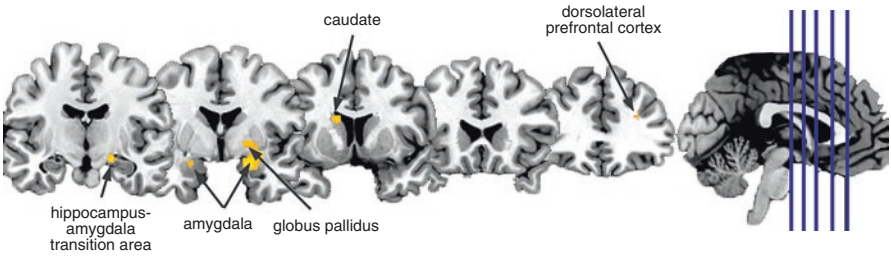

Fig. 2 Meta-analysis of functional imaging studies of behaviorally inhibited adolescents and young adults. Adapted from Clauss et al. (2015)

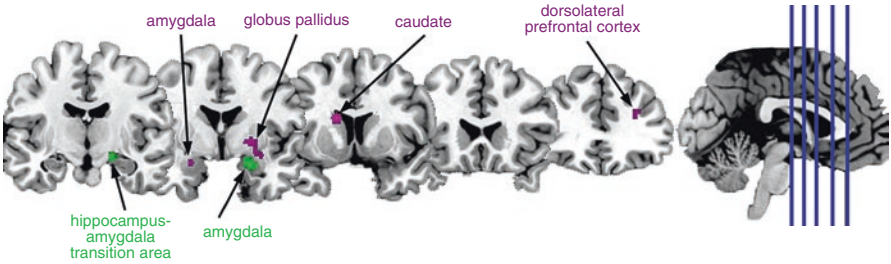

Fig. 3 Meta-analysis of functional differences in behavioral inhibition by type of task. The passive viewing, emotional tasks are shown in green and the cognitive tasks are shown in purple

differences in behavioral inhibition across 13 fMRI studies (Clauss et al., 2015). As shown in Fig. 2, several brain regions had significantly increased activation in inhibited individuals: left and right amygdala, right globus pallidus/putamen, left caudate, and left dorsolateral prefrontal cortex. There were no regions with significantly decreased activation in inhibited individuals. One issue with meta-analytic studies is that studies that contribute to the analysis can introduce heterogeneity. In the 13 fMRI studies of behavioral inhibition, one major source of heterogeneity was task differences.

Most of the tasks could be categorized as either emotional—more likely to engage subcortical brain regions—or cognitive, more likely to engage cortical brain regions. To determine the impact of the type of task (emotional versus cognitive) on the functional findings, we performed separate meta-analyses by task. Figure 3 illustrates the significant findings from the emotional tasks (green) and cognitive tasks (purple). In general, the emotional tasks resulted in increased activation in the amygdala and hippocampus in the inhibited group. The cognitive tasks resulted in increased activation in the amygdala, globus pallidus, putamen, caudate, and dorsolateral prefrontal cortex in the inhibited group (see Fig. 3). One interpretation of these findings is that the inhibited group displayed increased dorsolateral prefrontal cortex activation relative to controls but the activation of top-down control regions was insufficient to suppress the increased activation in subcortical regions such as the amygdala and basal ganglia. This failure of top-down regulation during

cognitive control tasks may be one developmental mechanism by which inhibited temperament confers increased risk for anxiety disorders. Thus, there is evidence that behaviorally inhibited individuals have alterations in both automatic, or "bottom-up," processes driven by subcortical regions like the amygdala and hippocampus and intentional, or "top-down," processes that are driven by cortical regions, like the prefrontal cortex.

Given that anxiety disorders typically have their onset in children, one limitation of the studies included in the meta-analysis is that they were all performed in adolescents and young adults. Most of those studies included several subgroups of inhibited individuals including: (1) individuals with a current anxiety disorder, (2) individuals with a past, but not current, anxiety disorder, and (3) individuals without a current or lifetime anxiety disorder. This heterogeneity introduces confounding between anxiety risk, anxiety disorders, and resilience to anxiety. One approach to disentangling risk and resilience is to compare high-risk, inhibited individuals with anxiety disorders versus those without anxiety disorders.

For example, we discovered that within inhibited young adults, increased activation in the rostral anterior cingulate cortex was positively correlated with adaptive coping skills and negatively associated with social anxiety symptoms. This additional analysis clarified that the group difference in rostral anterior cingulate cortex activation was driven by increased activation in the more resilient individuals—those with inhibited temperament who did not develop anxiety disorders (Clauss, Avery, et al., 2014). While these approaches are helpful for dissecting risk from resilience, they cannot provide adequate information to infer causation. The functional changes in inhibited temperament may be the results of either "scars" from past anxiety disorders or markers of current disease. Two recent studies have attempted to isolate risk by using neuroimaging to study brain function in inhibited young children (Clauss, Benningfield, Rao, & Blackford, 2016; Fu, Taber-Thomas, & Pérez-Edgar, 2015). Findings from these studies, reviewed in a later section, highlight the importance of studying behavioral inhibition early in development.

Finally, while it is important to identify alterations in structure and function in specific brain regions, it is also important to examine function in neural circuits because individual brain regions do not operate in isolation. The intrinsic architecture of neural circuits can be interrogated by examining the brain at "rest"—that is, in the absence of a task. To date, there have only been three studies of intrinsic functional connectivity in behavioral inhibition (Blackford et al., 2014; Roy et al., 2014; Taber-Thomas, Morales, Hillary, & Pérez-Edgar, 2016). These studies have varied sample characteristics and methodological approaches. A full review of these studies is beyond the scope of this chapter, but we will briefly summarize their findings.

All three studies found evidence for altered intrinsic functional connectivity in behavioral inhibition. Two prevailing themes are (1) increased connectivity in the salience network (Blackford et al., 2014; Taber-Thomas et al., 2016)—the intrinsic functional network that governs detection of and response to salient stimuli in the environment—and (2) reduced amygdala connectivity with the dorsal anterior cingulate (Blackford et al., 2014; Taber-Thomas et al., 2016) and

the rostral anterior cingulate (Blackford et al., 2014; Roy et al., 2014). Altered connectivity in both of these intrinsic networks may have functional implications for inhibited individuals.

For example, increased connectivity in the salience network may contribute to bottom-up processes, such as heightened detection and reaction to novelty and potential threat. Decreased connectivity between the prefrontal cortex and the amygdala may produce deficits in top-down regulation, such as the ability to regulate or dampen amygdala hyperactivity. These findings provide initial evidence that one biological mechanism of behavioral inhibition may be altered connectivity in intrinsic functional networks. While there are conceptual links between bottom-up hyper-reactivity and deficient top-down cognitive control and the subsequent development of anxiety disorders, the relationship between altered connectivity and the development of anxiety in inhibited individuals remains unclear. Behavioral inhibition moderated the relation between intrinsic functional connectivity and anxiety in a sample of children (Taber-Thomas et al., 2016) but not in the two adult samples (Blackford et al., 2014; Roy et al., 2014).

Given this evidence for alterations in brain structure and function, our next question is how might structural and functional alterations in the brain give rise to developmental mechanisms that sustain behavioral inhibition over time and lead to anxiety disorders? In the next section, we will focus on functional brain differences based on an assumption that differences in function are more closely linked to observable differences in emotion, cognition, and behavior. We propose that there are both bottom-up and top-down neurobiological mechanisms involved in the development of behavioral inhibition and anxiety vulnerability (see the chapter "The Neural Mechanisms of Behavioral Inhibition" by Jarcho and Guyer and the chapter "Psychobiological Processes in the Development of Behavioral Inhibition" by Buss and Qu). Here, we will describe two bottom-up mechanisms—heightened initial response to novelty and failure to habituate—and two top-down mechanisms, maladaptive anticipatory processing and lack of cognitive control, that may contribute to the developmental progression of behavioral inhibition and may also contribute to heightened risk for developing anxiety disorders.

Bottom-Up Mechanisms

Heightened Initial Response to Novelty

Some of the earliest theories of the biological basis of behavioral inhibition proposed that behaviorally inhibited children have a lower threshold for limbic-hypothalamic arousal to novel or unexpected events (Kagan, Reznick, & Snidman, 1998) and that the amygdala was likely critical in detecting and reacting to these events (Kagan, Reznick, & Snidman, 1998; Kagan & Snidman, 2004). The first neuroimaging study of young adults with a history of childhood inhibition provided initial evidence for amygdala hyperactivity (Schwartz, Wright, Shin, Kagan, & Rauch, 2003).

Several subsequent studies from our lab and others failed to find support for the idea that the amygdala has a heightened initial response to novel faces in inhibited temperament (Blackford, Allen, Cowan, & Avery, 2013; Blackford, Avery, Cowan, Shelton, & Zald, 2011; Schwartz et al., 2012). However, as we will discuss in the next section, hyper-reactivity includes two distinct responses: an exaggerated initial response to novel stimuli and diminished habituation to repeated presentations. The previous studies had averaged brain response over a time, conflating initial response and habituation.

In an early attempt to investigate separate components, we measured the temporal dynamics of each individual's amygdala response to novel or familiar faces (Blackford, Avery, Shelton, & Zald, 2009). Inhibited young adults did not have a higher peak response to novel faces, but did have a shorter latency to respond to novel faces. In a recent study where we explicitly measured the response to only the first presentation of a stimulus, there was a trend ($p = 0.06$) toward a higher initial amygdala response in young adults with higher social inhibition scores (Avery, 2015). Importantly, several other brain regions show heightened initial responses to novelty in inhibited individuals: the hippocampus and the vmPFC (Avery & Blackford, 2016).

The hippocampus plays a key role in memory, especially in detecting novel relative to familiar stimuli (Fried, MacDonald, & Wilson, 1997; Rutishauser, Mamelak, & Schuman, 2006; Wilson & Rolls, 1993). The vmPFC has multiple roles, including emotional reactivity and implicit emotion regulation (but not explicit emotion regulation, see Buhle et al. (2014)). The vmPFC inhibits amygdala responses to aversive stimuli (Motzkin, Philippi, Wolf, Baskaya, & Koenigs, 2015) likely through bidirectional connections between the amygdala and vmPFC (Ghashghaei, Hilgetag, & Barbas, 2007). Thus, while the amygdala was initially proposed as the driver of fear responses in inhibited children, evidence for amygdala hyper-reactivity is mixed. Instead, evidence points to hyper-reactivity of the hippocampus and vmPFC, two regions which are highly interconnected with the amygdala and form a functional neural circuit. While more systematic investigations are warranted, the evidence to date suggests that behavioral inhibition is associated with faster and potentially stronger, initial responses to novelty. Hyper-reactivity in this amygdala-hippocampus-vmPFC circuit during first exposures to novel stimuli likely underlies the commonly observed freezing and/or avoidant behavior in inhibited children and juvenile nonhuman primates.

Failure to Habituate

Habituation—the process by which response to a stimulus diminishes systematically following repeated presentation—is a fundamental learning process that is altered in individuals with behavioral inhibition. Habituation to repeated stimulation is evolutionarily adaptive and observed across species, from social animals, like humans and nonhuman primates, to nonsocial species including *Aplysia californica* and *C. elegans*. Organisms are wired to rapidly detect a novel stimulus, to allocate

resources to determine the stimulus' value (aversive, rewarding, neutral), and then to reduce attentional resources when that same stimulus is encountered again. Without habituation, the constant barrage of incoming sensory data would overwhelm the organism. Habituation was initially described as a behavioral phenomenon (Rankin et al., 2009; Thompson & Spencer, 1966), and in humans, habituation can be observed as behavioral responses to novel stimuli. Indeed, behavioral inhibition in children is often measured as the time course of responses to novel stimuli, for example, latency to play with novel toys, latency to approach a stranger, and latency to speak to a stranger (García Coll, Kagan, & Reznick, 1984; Kagan, Reznick, Snidman, Gibbons, & Johnson, 1988). These are traits that are observable in day-to-day interactions with inhibited children—often described as "slow to warm up"—including freezing or hiding upon first meeting of a new person with a gradual warming following multiple interactions.

We propose that habituation is an innate and biologically based trait, based on evidence that individual differences in habituation appear as early as infancy (Bushnell, 1982; Turk-Browne, Scholl, & Chun, 2008) and that differences in the timing of responses to emotional stimuli underlie differences in temperament and personality (Davidson et al., 2002; Schuyler et al., 2014). Over the past decade, evidence of a neurobiological basis of habituation has emerged (see the chapter "The Biological Bridge Between Behavioral Inhibition and Psychopathology" by Sylvester and Pine). For example, in humans, the amygdala and hippocampus both habituate to novel faces and objects (Blackford, Buckholtz, Avery, & Zald, 2010; Breiter et al., 1996; Fried et al., 1997; Plichta et al., 2014; Strange et al., 1999; Wright et al., 2001; Yamaguchi, Hale, D'Esposito, & Knight, 2004). Furthermore, the amygdala also habituates to repeated presentations of emotionally neutral faces (Plichta et al., 2014; Schwartz et al., 2003).

We have been exploring individual differences in neural habituation as a biological mechanism underlying behavioral inhibition. Neural habituation has been most commonly interrogated by assessing neural response to repeated presentations of stimuli over a short period of time to capture the rapid habituation. For example, in a 2-min habituation session, we showed a set of six neutral faces, eight times each (Blackford et al., 2013). Uninhibited young adults showed a pattern of neural habituation in both the amygdala and the hippocampus. That is, there was a robust initial response followed by a successive decrement in response with repeated presentations. In contrast, the inhibited group failed to show habituation and instead had a moderate amygdala and hippocampal response that remained consistent across repeated presentations of the same stimuli. Schwartz et al. (2012) found this same pattern of response in young adults who were identified during infancy as high-reactive (a developmental precursor to behavioral inhibition). In that study, using a very similar task, adult men who were high-reactive infants showed a persistent amygdala response over time, whereas both the adults who were low-reactive infants and the females who were high-reactive infants showed the typical pattern of habituation to repeated stimuli. Thus the amygdala failure to habituate has been found by two different studies in two different samples. The sex difference was only

found in one of the studies (Schwartz et al., 2012), but sex differences should continue to be investigated in future studies.

In behavioral inhibition, the heightened amygdala brain response to repeated stimuli is sustained over longer periods of time. Following the initial habituation task, participants were shown individual presentations of the faces they had just seen—which were now familiar—and novel faces (Blackford et al., 2011). Consistent with studies of healthy controls (e.g., Schwartz, Wright, Shin, Kagan, & Rauch, 2003), the uninhibited groups in both studies showed a robust amygdala response to the novel faces and a small amygdala response to the familiarized faces, suggesting habituation. However, the inhibited group had the same magnitude of amygdala response to both the novel and recently familiarized faces, showing that the failure of amygdala habituation during the familiarization process was maintained across the next 30 minutes of face presentations. Consistent with this finding, Schwartz et al. (2012) reported a trend ($p = 0.06$) for high-reactive males to have persistently greater amygdala response to familiar faces compared to low-reactive males.

Failure to habituate is observed across multiple brain regions and reflects alterations in bottom-up processes. Across two studies from our lab (Avery & Blackford, 2016; Blackford et al., 2011), we have found that behavioral inhibition is associated with sustained activation to repeated face presentations in brain regions involved in: (1) emotion processing, amygdala, hippocampus, insula, thalamus, caudate, and dorsal anterior cingulate; (2) visual processing, fusiform gyrus, primary visual cortex, and extrastriate visual cortex; and (3) cognitive control, dorsolateral prefrontal cortex, rostral anterior cingulate, vmPFC, and medial orbitofrontal cortex. Using functional connectivity, we also showed that the failure of amygdala habituation was driven by connectivity with the visual cortex and not the prefrontal cortex. This finding suggests that differences in habituation are related to bottom-up processes, such as baseline sensitivity of the amygdala and visual cortex to incoming sensory data, and not top-down processes, such as failure of the prefrontal cortex to inhibit amygdala activity. Increased baseline sensitivity of the amygdala provides neurobiological evidence for the original theory of behavioral inhibition as heightened reactivity to novelty and a failure to habituate.

A failure to habituate to neutral stimuli may be a key neurobiological signature of behavioral inhibition; however, is it one of the developmental mechanisms that predicts risk for anxiety disorders? Previous neuroimaging studies were not able to address this question due to either lack of diagnostic interviews or small sample sizes. However, a study by Reeb-Sutherland (2009) may provide some clues. They examined fear-potentiated startle—an amygdala-mediated process (Walker & Davis, 1997)—to fear cues and safety cues in adolescents identified as behaviorally inhibited or uninhibited as children. Although startle response did not differ during the habituation phase, startle response to the safety cue (akin to the familiar faces) was significantly higher in the group who had both anxiety disorders and behavioral inhibition, suggesting that failure to habituate may be associated with the later development of anxiety disorders.

The Role of Bottom-Up Mechanisms in Development

The amygdala plays a prominent role in novelty detection (Blackford et al., 2010; Schwartz, Wright, Shin, Kagan, Whalen, et al., 2003), salience processing (Seeley et al., 2007), and normative fear (Davis, 1992; Kalin, Shelton, & Davidson, 2004). Thus, both heightened responses to novelty and failure to habituate—or sustained responses—suggest that inhibited individuals process novel stimuli differently than non-inhibited individuals. For example, a heightened and sustained response to novelty will produce a state of hyperarousal and hypervigilance as the subcortical brain regions continue to process and monitor incoming information as novel and potentially threatening. We propose that these differences are present very early in development, based on the fact that the key components of the fear circuitry mature early in development (Gullone, 2000), early childhood has several distinct periods where normative fears emerge (Scarr & Salapatek, 1970), and individual differences in response to novelty are observable by 6 months of age (Bushnell, 1982; Kagan, Snidman, & Arcus, 1998). A likely result is that behaviorally inhibited infants and young children learn to associate novelty with hyperarousal.

As young children develop independence, they begin to avoid feelings of hyperarousal associated with novel people, places, and things and instead seek familiar people and environments—a classic example of active gene-environment correlation (Plomin, DeFries, & Loehlin, 1977). While the preference for the familiar can reduce the short-term hyperarousal, avoiding novelty can also have a negative impact on development. For example, reduced exposure to novelty can impact developmental trajectories through multiple mechanisms including learning, reduced opportunity for positive experiences associated with novelty; emotion regulation, fewer opportunities to develop neural and behavioral strategies for managing emotional reactions and hyperarousal; and social development, restricted social experiences and fewer opportunities to develop peer relationships. Thus, the early emerging neurobiological differences in bottom-up novelty and fear circuits produce a heightened and sustained processing of novelty that can influence developmental trajectories through deficits in learning, emotion regulation, and social experiences (see the chapter "Attention Mechanisms in Behavioral Inhibition: Exploring, and Exploiting, the Environment" by Pérez-Edgar; chapter "Behavioral Inhibition and the Associative Learning of Fear" by Reynolds et al.)

Top-Down Mechanisms

Maladaptive Anticipatory Processing

Activity of the PFC, specifically the anterior cingulate cortex (ACC) and dorsolateral PFC (dlPFC), is critical for anticipatory processing and expectancy. During anticipation of an aversive event, an individual can engage in adaptive behavior, such as planning and preparation, which is governed by activity of the prefrontal cortex,

including ACC and dlPFC (see the chapter "The Neural Mechanisms of Behavioral Inhibition" by Jarcho and Guyer). Conversely, the individual can engage in maladaptive behavior, such as worry and avoidance. For example, individuals with anxiety disorders fail to effectively prepare for upcoming events and engage in avoidance behavior (Grupe & Nitschke, 2013). In the first neuroimaging investigation of prefrontal cortical function in inhibited adults, Clauss, Cowan, and Blackford (2011) manipulated the expectation of viewing fear faces across inhibited and uninhibited young adults. Half of the subjects in each group were told that they would see fear faces (expected group); the other half were not warned (not-expected group). Consistent with findings in healthy adults, the uninhibited subjects in the expected group had greater dACC and dlPFC activation and decreased amygdala activation, compared to the uninhibited subjects in the not-expected group. The findings in the inhibited subjects were opposite: the inhibited subjects in the expected group had less activation in prefrontal cortical regions and increased amygdala activation relative to the inhibited participants in the not-expected condition, suggesting that they had not adequately prepared to view the upcoming fear faces and had a sensitized amygdala response.

Maladaptive anticipation, including worry, and increased amygdala activation may be one developmental mechanism in behaviorally inhibited individuals and may contribute to the development of anxiety disorders. To understand how inhibited temperament alters brain activation during anticipation, Clauss, Seay, et al. (2014) used a cued anticipation task. During anticipation of viewing fear faces, inhibited young adults had increased activation in the dACC and dlPFC. However, there were no group differences in amygdala activation. Within the inhibited group, greater activation of the PFC was correlated with fewer symptoms of social anxiety disorder and more frequent use of emotion regulation skills. The ability to engage prefrontal cortex during anticipation of negative social stimuli may be a protective factor, preventing the development of anxiety disorder symptoms. Furthermore, individuals may develop the ability to engage prefrontal cortex over time in response to anxiety-provoking cues, resulting in resilience.

To date, only two studies have tested for differences in brain activation in young children with behavioral inhibition prior to the onset of social anxiety disorder. Using a cued anticipation task, Clauss et al. (2016) showed that 8–10-year-old inhibited children had less activation of the dorsomedial prefrontal cortex (dmPFC) and dACC during anticipation of viewing fear faces. In contrast, inhibited children had increased engagement of similar PFC regions during viewing of faces generally. In an independent sample, Fu et al. (2015) found that 9–12-year-old inhibited children had increased dlPFC activation during incongruent trials of a dot-probe task and that level of behavioral inhibition mediated the relation between increased dlPFC activity and current anxiety symptoms. These findings suggest that PFC activation may develop over time as inhibited individuals become resilient to anxiety disorders; however, longitudinal neuroimaging studies with clinical assessments are critical to test this hypothesis.

Lack of Cognitive Control

Two critical functions of the prefrontal cortex are to adapt to conflict and to control attention. These functions can be impaired in anxiety disorders. Jarcho et al. (2013) examined conflict monitoring and conflict adaptation in young adults with a history of inhibited temperament. Conflict was created by labeling emotional faces with either the emotion on the face (congruent) or labeled with a different emotion (incongruent). During incongruent trials, compared with congruent trials, inhibited individuals had greater activation in the dmPFC, insula, and parietal cortex. Inhibited individuals had greater activity during conflict adaptation (response to incongruent trial following an incongruent trial minus response to an incongruent trial following a congruent trial) in the putamen, precuneus, and occipital cortex. Inhibited individuals also had greater activity during conflict detection in the dmPFC. Finally, individuals with a history of internalizing disorders had less dlPFC activation to incongruent trials, relative to congruent trials, and did not exhibit conflict adaptation (did not get faster to the second incongruent trial in a row).

In a second study, Jarcho et al. (2014) tested for differences in attentional control. Participants saw male and female emotional faces that were labeled with the words "male" and "female." During incongruent trials (face gender and word did not match) while viewing fear faces, inhibited subjects had greater activation of the dmPFC, anterior cingulate cortex, dlPFC, precuneus, and basal ganglia (caudate and globus pallidus). These findings suggest that during more mild tasks that engage the PFC, such as preparing to view individual fear faces or viewing incongruent face-word pairs, inhibited individuals may have greater activation of the dlPFC, dmPFC, and ACC. However, during more demanding tasks, such as viewing large blocks of expected fear faces, inhibited individuals have less PFC activity. Increased PFC activation to more mild tasks may represent a hypervigilance to stimuli, whereas lack of PFC activation to more emotionally demanding tasks may represent a failure of the PFC to inhibit heightened subcortical activation.

A limited number of neuroimaging studies have examined the relations between brain activation and anxiety symptoms in inhibited individuals. However, the few studies that have examined this question have found a relation between prefrontal cortex and anxiety disorder symptoms. In inhibited young adults, more anxiety symptoms was associated with less rostral anterior cingulate activation during anticipation of fearful faces relative to neutral faces (Clauss, Avery, et al., 2014). In another group of young adults who were inhibited as children, less activation of the dlPFC during conflict adaptation was associated with lifetime development of internalizing diagnoses (Jarcho et al., 2013). PFC activation across two paradigms (anticipation and word-face conflict) was associated with fewer anxiety symptoms or disorders.

Additionally, behavioral data in inhibited children highlights a role for cognitive control processing in risk for anxiety disorders. Inhibited children who engaged in less inhibitory control, less response monitoring, and more attention shifting, were less likely to have an anxiety disorder (McDermott et al., 2009; White, McDermott, Degnan, Henderson, & Fox, 2011). Based on these findings, we suggest

that one putative mechanism contributing to the development of anxiety disorders in inhibited youth is the flexible and context-specific engagement of the prefrontal cortex (see the chapter "Relations Between Behavioral Inhibition, Cognitive Control and Anxiety: Novel Insights Provided by Parsing Subdomains of Cognitive Control" by Buzzell et al.)

Flexible engagement of the prefrontal cortex may be modified by treatments and could be a target for intervention in high-risk inhibited children. Activity of the prefrontal cortex can be modified by psychotherapy (Klumpp, Fitzgerald, & Phan, 2013) and drug treatments (Aupperle et al., 2011). Given that the prefrontal cortex undergoes protracted development over time (Casey, Giedd, & Thomas, 2000; Huttenlocher, 1990), there may be particular critical periods during which interventions are most effective. To date, no studies have examined interventions developmentally, but this is a critical future direction for psychiatric research. If critical periods for prefrontal cortex development could be identified, targeted interventions could be developed for inhibited children.

The Role of Top-Down Mechanisms in Development

Models of fear neurocircuitry development (Casey, Pattwell, Glatt, & Lee, 2013) and motivated behavior (Ernst & Fudge, 2009) propose that a relative imbalance in the development of cortical and subcortical regions contributes to the behavioral changes observed through childhood and adolescence (see Fig. 4). In children and

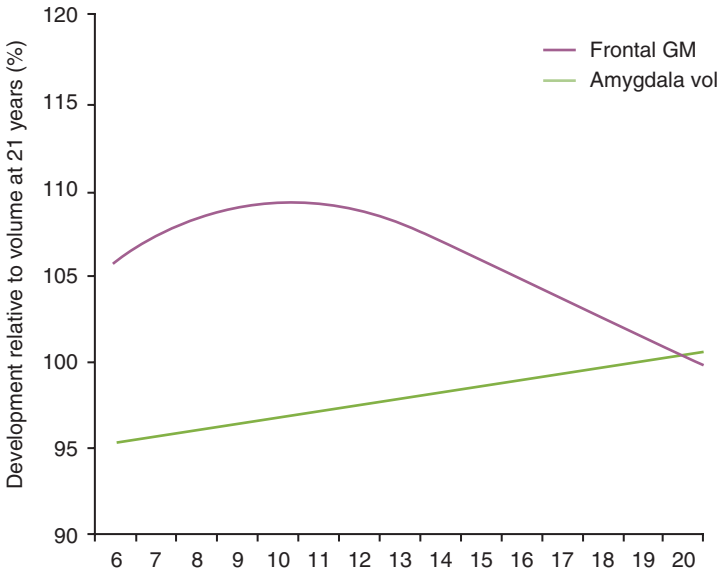

Fig. 4 The balance of amygdala and prefrontal cortex across development. The prefrontal cortex undergoes an early expansion, and then gray matter volume decreases through adolescence. Amygdala volume undergoes a modest increase across development. Figure adapted from Andersen and Teicher (2008)

adolescents, subcortical brain regions, such as the amygdala, mature earlier. In contrast to the amygdala, the prefrontal cortex undergoes protracted development from childhood through adolescence and into young adulthood, as measured by gray matter density, synaptogenesis, and myelination (Casey et al., 2000; Gogtay et al., 2004; Huttenlocher, 1990). Development of the prefrontal cortex parallels the development of cognitive control in children (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Pitskel, Bolling, Kaiser, Crowley, & Pelphrey, 2011).

This differential maturation leads to a relative imbalance between activity of the amygdala, which responds to fear stimuli, and activity of the prefrontal cortex, which regulates fear response. In children, cognitive control is associated with more dmPFC activity and less amygdala activity (Pitskel et al., 2011), and increased dlPFC activity correlates with better cognitive control (Bunge et al., 2002). During adolescence, this differential maturity between brain regions is accompanied by a corresponding increase in the prevalence of anxiety disorders (Kessler et al., 2005). For most adolescents, prefrontal cortex development will eventually "catch up" with the amygdala and restore balance between the two regions. However, for some children, the mature prefrontal cortex and amygdala will continue to be imbalanced, which may result from either a relative strength in the amygdala or relative weakness in the prefrontal cortex.

Given that inhibited children likely have a hyperactive amygdala, the development of an equally strong prefrontal cortex is critical. We propose that this is a critical point for a divergence of developmental trajectories in inhibited children. Inhibited individuals whose prefrontal cortex develops in balance with the amygdala will have the executive function skills needed to inhibit responses to novel or threatening stimuli. Combined with a positive environment, these children should return to a normative developmental trajectory and be buffered against the development of anxiety disorders. However, for inhibited individuals who remain imbalanced, we would predict a steady developmental course with heightened risk for anxiety.

Nurture as a Modifier of Nature

While this chapter has focused on neurobiological mechanisms, it is important to acknowledge the critical role of nurture in both the development of behaviors and the development of the brain itself. A decade of elegant studies of the attachment and fear systems in infant rats has shown that the amygdala-dependent fear system typically develops at the midway point between birth and weaning/independence and that the maturation of this system is flexible and dependent on the both internal (i.e., hormones) and external environmental factors (Debiec & Sullivan, 2017). For example, amygdala maturation can occur earlier than normal in response to either internal environment—increased levels of corticosterone—or external environment, maternal absence. Emerging evidence in humans supports the idea that early life adversity, for example, maternal depression or child maltreatment, is associated with a more mature pattern of amygdala function (Gee et al., 2013; Qiu et al., 2015).

For the prefrontal cortex, adolescence is an especially sensitive period for the impact of environment, consistent with the rapid prefrontal cortical maturation that occurs during this developmental stage. Like the amygdala, the prefrontal cortex is influenced by both internal and external environmental factors, including hormonal changes during puberty; exposure to negative environments, such as stress and trauma (Arnsten, Raskind, Taylor, & Connor, 2015; Cook & Wellman, 2004; McEwen & Morrison, 2013); and exposure to positive environments, such as moderate challenges or enriched school environments (Kolb et al., 2012).

Interactions with other humans comprise another major "nurture" influence on the development of behavioral inhibition. In the introduction, we described that context was a critical determinant of whether behavioral inhibition was a detriment or benefit. In the modern era where many people have sufficient resources for survival, the social group emerges as the critical context. Early in life, parents and close family members provide the primary social network and shape the development of behavioral inhibition. For example, in nonhuman primates, the long-term outcome for inhibited monkeys is dependent on parenting. Inhibited monkeys cross-fostered to skilled, nurturing mothers do significantly better than those raised by average mothers (Suomi, 1997). Inhibited children have fewer anxiety symptoms if their parents are warm but firm (Williams et al., 2009) and are less likely to develop post-traumatic stress disorder following trauma if parental emotional warmth is high (Asselmann, Wittchen, Lieb, Höfler, & Beesdo-Baum, 2015). While it remains unknown how good parenting buffers risk in inhibited children, evidence from rodent models suggests that enriched environments and attentive maternal care can induce neural proliferation and synaptogenesis in the brain (Kaffman & Meaney, 2007; Nithianantharajah & Hannan, 2006). Targeted interventions that address both parenting and the child's environment may induce prefrontal cortex proliferation in inhibited children (see the chapter "Behavioural Inhibition and the Prevention of Internalising Distress in Early Childhood" by Rapee and Bayer), which could promote resilience and steer development toward a normative trajectory. Longitudinal studies that follow inhibited children over time are critical for dissecting the complex brain and environmental factors that contribute to long-term developmental outcomes.

Conclusions

Early emerging individual differences in temperament can shape developmental pathways from early childhood to adulthood. The past decade of neuroimaging research has provided new insights into both the neurobiological bases of behavioral inhibition and the neural mechanisms that may influence developmental trajectories. We propose that differences in bottom-up brain mechanisms related to processing of novel social stimuli produce the early expressions of behavioral inhibition and serve to maintain inhibited behavior in early development. In inhibited individuals, a group of subcortical brain regions—including, but not limited to, the

amygdala and hippocampus—have a heightened initial response to novel social stimuli and a sustained response over time, or failure to habituate.

We propose that hyper-responsivity to novelty shapes the child's environment in a way that maintains behavioral inhibition over time. Changes in these neural mechanisms, either through intrinsic brain changes or environmental influences, may impact the early trajectories, although much remains unknown about these factors. We further proposed that during adolescence, the development of top-down mechanisms, including the ability to effectively prepare for upcoming events, inhibit emotional responses, and effectively manage conflicting information, become critically important. The most relevant brain regions for these processes are regions of the prefrontal cortex (PFC), including the dorsolateral PFC, dorsomedial PFC, and anterior cingulate cortex.

In inhibited adolescents, differences in the development of these top-down processes create a point of divergence in developmental trajectories. Adolescents who can flexibly deploy prefrontal cortical resources to prepare for upcoming events, inhibit hyperarousal, and manage conflicting information will be able to compensate for the bottom-up hyper-responsivity and will have a shift in their trajectory toward more normative development. In contrast, adolescents with deficits in top-down mechanisms—resulting from alterations in prefrontal cortical structure, function, or connectivity—will maintain an inhibited trajectory and have increased risk for developing anxiety and depressive disorders in early adulthood.

To further elucidate developmental mechanisms and trajectories in inhibited children, future studies must investigate brain structure, function, and connectivity across development; examine neurochemical mechanisms, including stress chemicals, hormones, and neurotransmitters, that differ among developmental trajectories; determine which neurobiological factors in inhibited temperament are malleable and therefore targets for preventive interventions; and assess the impact of environmental factors, including trauma and parenting, on developmental mechanisms.

References

Andersen, S. L., & Teicher, M. H. (2008). Stress, sensitive periods and maturational events in adolescent depression. *Trends in Neurosciences, 31*(4), 183–191.

Arnsten, A. F. T., Raskind, M. A., Taylor, F. B., & Connor, D. F. (2015). The effects of stress exposure on prefrontal cortex: Translating basic research into successful treatments for post-traumatic stress disorder. *Neurobiology of Stress, 1*(1), 89–99.

Asselmann, E., Wittchen, H. U., Lieb, R., Höfler, M., & Beesdo-Baum, K. (2015). The role of behavioral inhibition and parenting for an unfavorable emotional trauma response and PTSD. *Acta Psychiatrica Scandinavica, 131*(4), 279–289.

Aupperle, R. L., Ravindran, L., Tankersley, D., Flagan, T., Stein, N. R., Simmons, A. N., … Paulus, M. P. (2011). Pregabalin influences insula and amygdala activation during anticipation of emotional images. *Neuropsychopharmacology, 36*(7), 1466–1477.

Avery, S. N. (2015). *Slow to warm up: The role of habituation in social fear*. Nashville, TN: Vanderbilt University.

Avery, S. N., & Blackford, J. U. (2016). Slow to warm up: The role of habituation in social fear. *Social Cognitive and Affective Neuroscience, 11*(11), 1832–1840.

Bas-Hoogendam, J. M., Blackford, J. U., Brühl, A. B., Blair, K. S., van der Wee, N. J. A., & Westenberg, P. M. (2016). Neurobiological candidate endophenotypes of social anxiety disorder. *Neuroscience and Biobehavioral Reviews, 71*, 362–378.

Beesdo, K., Bittner, A., Pine, D. S., Stein, M. B., Hofler, M., Lieb, R., & Wittchen, H.-U. (2007). Incidence of social anxiety disorder and the consistent risk for secondary depression in the first three decades of life. *Archives of General Psychiatry, 64*(8), 903–912.

Biro, P. A., Post, J. R. (2008). Rapid depletion of genotypes with fast growth and bold personality traits from harvested fish populations. *Proceedings of the National Academy of Sciences of the United States of America, 105*(8), 2919–2922.

Biederman, J., Hirshfeld-Becker, D. R., Rosenbaum, J. F., Herot, C., Friedman, D., Snidman, N., … Faraone, S. V. (2001). Further evidence of association between behavioral inhibition and social anxiety in children. *American Journal of Psychiatry, 158*(10), 1673–1679.

Biederman, J., Rosenbaum, J. F., Bolducmurphy, E. A., Faraone, S. V., Chaloff, J., Hirshfeld, D. R., & Kagan, J. (1993). A 3-year follow-up of children with and without behavioral-inhibition. *Journal of the American Academy of Child and Adolescent Psychiatry, 32*(4), 814–821.

Blackford, J. U., Allen, A. H., Cowan, R. L., & Avery, S. N. (2013). Amygdala and hippocampus fail to habituate to faces in individuals with an inhibited temperament. *Social Cognitive and Affective Neuroscience, 8*(2), 143–150.

Blackford, J. U., Avery, S. N., Cowan, R. L., Shelton, R. C., & Zald, D. H. (2011). Sustained amygdala response to both novel and newly familiar faces characterizes inhibited temperament. *Social Cognitive and Affective Neuroscience, 6*(5), 621–629.

Blackford, J. U., Avery, S. N., Shelton, R. C., & Zald, D. H. (2009). Amygdala temporal dynamics: Temperamental differences in the timing of amygdala response to familiar and novel faces. *BMC Neuroscience, 10*, 145.

Blackford, J. U., Buckholtz, J. W., Avery, S. N., & Zald, D. H. (2010). A unique role for the amygdala in novelty detection. *NeuroImage, 50*(3), 1188–1193.

Blackford, J. U., Clauss, J. A., Avery, S. N., Cowan, R. L., Benningfield, M. M., & Vanderklok, R. M. (2014). Amygdala-cingulate intrinsic connectivity is associated with degree of social inhibition. *Biological Psychology, 99*, 15–25.

Breiter, H. C., Etcoff, N. L., Whalen, P. J., Kennedy, W. A., Rauch, S. L., Buckner, R. L., … Rosen, B. R. (1996). Response and habituation of the human amygdala during visual processing of facial expression. *Neuron, 17*(5), 875–887.

Brühl, A. B., Delsignore, A., Komossa, K., & Weidt, S. (2014). Neuroimaging in social anxiety disorder–a meta-analytic review resulting in a new neurofunctional model. *Neuroscience & Biobehavioral Reviews, 47*, 260–280.

Buckner, J. D., Schmidt, N. B., Lang, A. R., Small, J. W., Schlauch, R. C., & Lewinsohn, P. M. (2008). Specificity of social anxiety disorder as a risk factor for alcohol and cannabis dependence. *Journal of Psychiatric Research, 42*(3), 230–239.

Buhle, J. T., Silvers, J. A., Wager, T. D., Lopez, R., Onyemekwu, C., Kober, H., … Ochsner, K. N. (2014). Cognitive reappraisal of emotion: A meta-analysis of human neuroimaging studies. *Cerebral Cortex, 24*, 2981–2990.

Bunge, S. A., Dudukovic, N. M., Thomason, M. E., Vaidya, C. J., & Gabrieli, J. D. E. (2002). Immature frontal lobe contributions to cognitive control in children: Evidence from fMRI. *Neuron, 33*(2), 301–311.

Bushnell, I. W. R. (1982). Discrimination of faces by young infants. *Journal of Experimental Child Psychology, 33*(2), 298–308.

Casey, B. J., Giedd, J. N., & Thomas, K. M. (2000). Structural and functional brain development and its relation to cognitive development. *Biological Psychology, 54*(1–3), 241–257.

Casey, B. J., Pattwell, S. S., Glatt, C. E., & Lee, F. S. (2013). Treating the developing brain: Implications from human imaging and mouse genetics. *Annual Review of Medicine, 64*, 427–439.

Caspi, A., Moffitt, T. E., Newman, D. L., & Silva, P. A. (1996). Behavioral observations at age 3 years predict adult psychiatric disorders. Longitudinal evidence from a birth cohort. *Archives of General Psychiatry, 53*(11), 1033–1039.

Chronis-Tuscano, A., Degnan, K. A., Pine, D. S., Pérez-Edgar, K., Henderson, H. A., Diaz, Y., … Fox, N. A. (2009). Stable early maternal report of behavioral inhibition predicts lifetime social anxiety disorder in adolescence. *Journal of the American Academy of Child and Adolescent Psychiatry, 48*(9), 928–935.

Clauss, J. A., Avery, S. N., & Blackford, J. U. (2015). The nature of individual differences in inhibited temperament and risk for psychiatric disease: A review and meta-analysis. *Progress in Neurobiology, 127-128*, 23–45.

Clauss, J. A., Avery, S. N., VanDerKlok, R., Cowan, R. L., Benningfield, M. M., & Blackford, J. U. (2014). Neurocircuitry underlying risk and resilience to social anxiety disorder. *Depression and Anxiety, 31*, 822–833.

Clauss, J. A., Benningfield, M. M., Rao, U., & Blackford, J. U. (2016). Altered prefrontal cortex function marks heightened anxiety risk in children. *Journal of the American Academy of Child & Adolescent Psychiatry, 55*, 809–816.

Clauss, J. A., & Blackford, J. U. (2012). Behavioral inhibition and risk for developing social anxiety disorder: A meta-analytic study. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*(10), 1066–1075.

Clauss, J. A., Cowan, R. L., & Blackford, J. U. (2011). Expectation and temperament moderate amygdala and dorsal anterior cingulate cortex responses to fear faces. *Cognitive, Affective, & Behavioral Neuroscience, 11*(1), 13–21.

Clauss, J. A., Seay, A. L., Vanderklok, R., Avery, S., Cao, A., Cowan, R. L., … Blackford, J. U. (2014). Structural and functional bases of inhibited temperament. *Social Cognitive and Affective Neuroscience, 9*(12), 2049–2058.

Cook, S. C., & Wellman, C. L. (2004). Chronic stress alters dendritic morphology in rat medial prefrontal cortex. *Journal of Neurobiology, 60*(2), 236–248.

Davidson, R. J., Lewis, D. A., Alloy, L. B., Amaral, D. G., Bush, G., Cohen, J. D., … Peterson, B. S. (2002). Neural and behavioral substrates of mood and mood regulation. *Biological Psychiatry, 52*(6), 478–502.

Davis, M. (1992). The role of the amygdala in fear and anxiety. *Annual Review of Neuroscience, 15*, 353–375.

Debiec, J., & Sullivan, R. M. (2017). The neurobiology of safety and threat learning in infancy. *Neurobiology of Learning and Memory, 143*, 49–58.

Dilalla, L. F., Kagan, J., & Reznick, J. S. (1994). Genetic etiology of behavioral inhibition among 2-year-old children. *Infant Behavior & Development, 17*(4), 405–412.

Emde, R. N., Plomin, R., Robinson, J. A., Corley, R., DeFries, J., Fulker, D. W., … Zahn-Waxler, C. (1992). Temperament, emotion, and cognition at fourteen months: The MacArthur Longitudinal Twin Study. *Child Development, 63*(6), 1437–1455.

Ernst, M., Fudge, J. L. (2009). A developmental neurobiological model of motivated behavior: Anatomy, connectivity and ontogeny of the triadic nodes. *Neuroscience and Biobehavioral Reviews, 33*(3), 367–382.

Essex, M. J., Klein, M. H., Slattery, M. J., Goldsmith, H. H. H., & Kalin, N. H. (2010). Early risk factors and developmental pathways to chronic high inhibition and social anxiety disorder in adolescence. *American Journal of Psychiatry, 167*(1), 40–46.

Frick, A., Howner, K., Fischer, H., Eskildsen, S. F., Kristiansson, M., & Furmark, T. (2013). Cortical thickness alterations in social anxiety disorder. *Neuroscience Letters, 536*, 52–55.

Fried, I., MacDonald, K. A., & Wilson, C. L. (1997). Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. *Neuron, 18*(5), 753–765.

Fu, X., Taber-Thomas, B. C., & Pérez-Edgar, K. (2015). Frontolimbic functioning during threat-related attention: Relations to early behavioral inhibition and anxiety in children. *Biological Psychology, 122*, 98–109.

García Coll, C., Kagan, J., & Reznick, J. S. (1984). Behavioral inhibition in young children. *Child Development, 55*(3), 1005–1019.

Gee, D. G., Humphreys, K. L., Flannery, J., Goff, B., Telzer, E. H., Shapiro, M., … Tottenham, N. (2013). A developmental shift from positive to negative connectivity in human amygdala-prefrontal circuitry. *The Journal of Neuroscience, 33*(10), 4584–4593.

Ghashghaei, H., Hilgetag, C. C., & Barbas, H. (2007). Sequence of information processing for emotions based on the anatomic dialogue between prefrontal cortex and amygdala. *NeuroImage, 34*(3), 905–923.

Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., … Thompson, P. M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences of the United States of America, 101*(21), 8174–8179.

Gosling, S. D. (2001). From mice to men: What can we learn about personality from animal research? *Psychological Bulletin, 127*(1), 45–86.

Grupe, D. W., & Nitschke, J. B. (2013). Uncertainty and anticipation in anxiety: An integrated neurobiological and psychological perspective. *Nature Reviews Neuroscience, 14*(7), 488–501.

Gullone, E. (2000). The development of normal fear: A century of research. *Clinical Psychology Review, 20*(4), 429–451.

Hill, S. Y., Tessner, K., Wang, S., Carter, H., & Mcdermott, M. (2010). Temperament at 5-years of age predicts amygdala and orbitofrontal volume in the right hemisphere in adolescence. *Psychiatry Research: Neuroimaging, 182*(1), 14–21.

Hirshfeld, D. R., Rosenbaum, J. F., Biederman, J., Bolduc, E. A., Faraone, S. V., Snidman, N., … Kagan, J. (1992). Stable behavioral-inhibition and its association with anxiety disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 31*(1), 103–111.

Huttenlocher, P. R. (1990). Morphometric study of human cerebral cortex development. *Neuropsychologia, 28*(6), 517–527.

Jarcho, J. M., Fox, N. A., Pine, D. S., Etkin, A., Leibenluft, E., Shechner, T., & Ernst, M. (2013). The neural correlates of emotion-based cognitive control in adults with early childhood behavioral inhibition. *Biological Psychology, 92*(2), 306–314.

Jarcho, J. M., Fox, N. A., Pine, D. S., Leibenluft, E., Shechner, T., Degnan, K. A., … Ernst, M. (2014). Enduring influence of early temperament on neural mechanisms mediating attention-emotion conflict in adults. *Depression and Anxiety, 31*(1), 53–62.

Kaffman, A., & Meaney, M. J. (2007). Neurodevelopmental sequelae of postnatal maternal care in rodents: Clinical and research implications of molecular insights. *Journal of Child Psychology and Psychiatry, and Allied Disciplines, 48*(3–4), 224–244.

Kagan, J., Reznick, J. S., & Snidman, N. (1998). Biological bases of childhood shyness. *Science, 240*(4849), 167–171.

Kagan, J., Reznick, J. S., Snidman, N., Gibbons, J., & Johnson, M. O. (1988). Childhood derivatives of inhibition and lack of inhibition to the unfamiliar. *Child Development, 59*(6), 1580–1589.

Kagan, J., & Snidman, N. (2004). *The long shadow of temperament*. Cambridge, MA: Harvard University Press.

Kagan, J., Snidman, N., & Arcus, D. (1998). Childhood derivatives of high and low reactivity in infancy. *Child Development, 69*(6), 1483–1493.

Kalin, N. H., Shelton, S. E., & Davidson, R. J. (2004). The role of the central nucleus of the amygdala in mediating fear and anxiety in the primate. *Journal of Neuroscience, 24*(24), 5506–5515.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*(6), 593–602.

Klumpp, H., Fitzgerald, D. A., & Phan, K. L. (2013). Neural predictors and mechanisms of cognitive behavioral therapy on threat processing in social anxiety disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 45*, 83–91.

Kolb, B., Mychasiuk, R., Muhammad, A., Li, Y., Frost, D. O., & Gibb, R. (2012). Experience and the developing prefrontal cortex. *Proceedings of the National Academy of Sciences, 109*(Supplement_2), 17186–17193.

McDermott, J. M., Pérez-Edgar, K., Henderson, H. A., Chronis-Tuscano, A., Pine, D. S., & Fox, N. A. (2009). A history of childhood behavioral inhibition and enhanced response monitoring in adolescence are linked to clinical anxiety. *Biological Psychiatry, 65*(5), 445–448.

McEwen, B. S., & Morrison, J. H. (2013). The brain on stress: Vulnerability and plasticity of the prefrontal cortex over the life course. *Neuron, 79*(1), 16–29.

Motzkin, J. C., Philippi, C. L., Wolf, R. C., Baskaya, M. K., & Koenigs, M. (2015). Ventromedial prefrontal cortex is critical for the regulation of amygdala activity in humans. *Biological Psychiatry, 77*(3), 276–284.

Nithianantharajah, J., & Hannan, A. J. (2006). Enriched environments, experience-dependent plasticity and disorders of the nervous system. Nature reviews. *Neuroscience, 7*(9), 697–709.

Pitskel, N. B., Bolling, D. Z., Kaiser, M. D., Crowley, M. J., & Pelphrey, K. a. (2011). How grossed out are you? The neural bases of emotion regulation from childhood to adolescence. *Developmental Cognitive Neuroscience, 1*(3), 324–337.

Plichta, M. M., Grimm, O., Morgen, K., Mier, D., Sauer, C., Haddad, L., … Meyer-Lindenberg, A. (2014). Amygdala habituation: A reliable fMRI phenotype. *NeuroImage, 103*, 383–390.

Plomin, R., & Daniels, D. (1986). Genetics and shyness. In W. H. Jones, J. M. Cheek, & S. R. Briggs (Eds.), *Shyness: Perspectives on research and treatment* (pp. 63–80). New York, NY: Plenum.

Plomin, R., DeFries, J. C., & Loehlin, J. C. (1977). Genotype-environment interaction and correlation in the analysis of human behavior. *Psychological Bulletin, 84*(2), 309–322.

Qiu, A., Anh, T. T., Li, Y., Chen, H., Rifkin-Graboi, A., Broekman, B. F. P., … Meaney, M. J. (2015). Prenatal maternal depression alters amygdala functional connectivity in 6-month-old infants. *Translational Psychiatry, 5*(2), e508.

Rankin, C. H., Abrams, T., Barry, R. J., Bhatnagar, S., Clayton, D. F., Colombo, J., … Thompson, R. F. (2009). Habituation revisited: An updated and revised description of the behavioral characteristics of habituation. *Neurobiology of Learning and Memory, 92*(2), 135–138.

Reeb-Sutherland, B. C. (2009). Startle response in behaviorally inhibited adolescents with a lifetime occurrence of anxiety disorders. *Journal of the American Academy of Child & Adolescent Psychiatry, 48*(6), 610–617.

Robinson, J. L., Reznick, J. S., Kagan, J., & Corley, R. (1992). The heritability of inhibited and uninhibited behavior: A twin study. *Developmental Psychology, 28*(6), 1030–1037.

Roy, A. K., Benson, B. E., Degnan, K. A., Pérez-Edgar, K., Pine, D. S., Fox, N. A., & Ernst, M. (2014). Alterations in amygdala functional connectivity reflect early temperament. *Biological Psychology, 103*, 248–254.

Rutishauser, U., Mamelak, A. N., & Schuman, E. M. (2006). Single-trial learning of novel stimuli by individual neurons of the human hippocampus-amygdala complex. *Neuron, 49*(6), 805–813.

Scarr, S., & Salapatek, P. (1970). Patterns of fear development during infancy. *Merrill-Palmer Quarterly, 16*(1), 53–90.

Schuyler, B. S., Kral, T. R. A., Jacquart, J., Burghy, C. A., Weng, H. Y., Perlman, D. M., … Davidson, R. J. (2014). Temporal dynamics of emotional responding: Amygdala recovery predicts emotional traits. *Social Cognitive and Affective Neuroscience, 9*(2), 176–181.

Schwartz, C. E., Kunwar, P. S., Greve, D. N., Kagan, J., Snidman, N. C., & Bloch, R. B. (2012). A phenotype of early infancy predicts reactivity of the amygdala in male adults. *Molecular Psychiatry, 17*(10), 1042–1050.

Schwartz, C. E., Kunwar, P. S., Greve, D. N., Moran, L. R., Viner, J. C., Covino, J. M., … Wallace, S. R. (2010). Structural differences in adult orbital and ventromedial prefrontal cortex predicted by infant temperament at 4 months of age. *Archives of General Psychiatry, 67*(1), 78–84.

Schwartz, C. E., Snidman, N., & Kagan, J. (1999). Adolescent social anxiety as an outcome of inhibited temperament in childhood. *Journal of the American Academy of Child and Adolescent Psychiatry, 38*(8), 1008–1015.

Schwartz, C. E., Wright, C. I., Shin, L. M., Kagan, J., & Rauch, S. L. (2003). Inhibited and uninhibited infants "grown up": Adult amygdalar response to novelty. *Science, 300*(5627), 1952–1953.

Schwartz, C. E., Wright, C. I., Shin, L. M., Kagan, J., Whalen, P. J., McMullin, K. G., & Rauch, S. L. (2003). Differential amygdalar response to novel versus newly familiar neutral faces: A functional MRI probe developed for studying inhibited temperament. *Biological Psychiatry, 53*(10), 854–862.

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., … Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *Journal of Neuroscience, 27*(9), 2349–2356.

Strange, B. A., Fletcher, P. C., Henson, R. N. A., Friston, K. J., Dolan, R. J., Square, Q., … Street, R. H. (1999). Segregating the functions of human hippocampus. *Proceedings of the National Academy of Sciences of the United States of America, 96*(7), 4034–4039.

Suomi, S. J. (1997). Early determinants of behaviour: Evidence from primate studies. *British Medical Bulletin, 53*(1), 170–184.

Sylvester, C. M., Barch, D. M., Harms, M. P., Belden, A. C., Oakberg, T. J., Gold, A. L., … Pine, D. S. (2015). Early childhood behavioral inhibition predicts cortical thickness in adulthood. *Journal of the American Academy of Child & Adolescent Psychiatry, 55*(2), 122.e1–129.e1.

Taber-Thomas, B. C., Morales, S., Hillary, F. G., & Pérez-Edgar, K. E. (2016). Altered topography of intrinsic functional connectivity in childhood risk for social anxiety. *Depression and Anxiety, 33*(11), 995–1004.

Thompson, R. F., & Spencer, W. A. (1966). Habituation: A model phenomenon for the study of neuronal substrates of behavior. *Psychological Review, 73*(1), 16–43.

Turk-Browne, N. B., Scholl, B. J., & Chun, M. M. (2008). Babies and brains: Habituation in infant cognition and functional neuroimaging. *Frontiers in Human Neuroscience, 2*, 16.

Walker, D. L., & Davis, M. (1997). Double dissociation between the involvement of the bed nucleus of the stria terminalis and the central nucleus of the amygdala in startle increases produced by conditioned versus unconditioned fear. *The Journal of Neuroscience, 17*(23), 9375–9383.

White, L. K., McDermott, J. M., Degnan, K. A., Henderson, H. A., & Fox, N. A. (2011). Behavioral inhibition and anxiety: The moderating roles of inhibitory control and attention shifting. *Journal of Abnormal Child Psychology, 39*(5), 735–747.

Williams, L. R., Degnan, K. A., Pérez-Edgar, K., Henderson, H. A., Rubin, K. H., Pine, D. S., … Fox, N. A. (2009). Impact of behavioral inhibition and parenting style on internalizing and externalizing problems from early childhood through adolescence. *Journal of Abnormal Child Psychology, 37*(8), 1063–1075.

Wilson, F. A., & Rolls, E. T. (1993). The effects of stimulus novelty and familiarity on neuronal activity in the amygdala of monkeys performing recognition memory tasks. *Experimental Brain Research, 93*(3), 367–382.

Wittchen, H. U., Fröhlich, C., Behrendt, S., Günther, A., Rehm, J., Zimmermann, P., … Perkonigg, A. (2007). Cannabis use and cannabis use disorders and their relationship to mental disorders: A 10-year prospective-longitudinal community study in adolescents. *Drug and Alcohol Dependence, 88*(Suppl. 1), 60–70.

Woodward, L. J., & Fergusson, D. M. (2001). Life course outcomes of young people with anxiety disorders in adolescence. *Journal of the American Academy of Child and Adolescent Psychiatry, 40*(9), 1086–1093.

Wright, C. I., Fischer, H., Whalen, P. J., McInerney, S., Shin, L. M., & Rauch, S. L. (2001). Differential prefrontal cortex and amygdala habituation to repeatedly presented emotional stimuli. *Neuroreport, 12*(2), 379–383.

Yamaguchi, S., Hale, L. A., D'Esposito, M., & Knight, R. T. (2004). Rapid prefrontal-hippocampal habituation to novel events. *Journal of Neuroscience, 24*(23), 5356–5363.

The Social World of Behaviorally Inhibited Children: A Transactional Account

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Abstract In this chapter, we describe the social worlds of behaviorally inhibited children. We organize the review around a transactional model of development in which behavioral inhibition (BI) impacts children's perceptions and interpretations of their social worlds, which in turn guide their behaviors. In parallel, the perceptions and interpretations of behavioral inhibition held by critical socialization partners (teachers, peers, parents) alter their behavior with behaviorally inhibited children. Although these transactions continue throughout the lifespan, we focus our review on childhood and adolescence in order to provide a detailed picture of the developmental milieu of behaviorally inhibited children. We describe social processes and interactions that foster continuity in expression of core behavioral inhibition traits, as well as those that promote discontinuity, noting similarities across key socialization contexts. We conclude with suggestions for future research that focus on the overlap of different socialization contexts (e.g., school, home), the basic mechanisms (e.g., attention) underlying behaviorally inhibited children's experiences in naturalistic environments, and extending research beyond childhood and adolescence to understand the unique social worlds of individuals with a history of childhood behavioral inhibition across the lifespan.

Introduction

Behavioral inhibition (BI) is a temperament trait that appears early in life and shows a good deal of stability across development (Calkins, Fox, & Marshall, 1996). This trait is marked by negative reactions to novelty during infancy and withdrawal from novel and unfamiliar social and nonsocial situations during toddlerhood (Coplan & Armer, 2007; Kagan, Reznick, Clarke, Snidman, & Garcia-Coll, 1984). In older children, the core behavioral inhibition traits include hyper-vigilance, fearfulness, and withdrawal in novel contexts. Behavioral inhibition is also characterized by a distinct physiological profile including increased baseline salivary cortisol, higher

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and less variable heart rate in response to stressors, and greater resting right frontal electroencephalography (EEG) asymmetry (Fox, Henderson, Marshall, Nichols, & Ghera, 2005). Behavioral inhibition impacts attention, cognition, and learning (see the chapter "Relations Between Behavioral Inhibition, Cognitive Control and Anxiety: Novel Insights Provided by Parsing Subdomains of Cognitive Control" by Buzzell et al.; chapter "Attention Mechanisms in Behavioral Inhibition: Exploring, and Exploiting, the Environment by Pérez-Edgar"; chapter "Behavioral Inhibition and the Associative Learning of Fear" by Reynolds et al.), processes that contribute to an increased risk of internalizing problems among behaviorally inhibited children (Brozina & Abela, 2006).

However, and equally important for studies of developmental risk and resilience, not all children who display early behavioral inhibition experience maladaptation at later ages. Instead, both contextual and within-child factors significantly moderate the impact of early behavioral inhibition on later development (Muris, van Brakel, Arntz, & Schouten, 2011). In this chapter, we describe a transactional model of development in which we discuss how core behavioral inhibition traits change children's experiences of their social worlds and how, in turn, critical socializing agents (e.g., teachers, peers, parents) interpret and respond to core behavioral inhibition traits in children (see also the chapter "Behavioural Inhibition and the Prevention of Internalising Distress in Early Childhood" by Rapee and Bayer). We propose that over time, these transactions between behaviorally inhibited children and their social worlds guide and shape unique developmental trajectories (see Fig. 1).

Numerous terms are used in the literature to describe the behavioral manifestations of behavioral inhibition across development. In this chapter we use the umbrella term shyness to describe the various manifestations of behavioral inhibition traits across development. We do so because we believe that as children age, the term behavioral inhibition is no longer adequate to describe the complex internal and external manifestations of core behavioral inhibition traits. That is, we believe that the hyper-vigilance, fear, and withdrawal that form the core of behavioral inhibition become subsumed within the child's developing personality. Specifically, we believe that these behavioral inhibition traits form the core of the personality dimension of shyness which is characterized by tension, discomfort, self-consciousness, concern, and awkwardness in novel and/or social-evaluative contexts (Cheek & Buss, 1981; Crozier, 1979; Melchior & Cheek, 1990).

Whereas behavioral inhibition describes a constellation of observable behaviors, shyness is embedded in a more complex system of attention, memory, and cognition (Henderson, Zimbardo & Carducci, 2010), which means shyness, unlike behavioral inhibition, is experienced both in reaction to, and also in anticipation of, novel and social-evaluative contexts (Pilkonis, 1977). We believe that continuities between early behavioral inhibition and later shyness (e.g., Volbrecht & Goldsmith, 2010) and childhood shyness and adult adjustment (see the chapter "Peer Relations and the Behaviorally Inhibited Child" by Poole et al.) are driven by a stable motivational conflict between the desire to approach and interact with others and the fear and uncertainty of doing so. This motivational conflict differentiates behavioral inhibition and shyness from other forms of nonsocial behavior that simply reflect less interest in, and desire for, social contact (Coplan, Prakash, O'Neil, & Armer, 2004; Coplan, Rubin, Fox, Calkins, & Stewart, 1994).

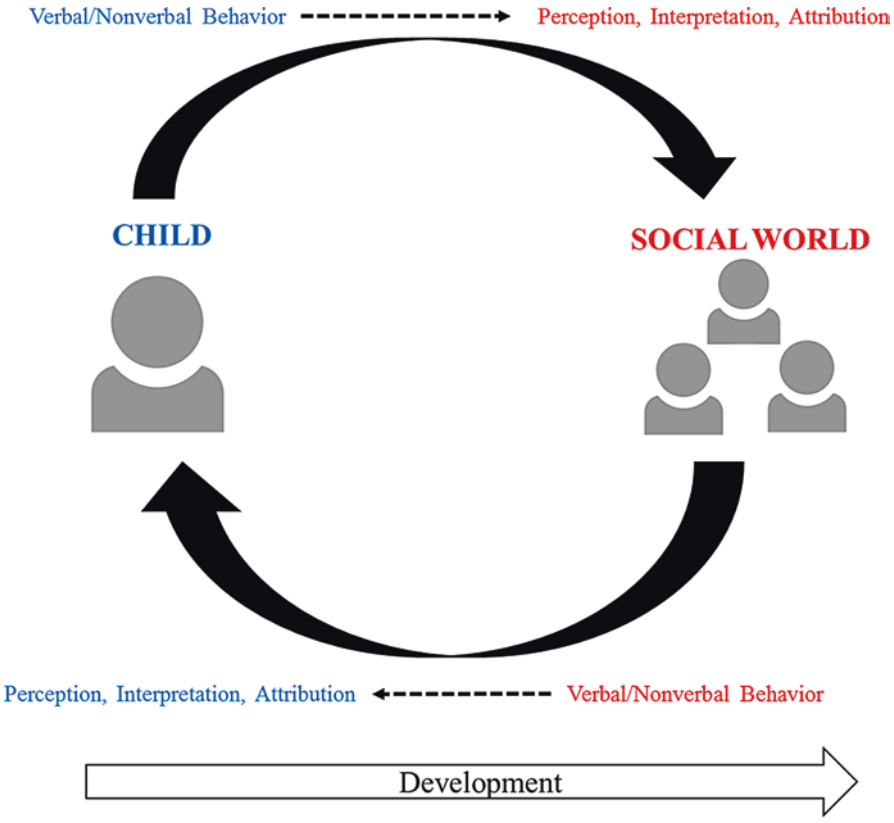

Fig. 1 Transactional model linking behavioral inhibition traits to social experiences

In support of this approach/avoidance interpretation of early behavioral inhibition and later shyness, a vast literature supports the notion that behavioral inhibition traits and shyness are associated with the tendency to attend to, and process deeply, others' behaviors and emotions. For example, recent data demonstrate that young children who are shy and highly observant develop the ability to think about and understand others' mental states more quickly than less shy children (Mink, Henning, & Aschersleben, 2014; Moore, Bosacki, & Macgillivray, 2011). Further, shy individuals' representations of others' thoughts and feelings about them strongly influence their overall well-being.

However, shy individuals appear biased in their perceptions of others' beliefs. For example, in a study examining dyadic interactions between shy and non-shy young adults, shy individuals rated themselves as less competent than their interaction partner actually reported they were (Melchior & Cheek, 1990). Over developmental time, these biases may have a snowballing effect on shyness, as demonstrated by the fact that adolescents who report low levels of social self-efficacy increase in their self-reported shyness over a 2-year period relative to shy adolescents without negative self-perceptions (Caprara, Steca, Cervone, & Artistico, 2003).

The goal of this chapter is to synthesize literatures on the effects of shyness on (a) children's *own* thoughts, emotions, and behaviors as well as (b) their *social partners*' thoughts, emotions, and behaviors. We propose that these transactions take place continually over development and that they shape shy children's unique developmental trajectories (Fig. 1). We review these transactional processes in the context of critical socialization relationships with (1) teachers, (2) peers, and (3) parents.

Shyness in School

Schools provide one of the most salient and enduring socialization contexts for children and adolescents. In addition to providing a context for peer socialization, school provides children the opportunity to form relationships with teachers. Teachers are integral to a child's school experience as they shape not only the academic but the social environment of the classroom, a role referred to as the "invisible hand" (Coplan & Rudasill, 2016). Research on the impact of temperamental shyness on school adjustment supports a transactional model in which shyness impacts children's beliefs, behaviors, and participation in school-based activities and, in turn, children's shyness influences teachers' and peers' beliefs and behaviors.

A variety of literatures suggest that shyness is a risk factor for school-adjustment difficulties (Kalutskaya, Archbell, Moritz Rudasill, & Coplan, 2015). Specifically, shyness is associated with poor attitudes toward school (e.g., Eggum-Wilkens, Valiente, Swanson, & Lemery-Chalfant, 2014), difficulties with classroom-based peer relationships (Buhs, Rudasill, Kalutskaya, & Griese, 2015), less engagement in formal and informal learning opportunities (Hughes & Coplan, 2010), poor academic achievement (Vitiello, Moas, Henderson, Greenfield, & Munis, 2012), and fewer positive interactions with teachers (Arbeau, Coplan, & Weeks, 2010; Hughes & Coplan, 2010). By early elementary school, shy children who are identified by their teachers and parents as experiencing less popularity or acceptance by their peers begin reporting that they like attending school less than their same-aged peers (Eggum-Wilkens et al., 2014). The early impact of shyness on attitudes, behaviors, and participation in school likely sets in motion a transactional cycle between teachers and shy children that impacts their later school adjustment.

Shyness is moderately associated with poor academic achievement, based on both teacher ratings and direct assessments, beginning in preschool. For example, at the beginning of the school year, preschoolers rated as more fearful and wary of novelty by their teacher scored lower on standardized math and language assessments relative to their more outgoing peers (Vitiello et al., 2012). Similarly, Spere and Evans (2009) found that shyness was associated with lower vocabulary, verbal fluency, and phonological awareness in kindergarten and first grade students. It is important to note, however, that some of these deficits may have to do with the context in which skills are assessed. Shy children performed more poorly than their

peers on a vocabulary task when it was completed in a face-to-face setting with an unfamiliar evaluator, but not when they completed the task in an anonymous group setting (Crozier & Hostettler, 2003), suggesting that altering the testing context may minimize the discrepancy between shy children's academic abilities and test performance.

One of the primary mechanisms through which academic achievement may be impacted by shyness is via the influence of shyness on children's classroom engagement. Social-evaluative concerns may make children hesitant to engage socially and with learning materials in the classroom. Over time, social-evaluative concerns may be further compounded by a history of poor peer relationships creating a cycle of increasing disengagement. For example, children who were rated by their teacher as experiencing peer rejection in kindergarten were less engaged in the first grade classroom relative to children who did not experience early rejection (Buhs et al., 2015; Ladd, Birch, & Buhs, 1999). By high school, shyness is associated with teacher reports of passivity which is characterized by a reluctance to present ideas to peers and teachers and a hesitancy to become actively involved in classroom discussions and projects (Paulsen & Bru, 2008).

Another mechanism through which social-evaluative concerns can affect academic achievement is through their direct impact on attention and learning (see the chapter "Behavioral Inhibition and the Associative Learning of Fear by Reynolds et al."; Eysenck, 1988; Pacheco-Unguetti, Acosta, Callejas, & Lupiáñez, 2010; Walker & Henderson, 2012). Specifically, shyness is associated with heightened self-focused attention, particularly in social-evaluative contexts, which detracts attention from ongoing activities and interactions (Deiters, Stevens, Hermann, & Gerlach, 2013). The inability to flexibly shift attention has been isolated as a critical mechanism linking shyness to a variety of maladaptive outcomes (Gramszlo, Geronimi, Arellano, & Woodruff-Borden, 2017; White, McDermott, Degnan, Henderson, & Fox, 2011). We hypothesize that this may be particularly true in classroom contexts where it is essential to rapidly and flexibly shift between internally and externally focused attention.

The verbal reticence that characterizes behavioral inhibition and shyness also directly impacts classroom engagement and participation. For example, shy children are less likely to participate in class discussions (Coplan et al., 2004) and take part in fewer one-on-one interactions with teachers and peers (Evans, 2010). When directly asked to produce a story to present to others, shy children's stories are shorter and show less varied vocabulary than their non-shy peers, even after vocabulary skills are controlled (Crozier & Perkins, 2002). During whole-class activities, shy children take longer to speak, and when they do speak, they are more likely to make sudden, impulsive remarks (Crozier & Hostettler, 2003).

Importantly, as early as kindergarten, classroom engagement is a critical predictor of academic growth and achievement (e.g., Ladd et al., 1999), suggesting that shy children's limited engagement places them at risk for poor academic outcomes (Kalutskaya et al., 2015). Given this connection between shyness, engagement, and achievement, it is not surprising that factors that support classroom engagement, including more advanced vocabulary skills, are particularly beneficial for shy students.

Coplan and Armer (2005) reported that shy preschoolers with greater vocabulary skills were rated by teachers as better adjusted in the classroom than were shy children with less well-developed vocabularies.

Teachers' attributions may affect their evaluation of shy students' abilities and, in turn, the way they interact with these students. In terms of attributions, teachers tend to believe that shy children are less intelligent, and they predict that shy students will do more poorly academically relative to more outgoing students (Coplan, Hughes, Bosacki, & Rose-Krasnor, 2011), despite the fact there is no evidence to date suggesting differences in general IQ between shy and non-shy students (Coplan & Rudasill, 2016). These biases reflect teachers' preconceived notions about shyness, as even preservice teachers (teachers who have not yet begun their careers) believe that shy children have lower language abilities and they predict that shy children will achieve less well academically, relative to more outgoing children (Deng et al., 2017). Interestingly, Coplan et al. (2011) found that these biases were particularly strong in teachers who rated their own personality as non-shy. That is, non-shy teachers were more likely than shy teachers to view shy children as less academically competent than non-shy children. Beyond concerns regarding academic abilities, teachers express worry for shy children and anticipate that these children will experience negative peer interactions, such as being ignored by fellow peers (Coplan, Bullock, Archbell, & Bosacki, 2015). Consistent with our transactional model, Coplan and Rudasill (2016) hypothesized that overtime, shy children may "live down" to the implicit and explicit concerns and expectations of their teachers.

One reason for these biased attributions regarding shy children's academic abilities may be teachers' interpretations of the causes of shy children's lowered classroom engagement (Asendorpf & Meier, 1993; Hughes & Coplan, 2010). Teachers may assume that shy children's limited engagement and participation in classroom activities reflect lower intelligence, a lack of knowledge, and less interest in learning (Arbeau & Coplan, 2007). At the same time, a lack of engagement may limit teachers' opportunities to objectively evaluate shy children's academic skills. A great deal of academic evaluation comes from presentations and group discussions. If a shy child does not participate, they will have fewer formal opportunities to demonstrate their knowledge relative to their more outgoing peers. The distress associated with public presentation may directly impede shy children's performance during common classroom activities. This may lead teachers to underestimate the abilities of shy students. Hughes and Coplan (2010) reported that shyness was inversely related to mathematics and reading skills as assessed by teacher ratings, but not when assessed using performance on standardized tests.

Teachers' perceptions and attributions also impact the quantity and quality of their direct interactions with shy children. Specifically, teachers' beliefs affect their decisions and behaviors in the classroom and their responses to children's bids for assistance and attention (Arbeau & Coplan, 2007). There is a mixed literature describing the actual behaviors teachers display when interacting with shy students.

In a detailed analysis of preschool teachers' classroom behaviors, Evans (1992) described teachers' conversational style with shy students as highly controlling, as characterized by repetitive and directive questioning. Teachers also report resorting to excessively praising shy children for classroom participation in an attempt to decrease shy children's classroom discomfort and to encourage continued participation. Interestingly, neither excessive control nor praise results in increased student participation. Evans (1992) noted that 62% of teachers' direct questions were either not answered or inadequately addressed. In addition, Coplan and Rudasill (2016) noted that excessive praise draws unwanted attention to shy students, creating a cycle of continuing discomfort. Furthermore, in a detailed analysis of teacher-reported classroom practices, teachers reported using more peer-focused (involving classmates in learning and problem-solving) and indirect social learning (e.g., involving other students in problem-solving) strategies with shy children as a means of fostering engagement (Coplan et al., 2011).

This preference for using social learning strategies over more "high-powered" strategies with shy students was reported by both experienced teachers and teachers just beginning their careers (Deng et al., 2017). It is interesting that the findings on teachers' classroom behaviors differ depending on whether they are directly observed or asked what they believe to be the best practice. The fact that teachers use high-powered strategies with shy students, despite reporting that they do not believe them to be effective, may suggest that high-powered strategies are elicited as an immediate reaction to try to alleviate shy students' discomfort in the moment. The data suggest, though, that these strategies are unlikely to be beneficial in the long run.

In contrast to the literature describing teachers' negative perceptions of shy children and poor academic outcomes, there is a small literature documenting positive effects of shyness on school adjustment. For example, teachers rate shy children as more cooperative and better regulated (Rudasill & Konold, 2008), less likely to disrupt classroom activities (Rimm-Kaufman & Kagan, 2005), and highly detail-oriented and sensitive to their environment (Coplan & Rudasill, 2016). Teachers also report that they are attentive and warm with shy students (Deng et al., 2017). Shy students' abilities to work quietly and without disrupting classroom activities may place fewer demands on teachers' time and in turn lead to fewer student-teacher conflicts (Rudasill, 2011; Rudasill & Rimm-Kaufman, 2009; Valiente, Swanson, & Lemery-Chalfant, 2012). While preschool-aged shy children receive *more* teacher-initiated interactions than their non-shy peers, older shy children (1st through 3rd grade) receive significantly *fewer* teacher-initiated interactions than their non-shy peers (Kalutskaya et al., 2015). While it could be that teachers pay less attention to older shy students, a more optimistic interpretation could be that teachers actively encourage more independence in shy students as they age. With findings showing that overly controlling and overly warm teaching styles do not benefit shy children, encouraging independence may be beneficial for shy students.

In terms of positive effects of shyness on academic achievement, DiLalla, Marcus, and Wright-Phillips (2004) found that anxious elementary school students, who were high in their social-evaluative concerns, showed higher rates of academic

success in high school than did their non-anxious peers. This suggests that there could be a curvilinear relation between social-evaluative concerns and academic success such that if these concerns are not too extreme, they may motivate students inside and outside the classroom. Another line of research suggests that there may be specific classroom practices that minimize the negative effects of shyness by optimizing classroom engagement and learning. Vitiello et al. (2012) reported that when in classrooms with high instructional support (e.g., teacher promotes higher order cognitive skills and provides informative feedback), shy preschoolers displayed more rapid gains in language and literacy over the course of a school year than did their more outgoing peers. Pulling these findings together suggests that shy students are better able to regulate their own fear and social-evaluative concerns when in classrooms with clear and well-structured expectations and learning goals. We believe that future research focused on the structural and instructional characteristics of classrooms that optimize learning in shy students at different points of development is of utmost importance for maximizing the goodness-of-fit between shy students and their learning environments.

In addition to the direct effect of teachers' behaviors on shy children's participation in the classroom, the quality of the student-teacher relationship serves as an important buffer against the negative impact of shyness on academic adjustment. Consistent with a transactional model of development, student-teacher relationship quality significantly impacts the developmental trajectories of shy children. Shy children who experience close, warm, and sensitive relationships with their teachers are more engaged in the classroom and have fewer social/emotional difficulties (Arbeau et al., 2010; Buhs et al., 2015). This pattern carries through into high school, as the association between shyness and classroom engagement is moderated by students' perceptions of teacher support. Specifically, shy students who feel well supported by their teachers report being more actively engaged in classroom activities than shy students who do not feel supported (Paulsen & Bru, 2008). Unfortunately, at least at younger ages, many shy children form *dependent* relationships with teachers that are characterized by excessive clinginess and question-asking from the student (Arbeau & Coplan, 2007). Dependent student-teacher relationships are associated with more negative academic and peer/social outcomes for shy children. Together these data suggest that teachers face the challenge of being warm and responsive to shy students while simultaneously fostering independent, active engagement in classroom activities.

Shyness and Peer Relationships

While the previous section focused on classroom engagement and student-teacher relationships, the quality and quantity of shy children's interactions with peers are another critical mechanism linking shyness to adjustment more generally. Beginning in the toddler years, behavioral inhibition is predictive of heightened social reticence with unfamiliar peers (Fox, Henderson, Rubin, Calkins, & Schmidt, 2001;

Kochanska & Radke-Yarrow, 1992; Rubin, Burgess, & Hastings, 2002). Reticence reflects the same approach-avoidance conflict underlying shyness in which there is a desire and interest in interacting with others, but these approach motivations are counteracted by strong fear or avoidance motivations. This motivational conflict leads to a pattern of unoccupied and onlooking behavior, in which young children watch others carefully but are hesitant to join in.

Importantly, reticent children tend to have their attention captured by the novel social context, and although they are not joining in play, they are also not engaging in meaningful solitary play. Rather, there is an empty wandering quality to their behavior. These shy children want to be involved in peer activities but are held back by their own fear and discomfort in response to social situations (Coplan et al., 2004). In their chapter in this volume, Rubin, Barstead, Smith, and Bowker (see the chapter "Peer Relations and the Behaviorally Inhibited Child") provide a comprehensive review and analysis of the impact of childhood reticence or shyness on the quality of children's peer interactions, including their participation and integration into broader peer networks in later childhood and adolescence (see also the chapter "The Neural Mechanisms of Behavioral Inhibition" by Jarcho and Guyer). Therefore, we limit our review in this section to a discussion of the impact of shyness on *other children's* attributions and interpretations and, in turn, the behaviors peers direct toward shy children. We argue that these evocative effects are consistent with our transactional model of development and provide a critical mechanism through which shyness impacts later adjustment (see Fig. 1).

Peers' reactions to shy children are the result of a temporal sequence through which peers make inferences about responsibility (i.e., is it the child's fault they are shy?), which in turn trigger specific emotional responses (i.e., sympathy vs. anger), which lead to supportive versus rejecting behaviors (Chen, 2015; Graham & Hoehn, 1995). There is evidence to suggest that shy children are perceived of as less attractive friends in everyday contexts like school and in the neighborhood and that this negative bias becomes stronger across childhood (Vernberg, Abwender, Ewell, & Beery, 1992). Coplan and Armer (2007) reported that 5- and 6-year-olds expressed less liking of, and less interest in playing with, a hypothetical shy peer compared to a hypothetical socially competent peer (although they rated shy peers as more likable than unsociable or aggressive peers). Younger and Piccinin (1989) reported that 5th and 7th grade students rated socially withdrawn children as less likeable than did 1st grade students, suggesting that children are more sensitive to violations of social norms as they age and judge these violations more harshly.

A variety of data demonstrate that beginning in early childhood, shyness influences not only a child's own behavior and emotion but the behavior and emotion of their peers. Shy children display social reticence (Rubin et al., 2002) and limited spontaneous affect (Kochanska & Radke-Yarrow, 1992) with unfamiliar peers. In addition, maternal reports of social fear (an early correlate of behavioral inhibition and precursor of shyness) at 2 years of age predicted children's displays of less competent and assertive behavior with peers and the use of more subtle and indirect communication styles (McElwain, Holland, Engle, & Ogolsky, 2014). Given the impact of shyness on observable behaviors in novel social contexts (e.g., physical

proximity, communication style, spontaneous affect), it is not surprising that peers react by changing their own behaviors and emotions during interactions with shy playmates.

Walker, Degnan, Fox, and Henderson (2015) examined the impact of maternal reports of social fear at 2 years of age on toddlers' own behaviors, and the behaviors of a previously unfamiliar play partner, during a social interaction at age 3 years. Using the actor-partner interdependence model (APIM; (Kashy & Kenny, 2000) to explore dyadic effects of social fear on children's peer interactions, Walker and colleagues reported that social fear was associated with lower levels of children's own social engagement but also less social engagement (interest, positive affect, activity level) and dysregulated behavior (negative affect, aggression) in their play partners. In contrast, social fear was associated with children's own social wariness (wariness, unfocused behavior, adult contact) but not their play partners' social wariness. This pattern of reduced engagement, but also reduced dysregulation, suggests that children as young of 3 years of age are sensitive to the distress and uncertainty expressed by their socially fearful peers and adjust their behaviors accordingly. Over time, altered social interactions qualitatively change the social experiences of shy children. For example, if other children engage less and reduce their dysregulated behavior, shy children may lose out on critical opportunities to learn social scripts and how to navigate common social problems (Walker, Degnan, Fox, & Henderson, 2013; Walker & Henderson, 2012).

Consistent with Weiner's (1986, 1995) attribution theory of interpersonal relations, the *motivational and causal attributions* that peers make for shy behavior are critical factors that predicts peers' responses to shyness. In the Coplan and Armer (2007) analysis, the more positive views regarding the social value of shy peers (vs. unsociable or aggressive peers) likely arise from peers' attributions for shy behavior and their associated emotional reactions. Specifically, hypothetical shy children were viewed by the children in the study as not behaving that way intentionally and as being higher in their motivation to interact with other children compared to unsociable and aggressive peers. In turn, children in the study reported feeling significantly more *sympathy* for hypothetical shy children than they did for hypothetical unsocial and aggressive children. This level of understanding and sympathy appears to change, though, with age.

Barnett, Wadian, Sonnentag, and Nichols (2015) examined the role of fault attributions in predicting children's anticipated responses to hypothetical peers. Children in 5th and 6th grade generally attributed the onset of shyness equally to the peer him-/herself and to his/her biology (but less to parents). However, when asked about the causes for perpetual shyness, they assigned the bulk of the blame to the peer him-/herself. These causal attributions, in turn, predicted children's anticipated responses to shy peers. Specifically, the more children believed that shy peers were at fault for their own shyness, the less favorably children anticipated they would respond to these peers. Together, these data suggest that children make sophisticated judgments regarding the motivations for others' behaviors, that the judgments regarding shyness change with development, and that across development, these judgments serve the function of regulating peers' behaviors and emotions in response to shy peers.

Despite these differences in the social experiences of shy children, a vast body of research suggests that shy children are as likely as their non-shy peers to establish reciprocated and stable best friendships (Ladd & Burgess, 2001; Oh et al., 2008; Rubin, Wojslawowicz, Rose-Krasnor, Booth-LaForce, & Burgess, 2006). While childhood shyness does not influence the formation, prevalence, or maintenance of friendships, there is some evidence to suggest that friendships may not be experienced as positively by shy children relative to their non-shy peers. Specifically, shy children tend to form lower-quality friendships, and their friends tend to be other withdrawn and/or victimized children (Rubin et al., 2006; Schneider, 1999). The nature and quality of shy children's friendships are important predictors of their developmental trajectory both in terms of social adaptation and emotional well-being. Friendships provide an important buffer against the development of internalizing symptoms in shy adolescents. Specifically, shy adolescents who have at least one close friendship develop significantly fewer depressive symptoms than do shy adolescents with no friendships (Bukowski, Laursen, & Hoza, 2010; Laursen, Bukowski, Aunola, & Nurmi, 2007). Similarly, Oh et al. (2008) reported that having unstable friendships, no mutual best friendships, or a friendship with a withdrawn friend all led to increases in anxious withdrawal over the transition to middle school.

In later childhood and adolescence, as discussed by Rubin and colleagues (see the chapter "Peer Relations and the Behaviorally Inhibited Child"), participation in larger peer groups and networks is critical for acquiring and practicing the specific norms of communicating and behaving with same-aged peers. Given the detailed review of the experiences of shy children and adolescents in chapter "Peer Relations and the Behaviorally Inhibited Child", we will not review that literature here. However, given our goal of describing the social worlds of shy children and adolescents, and in identifying social experiences that can provide a buffer for shy children, we will briefly review an interesting literature that is emerging on the nature and consequences of online social interactions for shy adolescents.

Over the last 10 years, social media has taken on a central role in the socialization experiences of all children and adolescents, regardless of their temperament. Emerging data suggest, however, that social media use may provide a particularly attractive networking forum for shy individuals that is associated with both risks and benefits. Li et al. (2016) examined the impact of several temperament traits (effortful control, sensation seeking, anger/frustration, and shyness) on adolescents' problematic or excessive Internet use (or Internet dependency) and their affiliation with deviant peers. Shyness, along with sensation seeking and anger, was positively associated with problematic Internet use. For adolescents high in sensation seeking and anger, associations with problematic Internet use were mediated through their tendencies to affiliate with deviant peers. This was not, however, the case for adolescents high in shyness.

For shy adolescents, the association with excessive use was driven by their tendencies to *not* affiliate with deviant peers. The different social mechanisms leading to excessive use for shy adolescents suggest that they use the Internet for qualitatively different reasons than their peers. Li et al. (2016) hypothesized that the Internet may provide a substitute for direct social interactions for shy adolescents but cautioned that the time spent in online communications may prevent shy

adolescents from improving their in vivo social skills over time—a developmental model referred to as a *poor-get-poorer perspective* (Sheldon, Abad, & Hinsch, 2011; Van Zalk, Van Zalk, Kerr, & Stattin, 2014).

In contrast to this view, Valkenburg and Peter (2009) emphasized the potential *positive* impact of online social interactions by focusing on the fact that online social interactions may provide a safe and controllable environment for adolescents to practice and experience social relationships. This *social compensation* perspective suggests that positive online social experiences can impact self-esteem and the quality of both online and offline exclusive friendships. Consistent with this perspective, Van Zalk and Kerr (2011) found that over a 24-month period, shy adolescents who reported exclusive online friendships increased their self-esteem and in turn, increased self-esteem predicted the formation more conjoint (online/offline) and offline exclusive friendships. These findings suggest that the slower-paced and more controlled interactions that take place online (i.e., one has time to consider multiple interpretations of others' comments and to plan one's own responses unlike one can during in vivo interactions) may be particularly beneficial for shy adolescents. This may provide a critical context for developing age-appropriate skills and scripts in a way that supports not only online but offline exclusive friendships as well.

Shyness and Family Relationships

Children's interactions with their parents provide the most proximal and enduring socialization experiences (see the chapter "Behavioural Inhibition and the Prevention of Internalising Distress in Early Childhood" by Rapee and Bayer). Historically, developmental science and lay interpretations of family influences on development focused on the effects of parenting beliefs and behaviors *on* the child. Due in large part to the study of the impact of child characteristics on family interactions (e.g., Bell, 1968), current developmental theories emphasize the transactional nature of family processes in the sense that children affect parents, parents affect children, and this back-and-forth influences parents, children, and their relationship over development. That is, families are best conceptualized as a dynamic system in which each part of the system is understood with reference to the other parts (Lamb & Lewis, 2005; McHale, 2007).

Parents' personalities and accumulated experiences provide a framework through which their parenting beliefs, interpretations, and behaviors are organized, and data suggest that shy children's family environments are unique from birth (and likely prenatally as well). Shyness is a highly heritable temperament trait (e.g., DiLalla, Kagan, & Reznick, 1994; Plomin et al., 1993; Robinson, Kagan, Reznick, & Corley, 1992), with infants of mothers who meet criteria for an anxiety disorder being more behaviorally and physiologically reactive to novelty compared to infants of mothers without anxiety disorders (Reck, Müller, Tietz, & Möhler, 2013).

Beyond affecting infants' initial reactions to novelty, parental anxiety influences patterns of stability in temperament over time. For example, when mothers' self-reported higher rates of depression and anxiety, their child's reactions to novelty at age 2 were more strongly related to social withdrawal in later childhood compared to equally reactive toddlers whose mothers did not report elevated symptoms (Degnan, Henderson, Fox, & Rubin, 2008). The impact of parent characteristics on the stability of behavioral inhibition is not limited to parents with clinically elevated symptoms. For example, observed behavioral inhibition at age 3 is more strongly associated with anxiety symptoms at age 9 when children have parents who retrospectively report experiencing more behavioral inhibition in their own childhood (Stumper et al., 2017).

While genetics likely account for higher initial levels of reactivity in the offspring of formerly inhibited or anxious parents, the impact of parental characteristics on stability over time suggests a critical mediating role of parenting beliefs and behaviors. Specifically, parents' own experiences likely affect their evaluations of the social context and their perceptions of their children's behaviors and emotions. Together these biases result in qualitatively different parenting behaviors. For example, anxious parents may avoid novel social situations, model certain behaviors in novel social situations, or emphasize potential risks of novel situations which together impact children's inhibition and wariness in response to novelty (Degnan et al., 2008; Lindhout et al., 2009). Anxious mothers who display greater avoidant behavior perceive their own 4- to 7-month-old infants as being more distressed by novel stimuli (Reck et al., 2013), and mothers' self-reported neuroticism predicts more overprotective parenting (Coplan, Reichel, & Rowan, 2009).

While a parent's own experiences guide their beliefs and behaviors, children's temperament traits also elicit specific parenting behaviors. Childhood shyness tends to elicit overprotectiveness from parents (Coplan et al., 2009). Overprotectiveness, or over-solicitousness, is a parenting style in which parents are described as *over*-involved with their child, remaining hyper-vigilant to their child and his/her environment, acting on the child's behalf (even when the child does not need help), and actively discouraging their child's independence (Thomasgard & Metz, 1993). Mothers who view their children as being highly fearful of social situations are more likely to respond in ways that involve "taking over" the situation and limiting chances for the child to solve common, every day social problems (e.g., joining a playgroup) by themselves (Hastings & Rubin, 1999).

Expressions of wariness and fear in children tend to elicit protective responses from parents, with parents feeling the need to protect their seemingly vulnerable child from potential harm (Rubin, Nelson, Hastings, & Asendorpf, 1999). The association between shyness and overprotectiveness is particularly strong when shyness is assessed using maternal reports as opposed to objective laboratory observations (Hastings & Rubin, 1999), suggesting that parents' perceptions and beliefs about their children drive their parenting behaviors. Rubin et al. (1999) found that this connection between beliefs and behaviors emerges over time, with parents' perceptions of shyness at age 2 predicting protective parenting behaviors that limited their child's exploration and independence at age 4. Perhaps the biggest challenge in

addressing the parenting behaviors of shy children is that overprotectiveness comes with the best of intentions. That is, overprotectiveness is not generally done as a way to control a child, rather it tends to come from a place where the parent believes that they are providing guidance, support, and affection (Padilla-Walker & Nelson, 2012).

While these protective parenting practices may minimize child and parent distress in the immediate context, they have more negative long-term consequences. Specifically, there are both direct and indirect consequences of overprotective parenting for shy children. When parents quickly jump in to "act for" their child, the child is prevented from actively engaging in, and learning from, these everyday challenges. Rubin et al. (1999) hypothesized that limited opportunities to explore and problem solve may lead to increases in observed wariness over time. That is, the child does not get to learn from the experience of directly solving every day social problems. Over time, these cycles will likely serve to maintain or even increase the amount of wariness and fear shy children experience in novel contexts (Chen & Schmidt, 2015). Several lines of empirical evidence support this notion.

For example, observed behavioral inhibition at age 3 was more highly predictive of observed behavioral inhibition at age 6 for children with mothers who used overprotective parenting practices (Johnson et al., 2016). Similarly, maternal ratings of social fear at 9 months of age predicted low levels of observed social engagement with an unfamiliar peer at 2 years. However, this association was significantly stronger when mothers were observed to display high levels of intrusiveness and low levels of sensitivity when with their toddler in novel contexts (Penela, Henderson, Hane, Ghera, & Fox, 2012). Similar relations hold in later childhood and adolescence, where the association between behavioral inhibition in infancy and childhood and later symptoms of social anxiety is significantly moderated by observed maternal overcontrol (Lewis-Morrarty et al., 2012). Specifically, childhood behavioral inhibition was more strongly associated with social anxiety symptoms in adolescence when mothers were coded as displaying excessively high levels of control during a free play interaction with their child at age 7. It is interesting to note the similarities in parents' and teachers' reactions to shy children—expressions of fear and wariness seem to elicit warm, yet controlling, responses in both school and home contexts. While these responses may alleviate the child's (and the adults') immediate distress, they appear to do little to foster the development of independent, constructive coping skills in children.

Indirect consequences of overprotective and controlling parenting include the impact of these experiences on children's representations of their own abilities to competently affect social situations in the future and their interpretations of the parents' motivations. That is, a child may interpret the parent's behavior as a direct signal of rejection or disapproval or an indirect signal that the child is not able to manage new or challenging social situations on their own. Some work has examined how shy children think their parents perceive them and how they interpret their parenting decisions. Shy adolescents perceive their parents as rejecting, low in warmth, and intrusive (Van Zalk & Kerr, 2011), perceptions that may fuel a continuing cycle of shyness and poor coping over time. Similarly, emerging adults who

were high in behavioral inhibition and who perceived their parents to be high in psychological control endorsed using maladaptive coping responses to interpersonal stress including active avoidance (Abaied & Emond, 2013).

A more optimistic interpretation of the above findings is that parenting behaviors that support the independence and autonomy of shy children may support the development of specific self-regulatory strategies that break down the connections between early shyness and later social and emotional maladjustment. This line of reasoning parallels a vast educational psychology literature that demonstrates the beneficial effects of fostering students' independence on standardized assessments of academic achievement and global adjustment (Grolnick & Ryan, 1989). Consistent with this, shy toddlers who received encouraging statements from their mothers during play interactions with unfamiliar peers were less socially wary relative to shy toddlers whose mothers responded with high levels of warmth and praise (Grady & Karraker, 2014).

Conclusions and Future Directions

The goal of this chapter was to describe the social worlds of behaviorally inhibited children. To do so, we organized our review around a transactional model of development in which we propose that early behavioral inhibition traits and their later manifestations in shyness impact children's perceptions of, and behaviors in, a variety of social contexts. Importantly, behavioral inhibition and later shyness elicit unique beliefs and behaviors in a variety of social partners. Over time, we propose that the ongoing transactions between shy children's own beliefs and behaviors and their social partners' beliefs and behaviors affect patterns of both developmental continuity and discontinuity. While we separated our review into three parts (school, peers, parents), implicit in our model is the awareness that these critical contexts are part of a larger dynamic system in which development takes place. As such, it is important for future research to consider the impact of the bidirectional influences between these systems on the development of shyness.

For example, how do parents' responses to their child's shyness impact children's reactions in school and peer contexts? What are the implications of having adult socialization figures (e.g., parents vs. teachers) with different perceptions of shyness for children's adjustment across contexts? In our synthesis of these literatures, we hypothesized that social experiences affect, and are affected by, individual differences in attention and cognition. For example, we hypothesized that social-evaluative concerns draw attention inward and, in turn, limit children's abilities to flexibly attend to their social worlds. We believe that future research focusing on the connections between shyness and basic attention processes as they occur in naturalistic environments, such as classrooms, will be critical for informing our understanding of the mechanisms linking shyness to altered social experiences. Finally, we focused our review primarily on childhood and adolescence. However, we believe it is of utmost basic and applied relevance to understand how shyness

impacts the cognitions and behaviors of adults and their social interaction partners in other salient contexts (e.g., the workplace) as discussed by the chapter "The Temperamentally Shy Child as the Social Adult: An Exemplar of Multifinality by Poole, Tang, and Schmidt".

References

Abaied, J. L., & Emond, C. (2013). Parent psychological control and responses to interpersonal stress in emerging adulthood: Moderating effects of behavioral inhibition and behavioral activation. *Emerging Adulthood, 1*(4), 258–270. https://doi.org/10.1177/2167696813485737

Arbeau, K. A., & Coplan, R. J. (2007). Kindergarten teachers' beliefs and responses to hypothetical prosocial, asocial, and antisocial children. *Merrill-Palmer Quarterly, 53*(2), 291–318. https://doi.org/10.1353/mpq.2007.0007

Arbeau, K. A., Coplan, R. J., & Weeks, M. (2010). Shyness, teacher-child relationships, and socioemotional adjustment in grade 1. *International Journal of Behavioral Development, 34*(3), 259–269. https://doi.org/10.1177/0165025409350959

Asendorpf, J. B., & Meier, G. H. (1993). Personality effects on children's speech in everyday life: Sociability-mediated exposure and shyness-mediated reactivity to social situations. *Journal of Personality and Social Psychology, 64*(6), 1072–1083. https://doi.org/10.1037/0022-3514.64.6.1072

Barnett, M. A., Wadian, T. W., Sonnentag, T. L., & Nichols, M. B. (2015). Role of various fault attributions and other factors in children's anticipated response to hypothetical peers with undesirable characteristics. *Social Development, 24*(1), 113–127. https://doi.org/10.1111/sode.12087

Bell, R. Q. (1968). A reinterpretation of the direction of effects in studies of socialization. *Psychological Review, 75*(2), 81–95. https://doi.org/10.1037/h0025583

Brozina, K., & Abela, J. R. Z. (2006). Behavioural inhibition, anxious symptoms, and depressive symptoms: A short-term prospective examination of a diathesis-stress model. *Behaviour Research and Therapy, 44*(9), 1337–1346. https://doi.org/10.1016/j.brat.2005.09.010

Buhs, E. S., Rudasill, K. M., Kalutskaya, I. N., & Griese, E. R. (2015). Shyness and engagement: Contributions of peer rejection and teacher sensitivity. *Early Childhood Research Quarterly, 30*, 12–19. https://doi.org/10.1016/j.ecresq.2014.07.010

Bukowski, W. M., Laursen, B., & Hoza, B. (2010). The snowball effect: Friendship moderates escalations in depressed affect among avoidant and excluded children. *Development and Psychopathology, 22*(4), 749–757. https://doi.org/10.1017/S095457941000043X

Calkins, S. D., Fox, N. A., & Marshall, T. R. (1996). Behavioral and physiological antecedents of inhibited and uninhibited behavior. *Child Development, 67*(2), 523–540. https://doi.org/10.2307/1131830

Caprara, G. V., Steca, P., Cervone, D., & Artistico, D. (2003). The contribution of self-efficacy beliefs to dispositional shyness: On social-cognitive systems and the development of personality dispositions. *Journal of Personality, 71*(6), 943–970. https://doi.org/10.1111/1467-6494.7106003

Cheek, J. M., & Buss, A. H. (1981). Shyness and sociability. *Journal of Personality and Social Psychology, 41*(2), 330–339. https://doi.org/10.1037/0022-3514.41.2.330

Chen, X. (2015). Culture, types of social withdrawal, and children's beliefs: An integrative perspective. *British Journal of Developmental Psychology, 33*(2), 174–176. https://doi.org/10.1111/bjdp.12086

Chen, X., & Schmidt, L. A. (2015). Temperament and personality. In R. Lerner (Ed.), *Handbook of child psychology and developmental science*. Hoboken, NJ: John Wiley & Sons, Inc..

Coplan, R. J., & Armer, M. (2005). Talking yourself out of being shy: Shyness, expressive vocabulary, and socioemotional adjustment in preschool. *Merrill-Palmer Quarterly, 51*(1), 20–41. https://doi.org/10.1353/mpq.2005.0004

Coplan, R. J., & Armer, M. (2007). A "multitude" of solitude: A closer look at social withdrawal and nonsocial play in early childhood. *Child Development Perspectives, 1*(1), 26–32. https://doi.org/10.1111/j.1750-8606.2007.00006.x

Coplan, R. J., Bullock, A., Archbell, K. A., & Bosacki, S. (2015). Preschool teachers' attitudes, beliefs, and emotional reactions to young children's peer group behaviors. *Early Childhood Research Quarterly, 30*, 117–127. https://doi.org/10.1016/j.ecresq.2014.09.005

Coplan, R. J., Hughes, K., Bosacki, S., & Rose-Krasnor, L. (2011). Is silence golden? Elementary school teachers' strategies and beliefs regarding hypothetical shy/quiet and exuberant/talkative children. *Journal of Educational Psychology, 103*(4), 939–951. https://doi.org/10.1037/a0024551

Coplan, R. J., Prakash, K., O'Neil, K., & Armer, M. (2004). Do you "want" to play? distinguishing between conflicted shyness and social disinterest in early childhood. *Developmental Psychology, 40*(2), 244–258. https://doi.org/10.1037/0012-1649.40.2.244

Coplan, R. J., Reichel, M., & Rowan, K. (2009). Exploring the associations between maternal personality, child temperament, and parenting: A focus on emotions. *Personality and Individual Differences, 46*(2), 241–246. https://doi.org/10.1016/j.paid.2008.10.011

Coplan, R. J., Rubin, K. H., Fox, N. A., Calkins, S. D., & Stewart, S. L. (1994). Being alone, playing alone, and acting alone: Distinguishing among reticence and passive and active solitude in young children. *Child Development, 65*(1), 129–137. https://doi.org/10.2307/1131370

Coplan, R. J., & Rudasill, K. (2016). *Quiet at school: An educator's guide to shy children*. New York, NY: Teachers College Press.

Crozier, W. R. (1979). Shyness as a dimension of personality. *British Journal of Social & Clinical Psychology, 18*(1), 121–128. https://doi.org/10.1111/j.2044-8260.1979.tb00314.x

Crozier, W. R., & Hostettler, K. (2003). The influence of shyness on children's test performance. *British Journal of Educational Psychology, 73*(3), 317–328. https://doi.org/10.1348/000709903322275858

Crozier, W. R., & Perkins, P. (2002). Shyness as a factor when assessing children. *Educational Psychology in Practice, 18*(3), 239–244. https://doi.org/10.1080/0266736022000010267

Degnan, K. A., Henderson, H. A., Fox, N. A., & Rubin, K. H. (2008). Predicting social wariness in middle childhood: The moderating roles of childcare history, maternal personality and maternal behavior. *Social Development, 17*(3), 471–487. https://doi.org/10.1111/j.1467-9507.2007.00437.x

Deiters, D. D., Stevens, S., Hermann, C., & Gerlach, A. L. (2013). Internal and external attention in speech anxiety. *Journal of Behavior Therapy and Experimental Psychiatry, 44*(2), 143–149. https://doi.org/10.1016/j.jbtep.2012.09.001

Deng, Q., Trainin, G., Rudasill, K., Kalutskaya, I., Wessels, S., Torquati, J., & Coplan, R. J. (2017). Elementary preservice teachers' attitudes and pedagogical strategies toward hypothetical shy, exuberant, and average children. *Learning and Individual Differences, 56*, 85–95.

DiLalla, L. F., Kagan, J., & Reznick, J. S. (1994). Genetic etiology of behavioral inhibition among 2-year-old children. *Infant Behavior & Development, 17*(4), 405–412. https://doi.org/10.1016/0163-6383(94)90032-9

DiLalla, L. F., Marcus, J. L., & Wright-Phillips, M. (2004). Longitudinal effects of preschool behavioral styles on early adolescent school performance. *Journal of School Psychology, 42*(5), 385–401. https://doi.org/10.1016/j.jsp.2004.05.002

Eggum-Wilkens, N., Valiente, C., Swanson, J., & Lemery-Chalfant, K. (2014). Children's shyness, popularity, school liking, cooperative participation, and internalizing problems in the early school years. *Early Childhood Research Quarterly, 29*(1), 85–94. https://doi.org/10.1016/j.ecresq.2013.10.002

Evans, M. A. (1992). Control and paradox in teacher conversations with shy children. *Canadian Journal of Behavioural Science/Revue Canadienne Des Sciences Du Comportement, 24*(4), 502–516. https://doi.org/10.1037/h0078758

Evans, M. A. (2010). Language performance, academic performance, and signs of shyness: A comprehensive review. In K. H. Rubin & R. J. Coplan (Eds.), *The development of shyness and social withdrawal* (pp. 179–212). New York, NY: Guilford Press.

Eysenck, M. W. (1988). Anxiety and attention. *Anxiety Research, 1*(1), 9–15. https://doi.org/10.1080/10615808808248216

Fox, N. A., Henderson, H. A., Marshall, P. J., Nichols, K. E., & Ghera, M. M. (2005). Behavioral inhibition: Linking biology and behavior within a developmental framework. *Annual Review of Psychology, 56*, 235–262. https://doi.org/10.1146/annurev.psych.55.090902.141532

Fox, N. A., Henderson, H. A., Rubin, K. H., Calkins, S. D., & Schmidt, L. A. (2001). Continuity and discontinuity of behavioral inhibition and exuberance: Psychophysiological and behavioral influences across the first four years of life. *Child Development, 72*(1), 1–21. https://doi.org/10.1111/1467-8624.00262

Grady, J. S., & Karraker, K. (2014). Do maternal warm and encouraging statements reduce shy toddlers' social reticence? *Infant and Child Development, 23*(3), 295–303. https://doi.org/10.1002/icd.1850

Graham, S., & Hoehn, S. (1995). Children's understanding of aggression and withdrawal as social stigmas: An attributional analysis. *Child Development, 66*(4), 1143–1161. https://doi.org/10.2307/1131804

Gramszlo, C., Geronimi, E. M. C., Arellano, B., & Woodruff-Borden, J. (2017). Testing a cognitive pathway between temperament and childhood anxiety. *Journal of Child and Family Studies, 27*, 580–590. https://doi.org/10.1007/s10826-017-0914-2

Grolnick, W. S., & Ryan, R. M. (1989). Parent styles associated with children's self-regulation and competence in school. *Journal of Educational Psychology, 81*(2), 143–154. https://doi.org/10.1037/0022-0663.81.2.143

Hastings, P. D., & Rubin, K. H. (1999). Predicting mothers' beliefs about preschool-aged children's social behavior: Evidence for maternal attitudes moderating child effects. *Child Development, 70*(3), 722–741. https://doi.org/10.1111/1467-8624.00052

Hughes, K., & Coplan, R. J. (2010). Exploring processes linking shyness and academic achievement in childhood. *School Psychology Quarterly, 25*(4), 213–222. https://doi.org/10.1037/a0022070

Henderson, L., Zimbardo, P., & Carducci, B. (2010). Shyness. In The Corsini Encyclopedia of Psychology. http://doi.org/10.1002/9780470479216.corpsy0870

Johnson, V. C., Olino, T. M., Klein, D. N., Dyson, M. W., Bufferd, S. J., Durbin, C. E., … Hayden, E. P. (2016). A longitudinal investigation of predictors of the association between age 3 and age 6 behavioural inhibition. *Journal of Research in Personality, 63*, 51–61. https://doi.org/10.1016/j.jrp.2016.04.008

Kagan, J., Reznick, J. S., Clarke, C., Snidman, N., & Garcia-Coll, C. (1984). Behavioral inhibition to the unfamiliar. *Child Development, 55*(6), 2212–2225. https://doi.org/10.2307/1129793

Kalutskaya, I. N., Archbell, K. A., Moritz Rudasill, K., & Coplan, R. J. (2015). Shy children in the classroom: From research to educational practice. *Translational Issues in Psychological Science, 1*(2), 149–157. https://doi.org/10.1037/tps0000024

Kashy, D. A., & Kenny, D. A. (2000). The analysis of data from dyads and groups. In H. T. Reis & C. M. Judd (Eds.), *Handbook of research methods in social and personality psychology* (pp. 451–477). New York, NY: Cambridge University Press.

Kochanska, G., & Radke-Yarrow, M. (1992). Inhibition in toddlerhood and the dynamics of the child's interaction with an unfamiliar peer at age five. *Child Development, 63*(2), 325–335. https://doi.org/10.2307/1131482

Ladd, G. W., Birch, S. H., & Buhs, E. S. (1999). Children's social and scholastic lives in kindergarten: Related spheres of influence? *Child Development, 70*(6), 1373–1400. https://doi.org/10.1111/1467-8624.00101

Ladd, G. W., & Burgess, K. B. (2001). Do relational risks and protective factors moderate the linkages between childhood aggression and early psychological and school adjustment? *Child Development, 72*(5), 1579–1601. https://doi.org/10.1111/1467-8624.00366

Lamb, M. E., & Lewis, C. (2005). The role of parent-child relationships in child development. In M. H. Bornstein & M. E. Lamb (Eds.), *Developmental science: An advanced textbook* (pp. 429–468). Mahwah, NJ: Lawrence Erlbaum Associates.

Laursen, B., Bukowski, W. M., Aunola, K., & Nurmi, J. (2007). Friendship moderates prospective associations between social isolation and adjustment problems in young children. *Child Development, 78*(4), 1395–1404. https://doi.org/10.1111/j.1467-8624.2007.01072.x

Lewis-Morrarty, E., Degnan, K. A., Chronis-Tuscano, A., Rubin, K. H., Cheah, C. S. L., Pine, D. S., … Fox, N. A. (2012). Maternal over-control moderates the association between early childhood behavioral inhibition and adolescent social anxiety symptoms. *Journal of Abnormal Child Psychology, 40*(8), 1363–1373. https://doi.org/10.1007/s10802-012-9663-2

Lindhout, I. E., Markus, M. T., Borst, S. R., Hoogendijk, T. H. G., Dingemans, P. M. A. J., & Boer, F. (2009). Childrearing style in families of anxiety-disordered children: Between-family and within-family differences. *Child Psychiatry and Human Development, 40*(2), 197–212. https://doi.org/10.1007/s10578-008-0120-y

Li, X., Newman, J., Li, D., & Zhang, H. (2016). Temperament and adolescent problematic Internet use: The mediating role of deviant peer affiliation. *Computers in Human Behavior, 60*, 342–350. http://dx.doi.org/10.1016/j.chb.2016.02.075

McElwain, N. L., Holland, A. S., Engle, J. M., & Ogolsky, B. G. (2014). Getting acquainted: Actor and partner effects of attachment and temperament on young children's peer behavior. *Developmental Psychology, 50*(6), 1757–1770. https://doi.org/10.1037/a0036211

McHale, J. P. (2007). *Charting the bumpy road of coparenthood*. Washington, DC: Zero to Three.

Melchior, L. A., & Cheek, J. M. (1990). Shyness and anxious self-preoccupation during a social interaction. *Journal of Social Behavior & Personality, 5*(2), 117–130.

Mink, D., Henning, A., & Aschersleben, G. (2014). Infant shy temperament predicts preschoolers theory of mind. *Infant Behavior & Development, 37*(1), 66–75. https://doi.org/10.1016/j.infbeh.2013.12.001

Moore, C., Bosacki, S. L., & Macgillivray, S. (2011). Theory of mind and social interest in zero-acquaintance play situations. *Child Development, 82*(4), 1163–1172. https://doi.org/10.1111/j.1467-8624.2011.01602.x

Muris, P., van Brakel, A. M. L., Arntz, A., & Schouten, E. (2011). Behavioral inhibition as a risk factor for the development of childhood anxiety disorders: A longitudinal study. *Journal of Child and Family Studies, 20*(2), 157–170. https://doi.org/10.1007/s10826-010-9365-8

Oh, W., Rubin, K. H., Bowker, J. C., Booth-LaForce, C., Rose-Krasno, L., & Laursen, B. (2008). Trajectories of social withdrawal from middle childhood to early adolescence. *Journal of Abnormal Child Psychology, 36*(4), 553–566. https://doi.org/10.1007/s10802-007-9199-z

Pacheco-Unguetti, A., Acosta, A., Callejas, A., & Lupiáñez, J. (2010). Attention and anxiety: Different attentional functioning under state and trait anxiety. *Psychological Science, 21*(2), 298–304. https://doi.org/10.1177/0956797609359624

Padilla-Walker, L. M., & Nelson, L. J. (2012). Black hawk down? Establishing helicopter parenting as a distinct construct from other forms of parental control during emerging adulthood. *Journal of Adolescence, 35*(5), 1177–1190. https://doi.org/10.1016/j.adolescence.2012.03.007

Paulsen, E., & Bru, E. (2008). Social passivity and grades achieved among adolescents in junior high school. *School Psychology International, 29*(2), 248–262. https://doi.org/10.1177/0143034308090063

Penela, E. C., Henderson, H. A., Hane, A. A., Ghera, M. M., & Fox, N. A. (2012). Maternal caregiving moderates the relation between temperamental fear and social behavior with peers. *Infancy, 17*(6), 715–730. https://doi.org/10.1111/j.1532-7078.2012.00114.x

Pilkonis, P. A. (1977). The behavioral consequences of shyness. *Journal of Personality, 45*(4), 596–611. https://doi.org/10.1111/j.1467-6494.1977.tb00174.x

Plomin, R., Emde, R. N., Braungart, J. M., Campos, J., Corley, R., Fulker, D. W., … DeFries, J. C. (1993). Genetic change and continuity from fourteen to twenty months: The MacArthur longitudinal twin study. *Child Development, 64*(5), 1354–1376. https://doi.org/10.2307/1131539

Reck, C., Müller, M., Tietz, A., & Möhler, E. (2013). Infant distress to novelty is associated with maternal anxiety disorder and especially with maternal avoidance behavior. *Journal of Anxiety Disorders, 27*(4), 404–412. https://doi.org/10.1016/j.janxdis.2013.03.009

Rimm-Kaufman, S., & Kagan, J. (2005). Infant predictors of kindergarten behavior: The contribution of inhibited and uninhibited temperament types. *Behavioral Disorders, 30*(4), 331–347.

Robinson, J. L., Kagan, J., Reznick, J. S., & Corley, R. (1992). The heritability of inhibited and uninhibited behavior: A twin study. *Developmental Psychology, 28*(6), 1030–1037. https://doi.org/10.1037/0012-1649.28.6.1030

Rubin, K. H., Burgess, K. B., & Hastings, P. D. (2002). Stability and social-behavioral consequences of toddlers' inhibited temperament and parenting behaviors. *Child Development, 73*(2), 483–495. https://doi.org/10.1111/1467-8624.00419

Rubin, K. H., Nelson, L. J., Hastings, P., & Asendorpf, J. (1999). The transaction between parents' perceptions of their children's shyness and their parenting styles. *International Journal of Behavioral Development, 23*(4), 937–958. https://doi.org/10.1080/016502599383612

Rubin, K. H., Wojslawowicz, J. C., Rose-Krasnor, L., Booth-LaForce, C., & Burgess, K. B. (2006). The best friendships of shy/withdrawn children: Prevalence, stability, and relationship quality. *Journal of Abnormal Child Psychology, 34*(2), 143–157. https://doi.org/10.1007/s10802-005-9017-4

Rudasill, K. M. (2011). Child temperament, teacher–child interactions, and teacher–child relationships: A longitudinal investigation from first to third grade. *Early Childhood Research Quarterly, 26*(2), 147–156. https://doi.org/10.1016/j.ecresq.2010.07.002

Rudasill, K. M., & Konold, T. R. (2008). Contributions of children's temperament to teachers' judgments of social competence from kindergarten through second grade. *Early Education and Development, 19*(4), 643–666. https://doi.org/10.1080/10409280802231096

Rudasill, K. M., & Rimm-Kaufman, S. (2009). Teacher–child relationship quality: The roles of child temperament and teacher–child interactions. *Early Childhood Research Quarterly, 24*(2), 107–120. https://doi.org/10.1016/j.ecresq.2008.12.003

Schneider, B. H. (1999). A multimethod exploration of the friendships of children considered socially withdrawn by their school peers. *Journal of Abnormal Child Psychology, 27*(2), 115–123. https://doi.org/10.1023/A:1021959430698

Sheldon, K. M., Abad, N., & Hinsch, C. (2011). A two-process view of facebook use and relatedness need-satisfaction: Disconnection drives use, and connection rewards it. *Journal of Personality and Social Psychology, 100*(4), 766–775. https://doi.org/10.1037/a0022407

Spere, K., & Evans, M. A. (2009). Shyness as a continuous dimension and emergent literacy in young children: Is there a relation? *Infant and Child Development, 18*(3), 216–237. https://doi.org/10.1002/icd.621

Stumper, A., Danzig, A. P., Dyson, M. W., Olino, T. M., Carlson, G. A., & Klein, D. N. (2017). Parents' behavioral inhibition moderates association of preschoolers' BI with risk for age 9 anxiety disorders. *Journal of Affective Disorders, 210*, 35–42. https://doi.org/10.1016/j.jad.2016.12.008

Thomasgard, M., & Metz, W. P. (1993). Parental overprotection revisited. *Child Psychiatry and Human Development, 24*(2), 67–80. https://doi.org/10.1007/BF02367260

Valiente, C., Swanson, J., & Lemery-Chalfant, K. (2012). Kindergartners' temperament, classroom engagement, and student–teacher relationship: Moderation by effortful control. *Social Development, 21*(3), 558–576. https://doi.org/10.1111/j.1467-9507.2011.00640.x

Valkenburg, P. M., & Peter, J. (2009). Social consequences of the internet for adolescents: A decade of research. *Current Directions in Psychological Science, 18*(1), 1–5. https://doi.org/10.1111/j.1467-8721.2009.01595.x

Van Zalk, M., Van Zalk, N., Kerr, M., & Stattin, H. (2014). Influences between online-exclusive, conjoint and offline-exclusive friendship networks: The moderating role of shyness. *European Journal of Personality, 28*(2), 134–146. https://doi.org/10.1002/per.1895

Van Zalk, N., & Kerr, M. (2011). Shy adolescents' perceptions of parents' psychological control and emotional warmth: Examining bidirectional links. *Merrill-Palmer Quarterly, 57*(4), 375–401. https://doi.org/10.1353/mpq.2011.0021

Vernberg, E. M., Abwender, D. A., Ewell, K. K., & Beery, S. H. (1992). Social anxiety and peer relationships in early adolescence: A prospective analysis. *Journal of Clinical Child Psychology, 21*(2), 189–196. https://doi.org/10.1207/s15374424jccp2102_11

Vitiello, V. E., Moas, O., Henderson, H. A., Greenfield, D. B., & Munis, P. M. (2012). Goodness of fit between children and classrooms: Effects of child temperament and preschool classroom quality on achievement trajectories. *Early Education and Development, 23*(3), 302–322. https://doi.org/10.1080/10409289.2011.526415

Volbrecht, M. M., & Goldsmith, H. H. (2010). Early temperamental and family predictors of shyness and anxiety. *Developmental Psychology, 46*(5), 1192–1205. https://doi.org/10.1037/a0020616

Walker, O. L., Degnan, K. A., Fox, N. A., & Henderson, H. A. (2013). Social problem solving in early childhood: Developmental change and the influence of shyness. *Journal of Applied Developmental Psychology, 34*(4), 185–193. https://doi.org/10.1016/j.appdev.2013.04.001

Walker, O. L., Degnan, K. A., Fox, N. A., & Henderson, H. A. (2015). Early social fear in relation to play with an unfamiliar peer: Actor and partner effects. *Developmental Psychology, 51*(11), 1588–1596. https://doi.org/10.1037/a0039735

Walker, O. L., & Henderson, H. A. (2012). Temperament and social problem solving competence in preschool: Influences on academic skills in early elementary school. *Social Development, 21*(4), 761–779. https://doi.org/10.1111/j.1467-9507.2011.00653.x

Weiner, B. (1986). Attribution, emotion, and action. In R. M. Sorrentino & E. T. Higgins (Eds.), *Handbook of motivation and cognition: Foundations of social behavior* (pp. 281–312). New York, NY: Guilford Press.

Weiner, B. (1995). *Judgments of responsibility: A foundation for a theory of social conduct*. New York, NY: Guilford Press.

White, L. K., McDermott, J. M., Degnan, K. A., Henderson, H. A., & Fox, N. A. (2011). Behavioral inhibition and anxiety: The moderating roles of inhibitory control and attention shifting. *Journal of Abnormal Child Psychology, 39*(5), 735–747. https://doi.org/10.1007/s10802-011-9490-x

Younger, A. J., & Piccinin, A. M. (1989). Children's recall of aggressive and withdrawn behaviors: Recognition memory and likability judgments. *Child Development, 60*(3), 580–590. https://doi.org/10.2307/1130724

Peer Relations and the Behaviorally Inhibited Child

Kenneth H. Rubin, Matthew G. Barstead, Kelly A. Smith, and Julie C. Bowker

Abstract In this chapter, we describe the peer relations of *socially wary* and *withdrawn* children. Nomenclature, in this regard, is of significance. This compendium is focused on the construct of *behavioral inhibition* (BI). The vast majority of published work on the peer relations of behaviorally inhibited children has focused on laboratory-based paradigms in which the focal children have been observed in the company of *unfamiliar* peers. However, if one is to describe the most meaningful experiences that children have with their peers, one must review the extant work that pertains to their social lives when they are in *familiar*, everyday settings. Consequently, in this chapter, we focus not only on the construct of behavioral inhibition as it was originally defined but also on the extant literature pertaining to the study of the peer interactions, friendships, peer reputations, and social groups of socially wary, shy, and anxiously withdrawn children in their school settings.

Peer Relations and the Behaviorally Inhibited Child

Imagine the following scenario. You have happened upon a schoolyard during recess. Through a fence, you note that groups of elementary school-age children (you guess that they may be 8–10 years of age) are interacting. Most are simply chatting with each other; some are playing games; and others are happily engaging in what appears to be the construction of a fantastical spaceship from large, "creative play" materials that are part and parcel of the playground landscape. You also notice that most groups are gender- and age-segregated. Nevertheless, you estimate that close to 90% of the children are socially engaged with peers. The remaining

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10% seem to be spending much of their time alone, watching others from afar, or simply walking the playground on their own. Some of these solitary children are using the playground equipment in a functional-sensorimotor capacity. They are repeatedly running up-and-down the slides or are using the "monkey bars" to practice what appears to be gymnastic activity. Still yet others are spending their time alone using whatever materials they can acquire to create novel structures … on their own. At one point in time, you notice that as members of a given social group walk by one of the seemingly socially withdrawn children, a member of the group appears to inadvertently jostle the solitary child. The child becomes emotionally upset, perhaps angry. The solitary child says nothing to the apparent antagonist and retreats to the comfort of a quieter, more remote area of the playground.

During the 15 min spent observing the elementary schoolers at recess, you are struck by three "bits"—first, those who have been engaging with each other in cliques of various sizes rarely approach those who have been spending their time alone (indeed, they rarely approach members of other distinct peer groups). Second, it was rare to observe a "loner" approach a given group. Third, when jostled by a peer, the solitary child did not engage any member of the perpetrator's group in conversation. Rather, he retreated to a safe zone where others were not present. You also noted that in some instances, a seemingly socially fearful child would approach a dyad with what appeared to be an interest to join this smallest of groups (two members). However, the focal child never took the necessary step to join the conversation or activity of the dyad. Instead, he or she hovered nearby, as if wishing that he or she would be invited to participate in the small group activity.

When the recess period has ended, you continue walking to your venue, but cannot stop thinking about the children who spent their entire recess period on the outside, looking in. As a novice observer of children, you may rush to judgment and assume that the loners were shy, socially fearful children who could not bring up the courage to join others in social engagement. But then, you remember that you had recently read a magazine article about introversion and the concept of "quiet" (Cain, 2012), in which it was suggested that some individuals are content to spend their time alone. Perhaps, as the article implied, the solitary children you observed were content with, maybe even appreciative of, silence and the opportunities for creative thought that relative seclusion purportedly allows. But in the hustle-bustle of the playground, such an account did not seem to fit your observations. Instead, most of the loners that you had noticed seemed to be members of that former group—shy, socially fearful children who spent time alone *while in the company of familiar peers*. These were 8- to 10-year-olds; no one was offering them an opportunity to join them in play or conversation. These children appeared friendless and perhaps excluded. Body language, facial expressions, and demeanor all hinted that they were unhappy, perhaps anxious, and fearful in the company of others.

As it happens, this more fearful group of solitary children represents the subjects of this chapter. Who are they? Why are they loners on the playground? Despite not interacting often with their peers, what might their social exchanges look like when they do occur? And might they have friends who were not present during your

observations? If they do have friends, who are they and what do the friendship partners think of each other and their relationship?

The goal of the above-described scenario was to demonstrate some of the many factors that are interconnected within each child's social universe. Some of these factors may describe the *individual* characteristics of each child (e.g., age, sex, race, temperament, or personality), some help define the very meaning of a specific *interaction* (e.g., is a jostle an intended attempt to injure or an inadvertent accident?), and some are focused on the nature of the *relationships* between the children (e.g., some dyads comprised children who were clearly friends, enjoying each other's company). It was also the case that some children "hung out" in *groups* that were clearly distinct from other groups—distinguished by gender, age, clothing, and preferred activities. In short, observing individuals from afar and attempting to fully understand what it is that is occurring require the consideration of children's individual characteristics, their relationships, their group memberships, and the communities and cultures within which they are dwelling. Put another way, the study of peer interactions, relationships, and groups is a rather complicated business. The study of individual differences within each of these dimensions of peer relations renders the business even more complex.

In this chapter, we describe the peer relations of children who may best be described as *socially wary* and *withdrawn*. Nomenclature, in this regard, is of significance. This compendium is focused on the construct of *behavioral inhibition* (BI). From our reading of the extant literature, however, the vast majority of published work on the peer relations of behaviorally inhibited children has focused on laboratory-based paradigms in which the focal children are observed in the company of *unfamiliar* peers. However, if one is to describe the most meaningful experiences that children have with their peers, one must most certainly review the extant work that pertains to their social lives when they are in *familiar*, everyday settings. Consequently, in this review, we will *not* focus solely on the construct of behavioral inhibition as it was originally defined (see below). Rather, we will also review studies of the peer relations of those children who have been described as *anxiously withdrawn* or *socially inhibited* (see Coplan & Rubin, 2010; Rubin, Coplan, & Bowker, 2009, for discussions of nomenclature).

Prior to reviewing the relevant research, however, we will examine those features of the social universe that have dominated the peer relations literature for the past quarter century. That is, we will deconstruct the peer relations literature into three "levels" (e.g., Hinde, 1987)—social *interactions*, dyadic *relationships*, and *group* reputation.

The Significance of Peers

The term *peer relations* refers to those direct and indirect experiences that individuals have with their non-familial age-mates (see Rubin, Bukowski, & Bowker, 2015, for a substantive review). The study of peer relations includes how it is that

individuals *interact* with their age-mates and how repeated interactions with others evolve, gradually, into dyadic *relationships* of one form or another (e.g., friendship). Finally, peer relations also encompass how the individual's personal and interpersonal characteristics, and the quality of the individual's expressed social or asocial behaviors, can lead to reputations within the *peer group* at large. These reputations, in turn, fuel reactions by the peer group to the individual and his or her behavioral "styles" and social relationships.

During the past 40 years or so, beginning with Willard Hartup's seminal chapter on peer relations that appeared in the *Handbook of Child Psychology* in 1970, there has been a noteworthy shift in the assumptions about the origins of, and proximal and distal influences on, children's peer experiences and the conclusions drawn regarding the developmental significance of children's interactions and relationships with peers. For example, the early literature on children's peer interactions and relationships was largely descriptive and normative-focused, emphasizing developmental milestones in the form, salience, or complexity of peer interaction and relationships. This early work deviates clearly from much of the contemporary literature in which a primary focus has been on the description and understanding of individual differences in peer interactions and relationships. The individual differences perspective has led contemporary researchers to conclude that experiences with peers directly promote, extend, discourage, or distort children's intra- and interpersonal growth and adjustment (see Bukowski, Laursen, & Rubin, 2018, for relevant reviews). The ability to initiate and maintain positive dyadic and group peer relationships is now regarded as significant developmental achievements. Indeed, it is assumed that children who experience success with peers are on track for adaptive and psychologically healthy outcomes. Children who have difficulty in the peer milieu are considered at risk for maladaptive intra- and interpersonal outcomes.

A Guiding Conceptual Model

The conceptual model that has guided much of the extant research on peer relations derives from a dialectical framework of social complexity originally described by Hinde (1987, 1995) and Hinde and Stevenson-Hinde (2014). This framework as it specifically applied to the study of peer relations, first appeared in the "post-Hartup" *Handbook of Child Psychology* chapters on peers as influences on typical and atypical child and adolescent development (see Rubin, Bukowski, & Parker, 1998). Hinde's model involves successive, interacting levels of social complexity that include transactions between levels of individual characteristics, interpersonal interactions, dyadic relationships, groups, and society (see the chapter "The Social World of Behaviorally Inhibited Children: A Transactional Account by Henderson et al."; the chapter "The Temperamentally Shy Child as the Social Adult: An Exemplar of Multifinality" by Poole et al.).

The Level of the Individual

Typically, individual characteristics studied by peer relations researchers include age, gender, ethnicity, and race. Biologically based characteristics such as temperament and personality (e.g., behavioral inhibition, shyness, anxious solitude, emotion regulation) also fall within the domain of individual characteristics. Other elements that comprise characteristics pertaining to the individual include social competence and social-cognitive prowess as well as internalized notions pertaining to the self and to social relationships. The essential notion pertaining to the level of the individual is that the relevant constructs pertain to the child/adolescent per se. In this chapter, the individual characteristics that are most relevant involve behavioral inhibition, anxious withdrawal, and emotional reactivity and regulation.

The Level of Interactions

Interactions refer to what individuals do to or with each other (Hinde, 1987). In this regard, interactions involve exchanges in which the participants' actions are interdependent; each individual's behavior is both a stimulus for, and a response to, another person's behavior. A paradigm case of an interaction is conversational turn taking. For example:

Zoe: "Do you have any pets?"
Bella: "I have a puppy; his name is Speedy. What about you?"
Zoe: "Yup … I've got two giant fluffy dogs and a mean old cat."
Bella: "I hate cats!" … and so on.

Interactions can be brief or enduring and simple or complex. During conversations, individuals self-disclose, do battle or resolve conflict, spread rumors and gossip, humor each other, and engage in co-constructive learning activities. They can help each other or make each other miserable. In our own previous writings (e.g., Rubin et al., 2015), we have categorized social interactions as involving the (1) movement *toward* one another, (2) movement *against* one another, and (3) movement *away* from others. As such, social interactions can generally involve (1) sociability and prosociality (helping, caring, sharing); (2) interpersonal conflict, aggression, and bullying; and (3) social withdrawal. A central construct in the peer *interactions* literature is *social competence*, or the ability to meet one's social goals through social exchanges that are both successful and approved of by the community at large (Rubin & Krasnor, 1986; Rubin & Rose-Krasnor, 1992). Given this perspective on interpersonal exchanges, it becomes clear that individual characteristics play no small role in the types of social interactions one may experience.

The Level of Relationships

A consequence of experiencing regular interactions with given individuals is the formation of relationships. Although Hinde (1987) and Hinde and Stevenson-Hinde (2014) focused mainly on individual characteristics and social interactions that contributed to the development of attachment relationships with primary caregivers, researchers who study peers have centered on the origins, stability, and quality of *friendships*. Hinde and others argue that past interactions (with parents or peers) are remembered in various ways that can lead to the development of internalized representations about the interactive partner. Such representations influence and are influenced by repeated social exchanges with given individuals. So too is the quality of the relationship. For example, positive peer interactions may lead to the development of supportive and trusting friendships, while negative exchanges may result in enmity.

In this regard, relationships are influenced by past and anticipated future interactions. But just as interactions are, in part, determined by the *individual* characteristics of the social partners, so too are relationships. For example, *homophily* is a particularly strong predictor of initial peer attraction and to the subsequent formation of friendships. Girls are typically friends with girls and boys with boys. Aggressive youth appear to be attracted to others much like them (e.g., Dishion, Andrews, & Crosby, 1995). The same is true of anxiously withdrawn youth (e.g., Rubin et al., 2006). Of course, the quality and stability of friendships are, in part, determined by the sorts of *interactions* that occur between friendship partners (e.g., Laursen, 2017; Poulin & Chan, 2010). So again, Hinde's "levels" of the social world are interrelated, dialectically, in meaningful and significant ways.

The Level of the Group

A *group* is a social network within which *individuals* interact and *relationships* are embedded (Santos, Vaughn, & Bost, 2008). Children spend a substantial proportion of their time in formal and informal group settings where membership is not defined solely by friendship. Peer groups are formed by youth of similar ages who engage in activities based on common interests and values. In childhood, peer groups often comprise same-sex peers, with more mixed-gender groups appearing in late adolescence (e.g., Berger & Rodkin, 2012; Chen, Chang, Liu, & He, 2008; Kindermann, 2007). Groups possess such properties as cohesiveness, norms, hierarchies, and homophily (Kindermann & Gest, 2009). Within each group, core members are typically popular and socially powerful. Thus, core members have the power to persuade other group members to think like, and agree with, them (Sussman, Pokhrel, Ashmore, & Brown, 2007).

Lastly, researchers tend to agree that the characteristics of a group are emergent. That is, groups are not reducible to the characteristics of the individuals comprising the collective. Unlike a dyadic friendship, the peer group represents a social context that is developed through the collective functioning of members based on group

norms and values. Children in the group are united as well as constrained by common interests and group norms. As a result, the "character" of the group serves to guide how children react to various situations and thus function as a context for social interactions and individual behaviors (e.g., Berger & Rodkin, 2012).

Summary

In summary, researchers who study peer relations focus on the dialectical relations between children's individual characteristics, the interactions they have with others, their involvements in peer relationships and groups, and the influences of culture on all the above. A major goal of this chapter is to provide researchers who study behavioral inhibition with an awareness of the complexity of studying peer interactions, relationships, and groups. As we began to explore the extant literature pertaining to meaningful associations between behavioral inhibition, per se, and these multiple levels of social complexity, it became rather obvious that there is a clear need for a meeting of the minds. In the section that follows, we review the literature on the peer interactions, relationships, and peer group relationships of behaviorally inhibited children.

Behavioral Inhibition

As readers of this volume are fully aware, behavioral inhibition has been defined variously as (a) an inborn bias to respond to *unfamiliar* events by showing anxiety (Kagan, 1999), (b) a specific vulnerability to the uncertainty all children feel when encountering *unfamiliar* events that cannot be assimilated easily (Reznick, Gibbons, Johnson, & McDonough, 1989), and (c) one end of a continuum of possible initial behavioral reactions to *unfamiliar* objects or challenging social situations (Kochanska, 1991). These definitions highlight some common elements: behavioral inhibition is (a) a pattern of responding or behaving, (b) biologically determined, such that (c) when *unfamiliar* and/or challenging situations are encountered, (d) the child shows signs of anxiety, distress, or disorganization. In plain English, behaviorally inhibited children are fearful and cautious when confronted by unfamiliarity. From Hinde's (1987) perspective and from the purview of peers researchers (e.g., Rubin et al., 2015), behavioral inhibition is an *individual characteristic* that may be associated, dialectically, with the aforementioned levels of interactions, relationships, and groups.

But, note well the underscore of the word *unfamiliar* as a defining property of behavioral inhibition. Most behavioral inhibition researchers who have studied peer *interactions*, or the lack thereof, have employed laboratory paradigms in which groups of *unfamiliar* peers are observed. When observations are not employed, parents may be asked how their children behave in social situations involving unfamiliar others. In these cases, the measures used have been designed to assess *social*

fearfulness, social anxiety, and/or shyness (e.g., the *Toddler Behavior Assessment Questionnaire*, Goldsmith, 1988; *Colorado Child Temperament Inventory*, Buss & Plomin, 1984). In the very few studies in which *familiar* peers have been considered, the quantity and quality of peer *interactions* have been assessed primarily by teachers (e.g., Dollar, Stifter, & Buss, 2017). We review the relevant literature below.

Behavioral Inhibition and Peer Interactions, Relationships, and Groups

It has been proposed that behaviorally inhibited children may struggle to engage effectively in social interactions with peers because their fear in novel social situations interferes with their ability to flexibly navigate social challenges (e.g., Fox, Henderson, Marshall, Nichols, & Ghera, 2005).

Behavioral Inhibition, Social Reticence, Social Withdrawal, and Social Competence Among Unfamiliar Peers

Most research on behavioral inhibition and children's social *interactions* (or the lack thereof) has focused on inhibition as a predictor of *social reticence* in the presence of unfamiliar peers (Coplan, Rubin, Fox, Calkins, & Stewart, 1994; see Rubin, Coplan, & Bowker, 2009, for a review). The raison d'etre for studying the associations between infant- and toddler-assessed behavioral inhibition and subsequent observational displays of social reticence is that the two constructs putatively represent developmentally relevant "phenotypes" of an underlying "genotype" representing fearfulness in the face of unfamiliarity—in the case of reticence, *social* unfamiliarity (see the chapter "The Neural Mechanisms of Behavioral Inhibition" by Jarcho and Guyer). In this regard, social reticence is a presumed equivalent to the construct of social inhibition (e.g., Kochanska & Radke-Yarrow, 1992; Rubin, Burgess, & Hastings, 2002; Rubin, Hastings, Stewart, Henderson, & Chen, 1997).

Operationally, social reticence can be defined as the frequency with which a given child expresses unoccupied and onlooker behavior when in the company of peers. Behavioral inhibition in infancy and early childhood has consistently been shown to be associated with, and predictive of, observed social reticence among unfamiliar peers during the toddler, preschool/kindergarten, and early elementary school years (e.g., Fox et al., 1995; Fox, Henderson, Rubin, Calkins, & Schmidt, 2001; Henderson, Marshall, Fox, & Rubin, 2004; Rubin et al., 1997; Rubin et al., 2002). In other studies, toddler behavioral inhibition, toddler social fearfulness, and preschoolers' fearfulness and/or social reticence among preschoolers has been found to predict observed socially withdrawn, solitary activity among *unfamiliar*

peers during the kindergarten and early elementary school years (Brooker, Kiel, & Buss, 2016; Buss et al., 2013; Degnan, Fox, Henderson, Rubin, & Nichols, 2008; Hane, Cheah, Rubin, & Fox, 2008; Kiel & Buss, 2011). Early behavioral inhibition has also been shown to predict a parent-reported measure of social withdrawal (that includes items pertaining to shyness) during early adolescence (e.g., Pérez-Edgar, Bar-Haim, et al., 2010) as well as social discomfort with an unfamiliar peer (Pérez-Edgar, McDermott, et al., 2010).

In addition to examining the stability of behavioral inhibition and conceptually related constructs (e.g., social reticence, shyness), researchers have explored the extent to which early behavioral inhibition is associated contemporaneously and predictively with observed social competence and prosociality, but again in laboratory contexts that comprise unacquainted age-mates. Thus, Penela, Walker, Degnan, Fox, and Henderson (2015) found that highly inhibited toddlers used less effective emotion regulation strategies (during a "disappointing gift task") at age 5 and that these dysregulated strategies predicted lower observed social competence with an unfamiliar peer at age 7. In this latter study, social competence was defined as the proportion of positive initiations made to an unfamiliar peer, the proportion of successful responses to these initiations, and the proportion of time spent in social play.

Relatedly, Walker, Henderson, Degnan, Penela, and Fox (2014) reported that toddler-assessed behavioral inhibition predicted 7-year-olds' poor interpersonal problem-solving skills when interacting with a same-age *unfamiliar* peer and two unfamiliar adults during an exclusion paradigm (Cyberball). Taken together, these findings suggest that early behavioral inhibition may place young children at risk for the development of poor social skills. It must be reiterated, however, that these findings derive from observations with *unfamiliar* peers. Furthermore, each of the studies described above is derived from two longitudinal studies of children from the same laboratory. Clearly then, researchers interested in the longitudinal relations between behavioral inhibition and subsequent social skills (or the lack thereof) in the peer group must extend their efforts to include familiar peers (and certainly must demonstrate the generalizability of their results beyond a single laboratory).

Why study behavioral inhibition and social inhibition/reticence and peer interactions, relationships, and groups among familiar peers? The theoretical origins of developmental research on social withdrawal can be traced, ironically, to the early writings of Piaget (1932), Mead (1934), and Sullivan (1953) examining the significance of social interaction for children's normal development. These researchers were among the first to stress that the peer group provided an important and unique context within which social and social-cognitive skills and dyadic relationships with peers ("chumships") developed. Moreover, interactions with familiar peers were posited to influence children's understanding of the rules and norms of their peer subcultures (e.g., Turiel, 1983). Also, it was proposed that another consequence of peer interaction was the development of an understanding of normative performance levels. It is this understanding that engenders, in the child, an ability to evaluate her/his own competencies against the perceived standards of the peer group at large. These writings led to the following question of interest in the early 1980s (Rubin, 1982a, 1982b, 1985): If peer interaction experiences lead to the development

of social competencies, social relationships, and the understanding of the self in relation to others, what are the developmental consequences for those children, who for whatever reason, refrain from engaging in social interaction and avoid the company of their peers?

In a developmental model that we conceptualized several decades ago (e.g., Rubin, Burgess, Kennedy, & Stewart, 2003; Rubin, Cheah, & Menzer, 2009; Rubin, Hymel, Mills, & Rose-Krasnor, 1991; Rubin & Krasnor, 1986; Rubin, LeMare, & Lollis, 1990), we argued that reticence to interact with peers at home and school impedes (a) the experience of normal social interactive play behaviors, (b) possibilities of establishing supportive dyadic relationships (e.g., friendships), and (c) the development of those social and cognitive skills that are supposedly encouraged by peer relationships and social play. Thus, we predicted a developmental sequence in which a socially inhibited (shy), fearful, insecure child withdraws from the social world of peers, fails to develop those skills derived from peer interaction, and, through a set of reciprocal processes, becomes increasingly anxious and isolated from the peer group. We also surmised that self-recognition of social failure would elicit thoughts and feelings of negative self-regard. Furthermore, we suggested that these negative thoughts and feelings would be continuously reinforced as the child develops an inadequate social repertoire to interact with and relate positively to peers.

Drawing from research on children's perceptions of their peers' social behaviors, we also posited that social withdrawal becomes more salient to the peer group with increasing age (e.g., Younger & Daniels, 1992). Given that deviation from age normative social behavior is associated with the establishment of negative peer reputations, we predicted that by the elementary school years, the consistent display of socially reticent and withdrawn behavior in the company of classmates would result in peer rejection, exclusion, and victimization. And finally, we argued that the constellation of anxiously withdrawn behavior, social failure in the peer group, negative self-regard, and peer rejection would conspire, in an insidious fashion, to maintain and exacerbate psychological problems of an internalizing nature—intrapersonal difficulties such as loneliness, rejection sensitivity, and social anxiety (see the chapter "Behavioral Inhibition as a Precursor to Psychopathology" by Klein and Mumper).

It is this particular conceptual model, and the relevant supportive research, (see discussion below) of the developmental course of socially reticent, shy, withdrawn behavior that has led us to believe that any research linking behavioral inhibition to the presentation of specific social interaction styles, social relationships, and experiences in the peer group at large *must* involve the study of *familiar* peers. The extant literature has consistently indicated that some, but certainly not all, children who display behavioral inhibition in the company of unfamiliar adults and social reticence among unfamiliar peers are at risk for the development of negative outcomes such as anxiety (and more specifically, social anxiety; e.g., Chronis-Tuscano, Degnan, et al., 2009; Lewis-Morrarty, Degnan et al., 2012). It is our contention that peer interactions and relationships with *familiar* peers play a significant role in the trajectory that putatively begins with behavioral inhibition and ends with social and emotional maladaptation.

Behavioral Inhibition and Familiar Peers

In support of the notion that behavioral inhibition and the corresponding lack of peer interaction predict deficits in the ability to comprehend the thoughts, feelings, and perspectives of their peers, Suway and colleagues reported that high behavioral inhibition at 2 years was associated with less advanced theory of mind understanding at 3 years among children who interacted negatively with peers (Suway, Degnan, Sussman, & Fox, 2012), a finding in keeping with earlier work demonstrating a negative association between both observed classroom and peer-rated social withdrawal and perspective-taking skills (e.g., LeMare & Rubin, 1987). Collectively, these findings may well explain why it is that behaviorally inhibited children may display less socially competent behavior than their less inhibited peers when in the company of *familiar* age-mates.

In support of this conjecture, Tarullo, Mliner, and Gunnar (2011) observed that highly inhibited preschoolers engaged in fewer positive peer interactions, appeared less confident, and displayed more frequent sad and fearful affect with classroom peers than less inhibited children. In addition, Bohlin, Hagekull, and Andersson (2005) found that behavioral inhibition at age 4 years negatively predicted parent-reported and observed socially competent and prosocial behavior with familiar peers at age 8 years. Lastly, Hastings and colleagues have reported that when socially wary, reticent preschoolers were physiologically dysregulated (lower respiratory sinus arrhythmia; RSA) and had mothers who were overprotective, they demonstrated poor social skills among familiar peers (as reported by teachers) 5 years later (Hastings, Kahle, & Nuselovici, 2014). This latter study strongly supports the developmental model of the course of socially inhibited, reticent behavior during the *early* years of childhood (e.g., Rubin, Coplan, & Bowker, 2009).

Summary

Recent research has consistently demonstrated significant contemporaneous and predictive associations between behavioral inhibition and children's displays of socially reticent behavior among unfamiliar peers. Evidence also supports a predictive relation between toddler and preschool behavioral inhibition and such maladaptive behaviors as social incompetence. Again, much of this work involves the study of children observed in the company of age-mates with whom they are unfamiliar. There exists limited research on the relations between behavioral inhibition and children's social interactions in classrooms or other venues within which they actually know their age-mates. Furthermore, the consequences of behavioral inhibition for peer relation constructs that involve *relationships* (e.g., friendship) and *groups* (e.g., peer rejection and exclusion; networks) are, for all purposes, unknown.

Note well that a primary defining characteristic of friendships is its *reciprocal and voluntary* nature. A "true" friendship can only exist when *both* individuals view each other as a friend. For this reason, researchers argue that reciprocal friendship nominations are required for the identification of a friendship (e.g., both children name each other as a friend; Parker & Asher, 1993). Similarly, to identify whether a given child is a member of a relationship network, one must rely on *multiple*, reciprocal nominations to identify the members of a given group (Rubin et al., 2015). Given these definitional constraints, it seems quite clear that researchers have yet to directly examine the relations between behavioral inhibition and children's friendships, peer networks, and social reputations.

In the sections that follow, we consider the associations between anxious withdrawal (also referred to as anxious solitude) and children's peer interactions, friendships, and group experiences. As it happens, there *is* an empirical link between behavioral inhibition, social reticence, and anxious withdrawal. Each has been empirically associated with the dispositional characteristic of *shyness* (e.g., Fox et al., 2001; Rubin, Nelson, Hastings, & Asendorpf, 1999; Schmidt et al., 1997). Although the construct was clearly viewed as a *fear-induced* response to unfamiliar adults and situations in the original studies of behavioral inhibition (García-Coll, Kagan, & Reznick, 1984; Kagan, Reznick, Clarke, Snidman, & García-Coll, 1984; Kagan, Reznick, & Snidman, 1987), in subsequent years it was construed as an early developing form of fearful/anxious *shyness* (e.g., Kagan, Reznick, & Snidman, 1988; see Buss, 1986, for a relevant discussion).

In this regard, Kagan and colleagues extended the original behavioral manifestation of fear in the face of *unfamiliarity* to fear-based shyness in the face of *unfamiliar social* situations (see Schmidt & Buss, 2010, for a relevant discussion). Perhaps then, this explains why behavioral inhibition researchers have not typically extended their work to the study of interactions and relationships with *familiar* others. Nevertheless, it is the case that the construct of anxious withdrawal (see below for discussion) has been consistently associated with indices of shyness. Given that many of the studies of anxious withdrawal and peer relations have focused on elementary and middle school attending youth, it may well be that the form of shyness being assessed is of a self-conscious nature—a form that develops later than anxious/fearful shyness and emerges during the preschool years and co-occurs with the development of self-awareness, self-conscious emotions, and perspective-taking (Buss, 1986; Schmidt & Buss, 2010). We review the relevant literature on anxious withdrawal and peer relations below.

Anxious Withdrawal and Peer Relations

A conceptual cousin of behavioral inhibition, anxious withdrawal, is frequently defined as anxiously motivated, self-imposed isolation in the presence of peers (Coplan & Rubin, 2010; Rubin, Bowker, Coplan, & Barstead, 2018). Although anxious withdrawal and behavioral inhibition share similar motivational underpinnings,

these two constructs are not synonymous, although some have treated them as such (e.g., Lewis-Morrarty et al., 2015). Unlike prototypical assessments of behavioral inhibition (e.g., Fox et al., 2001; Kagan, 1999; Reznick et al., 1989), anxious withdrawal requires that solitary behavior be displayed within the context of *familiar peers*, typically among class- or grade-mates (e.g., Gazelle, 2006; Gazelle & Ladd, 2003; Miller, Tserakhava, & Miller, 2011; Rubin et al., 2006).

One conceptualization of the developmental linkage between behavioral inhibition and anxious withdrawal is that behavioral inhibition may be a manifestation of an underlying genotype that gives rise, under the right circumstances, to the maladaptive phenotype embodied by anxious withdrawal (Fox et al., 2005; Rubin, Coplan, & Bowker, 2009). The fact that researchers have detected some moderate continuity between behavioral inhibition and socially reticent behavior in the company of unfamiliar peers is in line with this supposition (Degnan et al., 2008; Lewis-Morrarty et al., 2015). In addition, the fact that social reticence among familiar peers is associated with the same or similar indices of social fearfulness and shyness that are statistically and significantly associated with behavioral inhibition provides additional support for this assumption (e.g., Coplan & Rubin, 1998). Furthermore, researchers using various techniques (typically involving peer nominations in school) have identified extreme groups of children who appear to display relatively stable and high levels of anxious withdrawal (e.g., Booth-Laforce et al., 2012; Gazelle & Ladd, 2003; Ladd, Kochenderfer-Ladd, Eggum, Kochel, & McConnell, 2011; Oh et al., 2008; Rubin, Chen, McDougall, Bowker, & McKinnon, 1995; Schneider, Richard, Younger, & Freeman, 2000), which would seem to indirectly support the argument for a phenotype of anxious withdrawal.

If a child develops an anxiously withdrawn phenotype, three decades of research suggests that she or he will experience difficulty successfully engaging and forming positive relationships with age-mates. For example, the propensity to display reticent, withdrawn, socially wary behaviors in the presence of familiar peers has been frequently associated with and predictive of such peer difficulties as rejection, victimization, and exclusion (e.g., Avant, Gazelle, & Faldowski, 2011; Bukowski, Laursen, & Hoza, 2010; Coplan, Arbeau, & Armer, 2008; Gazelle & Ladd, 2003; Gazelle & Spangler, 2007; Hanish & Guerra, 2004; Hart et al., 2000; Ladd et al., 2011; Rubin, Chen, & Hymel, 1993). Relatedly, even though anxiously withdrawn children *do* develop mutual best friendships, the size of their friendship networks tends to be smaller (Ladd et al., 2011), and their friendships tend to be of lower quality (Rubin et al., 2006), findings that are described in greater detail below.

Not surprisingly, researchers have found that the negative social experiences of stably anxiously withdrawn children (e.g., rejection, victimization) are associated with, and predictive of, elevated loneliness, lower self-esteem, rejection sensitivity, and reduced confidence in social efficacy (e.g., Bukowski et al., 2010; Ladd et al., 2011; London, Downey, Bonica, & Paltin, 2007; Wang, McDonald, Rubin, & Laursen, 2012; see Rubin et al., 2018, for a review).

Repeated unpleasant interactions with peers, increased negative self-concept, feelings of isolation and loneliness, heightened sensitivity to being rejected by peers, and a dispositional bias toward withdrawing represent a toxic mix for the

child who remains anxiously withdrawn in the presence of peers into early and middle childhood. Indeed, young adolescents who withdraw from social interaction because of shyness or wariness and anxiety about interacting with peers tend to report especially elevated levels of anxiety and depressive symptoms (Coplan et al., 2013).

The reasons that anxiously withdrawn children find themselves disliked, rejected, and excluded by their peers are varied. Unlike aggressive and disruptive children, withdrawn children do not tend to act in ways that are overtly offensive to their peers, and yet, they still find themselves rejected and excluded (Oh et al., 2008; Rubin et al., 1993). Although anxious withdrawal may not be as salient or as aggravating as aggression, it nevertheless violates basic social norms for children who reside in cultures within which they are expected to be exuberant and peer-oriented (Rubin, Cheah, & Menzer, 2009).

Indeed, the very notion of social withdrawal runs counter to the fun, outgoing, and at times fearless images conjured by the term "childlike." Cultural messaging, particularly in Western societies, often casts shy and withdrawn behaviors in a negative light (Coplan, Hughes, & Roswell, 2010; Doey, Coplan, & Kingsbury, 2014), reinforcing its status as an aberrant form of behavior when exhibited in social company. Notably, very young children are often exposed to these cultural values through popular books written for and read to them (Coplan et al., 2010). Even kindergarteners report that children who are described as socially withdrawn are less attractive as potential playmates (Coplan, Girardi, Findlay, & Frohlick, 2007). With increasing age, there is evidence to suggest that social withdrawal becomes viewed as increasingly less desirable by peers (Gavinski-Molina, Coplan, & Younger, 2003; Ladd, 2006; Younger & Daniels, 1992), further exacerbating the social plights of children predisposed to withdraw in social contexts.

A key piece of evidence that has been frequently used to highlight the role that cultural norms play in explaining the link between anxious withdrawal and peer difficulties derives from a program of research that began in the early- and mid-1990s. This work showed that Chinese children who were identified as shy/sensitive did not suffer the same sorts of peer difficulties as similarly aged Canadian and American shy/sensitive youth (for a relevant review, see Chen, Li, & Chen, 2018; see also the chapter "The Temperamentally Shy Child as the Social Adult: An Exemplar of Multifinality" by Poole et al.). Interestingly, and in direct contrast to trends found in Canadian and American samples, shy/sensitive Chinese youth were viewed more positively (and were less likely to be rejected) by their schoolmates (Chen, Dong, & Zhou, 1997; Chen, Rubin, & Sun, 1992). The researchers involved in this work suggested that shy/sensitive behavior violated Western cultures' emphases on sociability, assertiveness, and independence and that shy/sensitive behavior was more acceptable in Eastern cultures within which social harmony, respect, and quiescence of children were valued.

However, the story of the data generated by these cross-cultural research teams began to change in the 2000s, particularly with regard to urban Chinese samples (Chen, 2010). As China increasingly opened to more Western cultural and business

practices, shyness/sensitivity among urban Chinese youth became increasingly associated with peer rejection and the sorts of inter- and intrapersonal difficulties commonly experienced by their shy/sensitive or anxiously withdrawn Western counterparts (Chen, Wang, & Wang, 2009; Yang, Chen, & Wang, 2015). As this opening to Western culture is more prevalent in urban settings, it is a further testament to the power of social norms that shyness/sensitivity in rural China continues to be unrelated to peer rejection and, in some instances, is linked to adaptive social outcomes (e.g., Chen et al., 2018).

Although there is considerable evidence to highlight the importance of social norms in setting the conditions within the peer context that link shy, anxious behavior to peer difficulties over time, it is also true that, in many instances, anxiously withdrawn children may behave in ways that make them targets for peer rejection and/or neglect. From an early age, withdrawn children have been observed to make fewer social overtures to their peers (Chen, DeSouza, Chen, & Wang, 2006; Rubin, 1985; Stewart & Rubin, 1995). When they do make requests of their age-mates, these overtures are often more passive, less direct, and less successful than those of their non-withdrawn counterparts (Chen et al., 2006; Rubin, 1982a, 1982b; Rubin & Borwick, 1984; Rubin & Krasnor, 1986; Stewart & Rubin, 1995). In addition, when social interactions do occur, the anxiously withdrawn child is often observed to avoid eye contact and blush, two indicators of social anxiety (Coplan et al., 2008; Gazelle, 2008).

Such socially incompetent bids are unlikely to be rewarded in terms of either achieving immediate social goals or engendering good will with the specific interaction partner going forward. Indeed, it has been shown that when the social bids of anxiously withdrawn children fail, they are more likely to give up or capitulate to alternative suggestions offered by a partner (Gazelle & Druhen, 2009; Rubin & Borwick, 1984; Stewart & Rubin, 1995). Being less capable of successfully initiating and maintaining social interactions only serves to further hamper withdrawn children's ability to acquire age-appropriate social competencies. This pattern of interaction may trigger a maladaptive developmental cycle whereby the anxiously withdrawn child frequently fails in the few social bids he or she makes, attributes his or her social failures to internal causes (e.g., something is wrong with *me*) rather than attributing them to other people or situations (Rubin & Krasnor, 1986; Wichmann, Coplan, & Daniels, 2004), increasingly fears future failure because of these disappointing interactions (rejection sensitivity; London et al., 2007), comes to believe that he or she is socially incompetent (e.g., Boivin & Hymel, 1997; Boivin, Hymel, & Bukowski, 1995; Rubin et al., 1993), and further distances him- or herself from classmates and grade-mates (Booth-Laforce et al., 2012; Ladd, 2006). Of course, peer avoidance means that the anxiously withdrawn child misses positive opportunities to build on his or her relatively inadequate social competencies, which in turn, further crystallizes his or her status as an unattractive interaction partner.

Other maladaptive cycles may evolve from the passive and socially incompetent behaviors of anxiously withdrawn children that become more apparent in

relatively stable peer groups where reputations can be hard to undo (see the chapter "The Social World of Behaviorally Inhibited Children: A Transactional Account" by Henderson et al.). For example, first impressions matter, and grade school peer groups are no exception. Socially passive and ineffective requests may signal more than social incompetence to some peers in these groups; they may signal an easy target for victimization (Erath, Flanagan, & Bierman, 2007; Hanish & Guerra, 2004). Indeed, for children who seek to victimize or use aggression as a means of establishing, maintaining, or increasing their social dominance, there are few easier pickings than an anxiously withdrawn child (e.g., Gazelle & Rudolph, 2004; Hodges & Perry, 1999; see Salmivalli & Peets, 2018, for a review). Their passive nature makes them unlikely to retaliate, and their relatively low standing in the peer group ensures that few allies will come to their aid.

Based on the confluence of dispositional and social factors unique to anxiously withdrawn children, some have gone as far to describe them as being at risk for becoming "whipping boys" within their peer groups (Olweus, 1993). This undesirable status of being victimized by more socially dominant peers may extend to computer-mediated social interactions as well (Katzer, Fetchenhauer, & Belschak, 2009; Kowalski, Morgan, & Limber, 2012; Raskauskas & Stoltz, 2007). Although these findings are not specific to anxiously withdrawn youth, the data do highlight an existing connection between being victimized in the real world and experiencing cyberbullying. As children's social worlds increasingly follow them home in their pockets and stream live through their screens, the borders between face-to-face and screen-mediated communication continue to crumble. Understanding how the possible ubiquity of the peer environment may affect the peer relations of socially withdrawn children represents a newly developing line of research.

In summary, although few, if any, studies have focused on the relations between infant and toddler behavioral inhibition as expressed in unfamiliar settings and socially reticent, anxiously withdrawn behavior among familiar peers, it may be that behavioral inhibition is an early indicator of risk for developing an anxiously withdrawn phenotype (Rubin, Coplan, & Bowker, 2009). Such a phenotype is related to a host of difficulties within the familiar peer group as it often represents a violation of social norms. Additionally, anxiously withdrawn children tend to engage in less socially competent behavior than their typical peers, which likely contributes to being rejected and excluded by peers and may even signal to more socially dominant children that a particular child is a suitable target for victimization. Many of these difficulties likely reinforce withdrawn children's initial tendencies to remove themselves from peers in the first place. Finally, although there are limited data on the topic, there is some evidence to suggest that social media may provide an avenue through which negative social experiences can continue absent the physical presence of peers. Certainly, at this time, this latter issue represents a relatively new line of research. Nevertheless, it should be of interest to both clinical and developmental researchers who are seeking to better understand contemporary social consequences of anxious withdrawal.

Anxious Withdrawal and Friendship

Although anxiously withdrawn children and adolescents, by definition, tend to withdraw from and avoid their peers, the extant literature suggests that such behaviors do not prevent them from forming and maintaining close friendships. In studies of children (Ladd et al., 2011; Ladd & Burgess, 1999) and adolescents (Markovic & Bowker, 2017; Rubin et al., 2006), researchers have revealed that anxiously withdrawn youth are as likely as their non-withdrawn classmates to have at least one stable and mutual (or reciprocated) friendship (determined by friendship nominations; e.g., Jonah and Julius nominate each other as a best friend). Thus, it may be most accurate to characterize anxiously withdrawn youth as withdrawing from *group*-level, but not dyadic-level, peer experiences.

Mutual friendship involvement and stability, however, are just two aspects of youths' friendship experiences. Indeed, investigators argue that it is essential to consider mutual friendship involvement and stability as well as the *characteristics of the friend* and the *quality* of the friendship to fully understand the nature and the influence of friendships in the lives of children and adolescents (Laursen, 2017; Rubin et al., 2015). When these aspects of friendship are studied, differences between the friendship experiences of anxiously withdrawn and typical youth have been found. For instance, in a study of young adolescents, Rubin et al. (2006) found that the friends of highly anxiously withdrawn young adolescents tend to be more withdrawn than the friends of non-withdrawn young adolescents. Similar findings have been reported in studies of socially reticent children during early childhood (e.g., Guimond et al., 2014). Several studies also show that highly anxious-withdrawn youth are similar to their friends in such group-level peer difficulties as peer victimization (Haselager, Hartup, Lieshout, & Riksen-Walraven, 1998; Rubin et al., 2006).

Theory and research suggests that youth are attracted to, and thus actively select, similar peers with whom to form friendships (Kandel, 1978). Thus, it is likely that one of the reasons that anxiously withdrawn youth appear to have little difficulty forming friendships is that they choose their friends based on the principals of homophily. It is equally plausible, however, that anxiously withdrawn youth desire *others* as friends but find themselves in relationships with behaviorally and reputationally similar age-mates because their group-level peer difficulties limit their friendship options. Consequently, anxiously withdrawn youth might be left with a pool of "leftovers" or behaviorally similar peers who are viewed by their more well-adjusted peers as undesirable as friends (Rubin, Cheah, & Menzer, 2009).

In terms of the *quality* of anxiously withdrawn youths' friendships, there is some indication that their friendships are lacking or poor in terms of positive qualities (Ponti & Tani, 2015; Rubin et al., 2006; Schneider, 2009). For instance, anxiously withdrawn children and young adolescents tend to describe their friendships as less fun, helpful, and intimate relative to non-withdrawn youth (Menzer et al., 2012; Rubin et al., 2006). Significantly, the friends of anxiously withdrawn youth likewise

have a negative perspective of their friendships (Rubin et al., 2006). Research also indicates that anxious withdrawal is associated with higher conflict in the friendships of young adolescent girls (Menzer et al., 2012).

There are several possible explanations to explain these findings. For one, anxious withdrawal likely interferes with shared intimate disclosure, which becomes a hallmark feature of friendships during early adolescence (Rubin et al., 2006). Friendships (which by definition, involve a *dyadic relationship*) oftentimes exist within larger friendship networks (or groups of friends that spend time together). Thus, we speculate that the anxieties and social fears associated with anxious withdrawal may also interfere with, or even prevent, engagement in certain types of group-based friendship activities (e.g., playing kickball after school). Shared misery (e.g., in terms of anxiety, peer difficulties) may also interfere with the enjoyment of the relationship (Rose, Carlson, & Waller, 2007; Rubin et al., 2006; Schwartz-Mette & Rose, 2009).

Anxiously withdrawn young adolescents also appear to have less sophisticated understandings of friendship than do their non-withdrawn counterparts (Fredstrom et al., 2012; Schneider & Tessier, 2007). For example, Schneider and Tessier (2007) found that anxiously withdrawn young adolescents reported prioritizing receiving help over intimate exchange with their close friends. As such, anxiously withdrawn young adolescents may perceive their friendships as unsatisfactory when their friends do not, or cannot, provide them with support, either because their requests for help overburden their friends or their friends have shared vulnerabilities.

Given the aforementioned characteristics and features of anxiously withdrawn youths' friendship experiences, one important question to ask is whether their friendships "matter" or can offset their risks for social and emotional maladjustment (e.g., negative self-regard, rejection sensitivity, loneliness, social anxiety)—much like friendships can do for most other youth (see Rubin et al., 2015, for a review). Relative to the research on anxious withdrawal and the impact of *group*-level peer difficulties (see previous section), little attention has been paid to the influence of friendships in the lives of anxiously withdrawn youth. Nevertheless, there is some evidence that their friendships may be helpful, particularly in terms of *social* outcomes (Bowker & Spencer, 2010; Ladd et al., 2011; Rubin et al., 2006). For instance, findings from one study showed that peers rated highly anxious-withdrawn young adolescents with mutual friends as more sociable and popular than those without mutual friends (Rubin et al., 2006). Involvement in mutual mixed-grade friendships (i.e., same-school, different-grade friendships; Bowker & Spencer, 2010) as well as *stable* mutual same-grade friendships (Ladd et al., 2011) has also been associated with lower levels of peer victimization among anxiously withdrawn youth. However, it is noteworthy that increases in the expression of anxiously withdrawn behavior from late childhood into early adolescence have been predicted by having a best friend who is likewise anxiously withdrawn (Oh et al., 2008).

With regard to *psychological* outcomes, similar protective effects have been noted (Bukowski et al., 2010; Markovic & Bowker, 2017; Ponti & Tani, 2015; Vanhalst, Luyckx, & Goossens, 2014). For instance, in two longitudinal studies, involvement in mutual friendships was found to diminish the psychological difficulties

(depressive symptoms, loneliness) associated with anxious withdrawal during childhood (Bukowski et al., 2010) and early adolescence (Markovic & Bowker, 2017). Similarly, shy children with a high-quality best-friend relationship experience less anxiety and more positive self-esteem than those who lack a high-quality best friendship (Fordham & Stevenson-Hinde, 1999). Thus, it appears that despite shared difficulties with their friends and a relative lack of intimate disclosure in their friendships, the protective power of anxiously withdrawn youths' friendships is not entirely diminished.

Why might this be the case? Specific mechanisms of influence have yet to be empirically evaluated. However, we posit that anxiously withdrawn youth who are able to form mutual friendships may still be able to feel socially secure and satisfied due to feelings of *belonging* that come with *mutual* friendship involvement. We also think it is possible that involvement in mutual friendships may diminish peer perceptions of weakness/vulnerability (by having a peer by one's side; Rubin et al., 2006) as well as anxiously withdrawn youths' social fears and negatively laden cognitions, including those pertaining to rejection. This, in turn, may help to improve social interactions with others as well as psychological well-being (e.g., Burgess et al., 2006; Oh et al., 2008). Finally, mutual friendships may present anxiously withdrawn children with a safe social space within which to practice and acquire certain social competencies that can be transferred to future social interactions with other peers.

In summary, anxiously withdrawn children and young adolescents are as likely as typical youth to have a best friendship. Nevertheless, their friends appear to be much like them behaviorally and reputationally, and both anxiously withdrawn youth and their best friends think relatively poorly of the quality of their friendship. Furthermore, having an anxiously withdrawn friend or a poor quality friendship increases the expression of anxious withdrawal over time. This latter finding raises the question of whether the friendships of anxiously withdrawn youth are likely to play an exacerbating role in the development of social anxiety.

Lastly, and not insignificantly, researchers have yet to study the longitudinal relations between infant and toddler behavioral inhibition and the quality of children's and adolescents' friendships. To do so would require that behavioral inhibition researchers leave their laboratories and enter the classroom or schoolyard. Clearly, this is a prospect that we look forward to reading about … especially given that best friendship can play both a protective and an exacerbating role in the development of social and emotional outcomes for anxiously withdrawn youth (Rubin et al., 2018).

Conclusions

The literature reviewed in this chapter clearly suggests that what is known about the relations, contemporaneous or predictive, between behavioral inhibition and children's peer relations is largely limited to situations that are unfamiliar and participants who are unknown to each other. And yet, the extant literature on the constructs

of anxious withdrawal and solitude is rich, theoretically driven, and informative. We have attempted to demonstrate that the quality of life among peers for anxiously withdrawn children is less than pleasant. They are socially deferent, lonely, rejected, victimized, and insecure in the company of peers. Anxiously withdrawn children fail to exhibit age-appropriate interpersonal problem-solving skills and tend to believe themselves to be deficient in social skills and relationships. It is also the case that the friendships of anxiously withdrawn youth are less fun and supportive than those of typical youth. Indeed, anxiously withdrawn children's best friends are often very much like them behaviorally and emotionally. Finally, several researchers have found links between the consistent display of anxious withdrawal among familiar peers and early adolescent psychological maladaptation. Taken together, these findings do not augur well for socially withdrawn youth.

If anxiously withdrawn children experience less than pleasant lives among their familiar schoolmates, what can we do about it? An obvious suggestion is to identify, in early childhood, children who are characteristically at risk for the development of poor peer relations and the associated negative outcomes described in this chapter and intervene to prevent this negative trajectory. Another obvious recommendation is to make certain that these interventions comprise "lesson plans" that will target not only the social fearfulness of inhibited, shy, young children (e.g., through mindfulness and emotion regulation training) but also the known social-cognitive and social skills that these children appear to lack.

One such newly developed intervention is the "Turtle Program" that combines 8 weeks of Parent-Child Interaction Therapy (PCIT) with a similar number of weeks of Social Skills and Facilitated Play (SSFP) sessions for extremely shy preschoolers in a peer group setting. Initial results of this newly developed program have proved rather promising. For example, preschoolers randomly assigned to the Turtle Program demonstrated significant decreases in teacher-reported anxiety symptoms (Chronis-Tuscano et al., 2015) and were observed to increase their frequency of observed classroom social interactions with, and initiations toward, peers compared to a waitlist control group (Barstead et al., 2018).

Thus, unlike previous early intervention efforts directed at young children who have been variously described as behaviorally inhibited or extremely shy (see the chapter "Behavioural Inhibition and the Prevention of Internalising Distress in Early Childhood" by Rapee and Bayer), the Turtle Program has demonstrated the transfer of intervention effects to the classroom, an extremely promising finding given that the classroom context is where many young shy/inhibited children display socially reticent behavior among familiar peers. This intervention is now in a larger, second phase that will comprise multiple cohorts of extremely shy/inhibited preschoolers who will be followed, into their classrooms, among familiar peers, for at least 1 year post-intervention. In the best of all worlds, one would hope that when these youngsters reach elementary school, they will not only demonstrate socially competent interactions with their familiar classmates but will avert the consequences of the above-described negative peer interactions and relationships associated with the continued display of anxiously withdrawn behavior.

References

Avant, T. S., Gazelle, H., & Faldowski, R. (2011). Classroom emotional climate as a moderator of anxious solitary children's longitudinal risk for peer exclusion: A child x environment model. *Developmental Psychology, 47*, 1711–1727. https://doi.org/10.1037/a0024021

Barstead, M. G., Danko, C. M., O'Brien, K. O., Coplan, R. J., Chronis-Tuscano, A., & Rubin, K. H. (2018). Generalization of an Early Intervention for Inhibited Preschoolers to the Classroom Setting, *Journal of Child and Family Studies, 27*, 2943–2953. https://doi.org/10.1007/s10826-018-1142-0

Berger, C., & Rodkin, P. C. (2012). Group influences on individual aggression and prosociality: Early adolescents who change peer affiliations. *Social Development, 21*(2), 396–413.

Bohlin, G., Hagekull, B., & Andersson, K. (2005). Behavioral inhibition as a precursor of peer social competence in early school age: The interplay with attachment and nonparental care. *Merrill-Palmer Quarterly, 51*, 1–19.

Boivin, M., & Hymel, S. (1997). Peer experiences and social self-perceptions: A sequential model. *Developmental Psychology, 33*, 135–145.

Boivin, M., Hymel, S., & Bukowski, W. M. (1995). The roles of social withdrawal, peer rejection, and victimization by peers in predicting loneliness and depressed mood in childhood. *Development and Psychopathology, 7*, 765–785. https://doi.org/10.1017/S0954579400006830

Booth-Laforce, C., Oh, W., Kennedy, A. E., Rubin, K. H., Rose-Krasnor, L., & Laursen, B. (2012). Parent and peer links to trajectories of anxious withdrawal from grades 5 to 8. *Journal of Clinical Child and Adolescent Psychology, 41*, 138–149.

Bowker, J. C., & Spencer, S. (2010). Friendship and adjustment: A focus on mixed-grade friendships. *Journal of Youth and Adolescence, 39*(11), 1318–1329. https://doi.org/10.1007/s10964-009-9474-0

Brooker, R. J., Kiel, E. J., & Buss, K. A. (2016). Early social fear predicts kindergarteners' socially anxious behaviors: direct associations, moderation by inhibitory control, and differences from nonsocial fear. *Emotion, 16*, 997–1010.

Bukowski, W. M., Laursen, B., & Hoza, B. (2010). The snowball effect: Friendship moderates escalations in depressed affect among avoidant and excluded children. *Development and Psychopathology, 22*, 749–757.

Bukowski, W., Laursen, B., & Rubin, K. H. (Eds.). (2018). *Handbook of peer interactions, relationships, and groups* (2nd ed.). New York, NY: Guilford.

Burgess, K. B., Wojslawowicz, J. C., Rubin, K. H., Rose-Krasnor, L., & Booth-LaForce, C. (2006). Social information processing and coping strategies of shy/withdrawn and aggressive children: Does friendship matter? *Child Development, 77*(2), 371–383. https://doi.org/10.1111/j.1467-8624.2006.00876.x

Buss, A. H. (1986). A theory of shyness. In W. H. Jones, J. M. Cheek, & S. R. Briggs (Eds.), *Shyness: Perspectives on research and treatment* (pp. 39–46). New York, NY: Plenum.

Buss, A.H., & Plomin, R. (1984). Colorado childhood temperament inventory. (Available from the Institute of Behavioral Genetics, University of Colorado, Boulder, CO 80309–0447).

Buss, K. A., Davis, E. L., Kiel, E. J., Brooker, R. J., Beekman, C., & Early, M. C. (2013). Dysregulated fear predicts social wariness and social anxiety symptoms during kindergarten. *Journal of Clinical Child & Adolescent Psychology, 42*, 603–616.

Cain, S. (2012). *Quiet: The power of introverts in a world that can't stop talking*. New York, NY: Broadway Books.

Chen, X. (2010). Shyness-inhibition in childhood and adolescence: A cross-cultural perspective. In K. H. Rubin & R. J. Coplan (Eds.), *The development of shyness and social withdrawal* (pp. 213–235). New York, NY: Guilford.

Chen, X., Chang, L., Liu, H., & He, Y. (2008). Effects of the peer group on the development of social functioning and academic achievement: A longitudinal study in Chinese children. *Child Development, 79*, 235–251.

Chen, X., DeSouza, A., Chen, H., & Wang, L. (2006). Reticent behavior and experiences in peer interactions in Canadian and Chinese children. *Developmental Psychology, 42*, 656–665.

Chen, X., Dong, Q., & Zhou, H. (1997). Authoritative and authoritarian parenting practices and social and school performance in Chinese children. *International Journal of Behavioral Development, 21*, 855–873.

Chen, X., Li, J., & Chen, L. (2018). Culture and peer relationships. In W. Bukowski, B. Laursen, & K. H. Rubin (Eds.), *Handbook of peer interactions, relationships, and groups* (2nd ed.). New York, NY: Guilford.

Chen, X., Rubin, K. H., & Sun, Y. (1992). Social reputation and peer relationships in Chinese and Canadian children: A cross-cultural study. *Child Development, 63*, 1336–1343. https://doi.org/10.2307/1131559

Chen, X., Wang, L., & Wang, Z. (2009). Shyness-sensitivity and social, school and psychological adjustment in rural migrant and urban children in China. *Child Development, 80*, 1499–1513. https://doi.org/10.1111/j.1467-8624.2009.01347.x

Chronis-Tuscano, A., Degnan, K., Pine, D., Pérez-Edgar, K., Henderson, H., Diaz, Y., … Fox, N. A. (2009). Stable early maternal report of behavioral inhibition predicts lifetime social anxiety disorder in adolescence. *Journal of the American Academy of Child & Adolescent Psychiatry, 48*, 928–935. https://doi.org/10.1097/CHI.0b013e3181ae09df

Chronis-Tuscano, A., Rubin, K. H., O'Brien, K. A., Coplan, R. J., Thomas, S. R., Dougherty, L. R., … Wimsatt, M. (2015). Preliminary evaluation of a multimodal early intervention program for behaviorally inhibited preschoolers. *Journal of Consulting and Clinical Psychology, 83*, 534–540.

Coplan, R. J., Arbeau, K. A., & Armer, M. (2008). Don't fret, be supportive! Maternal characteristics linking child shyness to psychosocial and school adjustment in kindergarten. *Journal of Abnormal Child Psychology, 36*, 359–371.

Coplan, R. J., Girardi, A., Findlay, L. C., & Frohlick, S. L. (2007). Understanding solitude: Young children's attitudes and responses toward hypothetical socially withdrawn peers. *Social Development, 16*(3), 390–409. https://doi.org/10.1111/j.1467-9507.2007.00390.x

Coplan, R. J., Hughes, K., & Roswell, H. C. (2010). Once upon a time there were a blushful hippo and a meek mouse: A content analysis of shy characters in young children's storybooks. In K. H. Rubin & R. J. Coplan (Eds.), *The development of shyness and social withdrawal* (pp. 262–274). New York, NY: Guilford.

Coplan, R. J., Rose-Krasnor, L., Weeks, M., Kingsbury, A., Kingsbury, M., & Bullock, A. (2013). Alone is a crowd: Social motivations, social withdrawal, and socioemotional functioning in later childhood. *Developmental Psychology, 49*, 861–875. https://doi.org/10.1037/a0028861

Coplan, R. J., & Rubin, K. H. (1998). Exploring and assessing nonsocial play in the preschool: The development and validation of the Preschool Play Behavior Scale. *Social Development, 7*, 72–91.

Coplan, R. J., & Rubin, K. H. (2010). Social withdrawal and shyness in childhood: History, definitions, theories, and assessments. In K. H. Rubin & R. J. Coplan (Eds.), *The development of shyness and social withdrawal* (pp. 1–20). New York, NY: Guilford.

Coplan, R. J., Rubin, K. H., Fox, N. A., Calkins, S. D., & Stewart, S. L. (1994). Being alone, playing alone, and acting alone: Distinguishing among reticence, and passive-, and active-solitude in young children. *Child Development, 65*, 129–138.

Degnan, K. A., Fox, N. A., Henderson, H. A., Rubin, K. H., & Nichols, K. (2008). Predicting social wariness in middle childhood: The moderating roles of childcare history, maternal personality and maternal behavior. *Social Development, 17*, 471–487. https://doi.org/10.1111/j.1467-9507.2007.00437.x

Dishion, T. J., Andrews, D. W., & Crosby, L. (1995). Antisocial boys and their friends in early adolescence: Relationship characteristics, quality, and interactional process. *Child Development, 66*, 139–151.

Doey, L., Coplan, R. J., & Kingsbury, M. (2014). Bashful boys and coy girls: A review of gender differences in childhood shyness. *Sex Roles, 70*, 255–266. https://doi.org/10.1007/s11199-013-0317-9

Dollar, J. M., Stifter, C. A., & Buss, K. A. (2017). Exuberant and inhibited children: Person-centered profiles and links to social adjustment. *Developmental Psychology, 53*, 1222–1229.

Erath, S. A., Flanagan, K. S., & Bierman, K. L. (2007). Social anxiety and peer relations in early adolescence: Behavioral and cognitive factors. *Journal of Abnormal Child Psychology, 35*, 405–416.

Fordham, K., & Stevenson-Hinde, J. (1999). Shyness, friendship quality, and adjustment during middle childhood. *The Journal of Child Psychology and Psychiatry and Allied Disciplines, 40*, 757–768.

Fox, N. A., Henderson, H. A., Marshall, P. J., Nichols, K. E., & Ghera, M. M. (2005). Behavioral inhibition: Linking biology and behavior within a developmental framework. *Annual Review of Psychology, 56*, 235–262. https://doi.org/10.1146/annurev.psych.55.090902.141532

Fox, N. A., Henderson, H. A., Rubin, K. H., Calkins, S. D., & Schmidt, L. (2001). Continuity and discontinuity of behavioral inhibition and exuberance: Psychophysiological and behavioral influences across the first four years of life. *Child Development, 72*, 1–21. https://doi.org/10.1111/1467-8624.00262

Fox, N. A., Rubin, K. H., Calkins, S. D., Marshall, T. R., Coplan, R. J., Porges, S. W., … Stewart, S. L. (1995). Frontal activation asymmetry and social competence at four years of age: Left frontal hyper- and hypo-activation as correlates of social behavior in preschool children. *Child Development, 66*, 1770–1784.

Fredstrom, B. K., Rose-Krasnor, L., Campbell, K., Rubin, K. H., Booth-LaForce, C., & Burgess, K. B. (2012). Brief report: How anxiously withdrawn preadolescents think about friendship. *Journal of Adolescence, 35*, 451–454.

García-Coll, C., Kagan, J., & Reznick, J. S. (1984). Behavioral inhibition in young children. *Child Development, 55*, 1005–1019.

Gavinski-Molina, M. H., Coplan, R. J., & Younger, A. (2003). A closer look at children's knowledge about social isolation. *Journal of Research in Childhood Education, 18*, 93–104.

Gazelle, H. (2006). Class climate moderates peer relations and emotional adjustment in children with an early history of anxious solitude: A child X environment model. *Developmental Psychology, 42*, 1179–1192. https://doi.org/10.1037/0012-1649.42.6.1179

Gazelle, H. (2008). Behavioral profiles of anxious solitary children and heterogeneity in peer relations. *Developmental Psychology, 44*, 1604–1624.

Gazelle, H., & Druhen, M. J. (2009). Anxious solitude and peer exclusion predict social helplessness, upset affect, and vagal regulation in response to behavioral rejection by a friend. *Developmental Psychology, 45*, 1077–1096. https://doi.org/10.1037/a0016165

Gazelle, H., & Ladd, G. W. (2003). Anxious solitude and peer exclusion: A diathesis-stress model of internalizing trajectories in childhood. *Child Development, 74*, 257–278. https://doi.org/10.1111/1467-8624.00534

Gazelle, H., & Rudolph, K. D. (2004). Moving toward and away from the world: Social approach and avoidance trajectories in anxious solitary youth. *Child Development, 75*, 829–849.

Gazelle, H., & Spangler, T. (2007). Early childhood anxious solitude and subsequent peer relationships: Maternal and cognitive moderators. *Journal of Applied Developmental Psychology, 28*, 515–535. https://doi.org/10.1016/j.appdev.2007.06.006

Goldsmith, H. H. (1988). The Toddler behavior assessment questionnaire (Tech. Rep. No. 88–04). Eugene: University of Oregon, Oregon Center for the Study of Emotion.

Guimond, F. A., Brendgen, M., Vitaro, F., Forget-Dubois, N., Dionne, G., Tremblay, R. E., & Boivin, M. (2014). Gene–environment interplay in the link of friends' and nonfriends' behaviors with children's social reticence in a competitive situation. *Developmental Psychology, 50*, 956.

Hane, A. A., Cheah, C. S. L., Rubin, K. H., & Fox, N. A. (2008). The role of maternal behavior in the relation between shyness and social withdrawal in early childhood and social withdrawal in middle childhood. *Social Development, 17*, 795–811.

Hanish, L. D., & Guerra, N. G. (2004). Aggressive victims, passive victims, and bullies: Developmental continuity or developmental change? *Merrill-Palmer Quarterly, 50*, 17–38.

Hart, C. H., Yang, C., Nelson, L. J., Robinson, C. C., Olsen, J. A., Nelson, D. A., … Wu, P. (2000). Peer acceptance in early childhood and subtypes of socially withdrawn behaviour in China, Russia and the United States. *International Journal of Behavioral Development, 24*, 73–81.

Haselager, G. J., Hartup, W. W., Lieshout, C. F., & Riksen-Walraven, J. M. A. (1998). Similarities between friends and nonfriends in middle childhood. *Child Development, 69*, 1198–1208.

Hastings, P. D., Kahle, S., & Nuselovici, J. M. (2014). How well socially wary preschoolers fare over time depends on their parasympathetic regulation and socialization. *Child Development, 85*, 1586–1600.

Henderson, H. A., Marshall, P. J., Fox, N. A., & Rubin, K. H. (2004). Psychophysiological and behavioral evidence for varying forms and functions of nonsocial behaviors in preschoolers. *Child Development, 75*(1), 251–263.

Hinde, R. A. (1987). *Individuals, relationships and culture*. Cambridge, England: Cambridge University Press.

Hinde, R. A. (1995). A suggested structure for a science of relationships. *Personal Relationships, 2*, 1–15. https://doi.org/10.1111/j.1475-6811.1995.tb00074.x

Hinde, R. A., & Stevenson-Hinde, J. (2014). Framing our analysis: A dialectical perspective. In L. F. Leckman, C. Panter-Brick, & R. Salah (Eds.), *Pathways to peace: The transformative power of children and families* (pp. 19–26). Cambridge, MA: MIT.

Hodges, E. V. E., & Perry, D. G. (1999). Personal and interpersonal antecedents and consequences of victimization by peers. *Journal of Personality and Social Psychology, 76*, 677–685.

Kagan, J. (1999). The concept of behavioral inhibition. In L. A. Schmidt & J. Schulkin (Eds.), *Extreme fear, shyness, and social phobia: Origins, biological mechanisms, and clinical outcomes* (pp. 3–13). New York, NY: Oxford University Press.

Kagan, J., Reznick, J. S., Clarke, C., Snidman, N., & García-Coll, C. (1984). Behavioral inhibition to the unfamiliar. *Child Development, 55*, 2212–2225.

Kagan, J., Reznick, J., & Snidman, N. (1987). The physiology and psychology of behavioral inhibition in children. *Child Development, 58*, 1459–1473.

Kagan, J., Reznick, J. S., & Snidman, N. (1988). Biological bases of childhood shyness. *Science, 240*, 167–171.

Kandel, D. B. (1978). Homophily, selection, and socialization in adolescent friendships. *American Journal of Sociology, 84*, 427–436.

Katzer, C., Fetchenhauer, D., & Belschak, F. (2009). Cyberbullying: Who are the victims? *Journal of Media Psychology, 21*(1), 25–36. https://doi.org/10.1027/1864-1105.21.1.25

Kiel, E. J., & Buss, K. A. (2011). Prospective relations among fearful temperament, protective parenting, and social withdrawal: The role of maternal accuracy in a moderated mediation framework. *Journal of Abnormal Child Psychology, 39*, 953–966.

Kindermann, T. A. (2007). Effects of naturally existing peer groups on changes in academic engagement in a cohort of sixth graders. *Child Development, 78*, 1186–1203.

Kindermann, T., & Gest, S. D. (2009). Assessment of the peer group: Identifying naturally occurring social networks and capturing their effects. In K. Rubin, W. Bukowski, & B. Laursen (Eds.), *Handbook of peer interactions, relationships and groups*. New York, NY: Guilford Press.

Kochanska, G. (1991). Patterns of inhibition to the unfamiliar in children of normal and affectively ill mothers. *Child Development, 62*, 250–263.

Kochanska, G., & Radke-Yarrow, M. (1992). Inhibition in toddlerhood and the dynamics of the child's interaction with an unfamiliar peer at age five. *Child Development, 63*, 325–335.

Kowalski, R. M., Morgan, C. A., & Limber, S. P. (2012). Traditional bullying as a potential warning sign of cyberbullying. *School Psychology International, 33*(5), 505–519. https://doi.org/10.1177/0143034312445244

Ladd, G. W. (2006). Peer rejection, aggressive or withdrawn behavior, and psychological maladjustment from ages 5 to 12: An examination of four predictive models. *Child Development, 77*(4), 822–846. https://doi.org/10.1111/j.1467-8624.2006.00905.x

Ladd, G. W., & Burgess, K. B. (1999). Charting the relationship trajectories of aggressive, withdrawn, and aggressive/withdrawn children during early grade school. *Child Development, 70*, 910–929.

Ladd, G. W., Kochenderfer-Ladd, B., Eggum, N. D., Kochel, K. P., & McConnell, E. M. (2011). Characterizing and comparing the friendships of anxious-solitary and unsociable preadolescents. *Child Development, 82*, 1434–1453. https://doi.org/10.1111/j.1467-8624.2011.01632.x

Laursen, B. (2017). Making and keeping friends: The importance of being similar. *Child Development Perspectives, 11*, 282–289.

LeMare, L. J., & Rubin, K. H. (1987). Perspective taking and peer interaction: Structural and developmental analyses. *Child Development, 58*, 306–315. https://doi.org/10.2307/1130508

Lewis-Morrarty, E., Degnan, K. A., Chronis-Tuscano, A., Pine, D. S., Henderson, H. A., & Fox, N. A. (2015). Infant attachment security and early childhood behavioral inhibition interact to predict adolescent social anxiety symptoms. *Child Development, 86*, 598–613. https://doi.org/10.1111/cdev.12336

Lewis-Morrarty, E., Degnan, K. A., Chronis-Tuscano, A., Rubin, K. H., Cheah, C. L., Pine, D. S., & Fox, N. A. (2012). Maternal over-control moderates the association between early childhood behavioral inhibition and adolescent social anxiety symptoms. *Journal of Abnormal Child Psychology, 40*, 1363–1373. https://doi.org/10.1007/s10802-012-9663-2

London, B., Downey, G., Bonica, C., & Paltin, I. (2007). Social causes and consequences of rejection sensitivity. *Journal of Research on Adolescence, 17*, 481–506. https://doi.org/10.1111/j.1532-7795.2007.00531.x

Markovic, A., & Bowker, J. C. (2017). Friends also matter: Examining friendship adjustment indices as moderators of anxious-withdrawal and trajectories of change in psychological maladjustment. *Developmental Psychology, 53*(8), 1462–1473.

Mead, G. H. (1934). *Mind, self and society from the standpoint of a social behaviorist*. Chicago, IL: University of Chicago Press.

Menzer, M. M., McDonald, K. L., Rubin, K. H., Rose-Krasnor, L., Booth-LaForce, C., & Schulz, A. (2012). Observed gossip moderates the link between anxious withdrawal and friendship quality in early adolescence. *International Journal of Developmental Science, 6*, 191–202.

Miller, S. R., Tserakhava, V., & Miller, C. J. (2011). My child is shy and has no friends: What does parenting have to do with it? *Journal of Youth and Adolescence, 40*, 442–452. https://doi.org/10.1007/s10964-010-9550-5

Oh, W., Rubin, K. H., Bowker, J. C., Booth-LaForce, C., Rose-Krasnor, L., & Laursen, B. (2008). Trajectories of social withdrawal from middle childhood to early adolescence. *Journal of Abnormal Child Psychology, 36*, 553–566. https://doi.org/10.1007/s10802-007-9199-z

Olweus, D. (1993). *Bullying at school: What we know and what we can do*. Malden, MA: Blackwell.

Parker, J. G., & Asher, S. R. (1993). Friendship and friendship quality in middle childhood: Links with peer group acceptance and feelings of loneliness and social dissatisfaction. *Developmental Psychology, 29*, 611–621.

Penela, E. C., Walker, O. L., Degnan, K. A., Fox, N. A., & Henderson, H. A. (2015). Early behavioral inhibition and emotion regulation: Pathways toward social competence in middle childhood. *Child Development, 86*, 1227–1240.

Pérez-Edgar, K., Bar-Haim, Y., McDermott, J. M., Chronis-Tuscano, A., Pine, D. S., & Fox, N. A. (2010). Attention biases to threat and behavioral inhibition in early childhood shape adolescent social withdrawal. *Emotion, 10*, 349–357.

Pérez-Edgar, K., McDermott, J. M., Korelitz, K., Degnan, K. A., Curby, T. W., Pine, D. S., & Fox, N. A. (2010). Patterns of sustained attention in infancy shape the developmental trajectory of social behavior from toddlerhood through adolescence. *Developmental Psychology, 46*, 1723–1730.

Piaget, J. (1932). *The moral judgment of the child*. London, England: Routledge & Kegan Paul.

Ponti, L., & Tani, F. (2015). Shyness and psychological adjustment: The moderating role of friendship relationships. *Journal of Psychopathology, 21*, 30–39.

Poulin, F., & Chan, A. (2010). Friendship stability and change in childhood and adolescence. *Developmental Review, 30*, 257–272.

Raskauskas, J., & Stoltz, A. D. (2007). Involvement in traditional and electronic bullying among adolescents. *Developmental Psychology, 43*, 564–575.

Reznick, J. S., Gibbons, J. L., Johnson, M. O., & McDonough, P. M. (1989). Behavioral inhibition in a normative sample. In J. S. Reznick (Ed.), *Perspectives on behavioral inhibition. The John D. and Catherine T. MacArthur Foundation series on mental health and development* (pp. 25–49). Chicago, IL: The University of Chicago Press.

Rose, A. J., Carlson, W., & Waller, E. M. (2007). Prospective associations of co-rumination with friendship and emotional adjustment: Considering the socioemotional trade-offs of co-rumination. *Developmental Psychology, 43*, 1019–1031. https://doi.org/10.1037/0012-1649.43.4.1019

Rubin, K. H. (1982a). Social and social-cognitive developmental characteristics of young isolate, normal and sociable children. In K. H. Rubin & H. S. Ross (Eds.), *Peer relationships and social skills in childhood* (pp. 353–374). New York, NY: Springer-Verlag.

Rubin, K. H. (1982b). Non-social play in preschoolers: Necessary evil? *Child Development, 53*, 651–657. https://doi.org/10.2307/1129376

Rubin, K. H. (1985). Socially withdrawn children: An "at risk" population? In B. Schneider, K. H. Rubin, & J. Ledingham (Eds.), *Children's peer relations: Issues in assessment and intervention* (pp. 125–139). New York, NY: Springer-Verlag.

Rubin, K. H., Bowker, J. C., Coplan, R. J., & Barstead, M. G. (2018). Withdrawing from the peer group. In W. Bukowski, B. Laursen, & K. H. Rubin (Eds.), *Handbook of peer interactions, relationships, and groups* (2nd ed.). New York, NY: Guilford.

Rubin, K. H., & Borwick, D. (1984). The communication skills of children who vary with regard to sociability. In H. Sypher & J. Applegates (Eds.), *Social cognition and communication* (pp. 152–170). Hillsdale, NJ: Erlbaum.

Rubin, K. H., Bukowski, W. M., & Bowker, J. C. (2015). Children in peer groups. In M. H. Bornstein & T. Leventhal (Eds.), *Handbook of child psychology and developmental science: Ecological settings and processes in developmental systems* (Vol. 4, 7th ed., pp. 175–222). New York, NY: Wiley.

Rubin, K. H., Bukowski, W., & Parker, J. G. (1998). Peer interactions, relationships, and groups. In N. Eisenberg (Ed.), *Handbook of child psychology: Social, emotional, and personality development* (Vol. 3, 5th ed., pp. 619–700). New York, NY: Wiley.

Rubin, K. H., Burgess, K. B., & Hastings, P. D. (2002). Stability and social–behavioral consequences of toddlers' inhibited temperament and parenting behaviors. *Child Development, 73*, 483–495.

Rubin, K. H., Burgess, K., Kennedy, A. E., & Stewart, S. (2003). Social withdrawal and inhibition in childhood. In E. Mash & R. Barkley (Eds.), *Child psychopathology* (2nd ed., pp. 372–406). New York, NY: Guilford.

Rubin, K. H., Cheah, C. S. L., & Menzer, M. (2009). Peer relationships. In M. Bornstein (Ed.), *Handbook of cross-cultural developmental science* (pp. 223–238). New York, NY: Psychology Press.

Rubin, K. H., Chen, X., & Hymel, S. (1993). The socio-emotional characteristics of extremely aggressive and extremely withdrawn children. *Merrill-Palmer Quarterly, 39*, 518–534.

Rubin, K. H., Chen, X., McDougall, P., Bowker, A., & McKinnon, J. (1995). The Waterloo Longitudinal Project: Predicting adolescent internalizing and externalizing problems from early and mid-childhood. *Development and Psychopathology, 7*, 751–764.

Rubin, K. H., Coplan, R. J., & Bowker, J. C. (2009). Social withdrawal in childhood. *Annual Review of Psychology, 60*, 141–171. https://doi.org/10.1146/annurev.psych.60.110707.163642

Rubin, K. H., Hastings, P. D., Stewart, S. L., Henderson, H. A., & Chen, X. (1997). The consistency and concomitants of inhibition: Some of the children, all of the time. *Child Development, 68*, 467–483. https://doi.org/10.2307/113167

Rubin, K. H., Hymel, S., Mills, R., & Rose-Krasnor, L. (1991). Conceptualizing different pathways to and from social isolation in childhood. In D. Cicchetti & S. Toth (Eds.), *The Rochester symposium on developmental psychopathology. Internalizing and externalizing expressions of dysfunction* (Vol. 2). New York, NY: Cambridge University Press.

Rubin, K. H., & Krasnor, L. R. (1986). Social-cognitive and social behavioral perspectives on problem solving. In M. Perlmutter (Ed.), *Cognitive perspectives on children's social and behavioral development. The Minnesota symposia on child psychology* (Vol. 18, pp. 1–68). Hillsdale, NJ: Erlbaum.

Rubin, K. H., & Rose-Krasnor, L. (1992). Interpersonal problem solving and social competence in children. In V. B. Van Hasselt & M. Hersen (Eds.), *Handbook of social development* (pp. 283–323). New York, NY: Plenum.

Rubin, K. H., LeMare, L. J., & Lollis, S. (1990). Social withdrawal in childhood: Developmental pathways to rejection. In S. R. Asher & J. D. Coie (Eds.), *Peer rejection in childhood* (pp. 217–249). New York, NY: Cambridge University Press.

Rubin, K. H., Nelson, L. J., Hastings, P. D., & Asendorpf, J. (1999). The transaction between parents' perceptions of their children's shyness and their parenting styles. *International Journal of Behavioral Development, 23*, 937–958. https://doi.org/10.1080/016502599383612

Rubin, K. H., Wojslawowicz, J. C., Rose-Krasnor, L., Booth-LaForce, C., & Burgess, K. B. (2006). The best friendships of shy/withdrawn children: prevalence, stability, and relationship quality. *Journal of Abnormal Child Psychology, 34*, 143–157. https://doi.org/10.1007/s10802-005-9017-4

Salmivalli, C., & Peets, K. (2018). Bullying and victimization. In W. Bukowski, B. Laursen, & K. H. Rubin (Eds.), *Handbook of peer interactions, relationships, and groups* (2nd ed.). New York, NY: Guilford.

Santos, A. J., Vaughn, B. E., & Bost, K. K. (2008). Specifying social structures in preschool classrooms: Descriptive and functional distinctions between affiliative subgroups. *Acta Ethologica, 11*, 101–113.

Schmidt, L. A., & Buss, A. H. (2010). Understanding shyness: Four questions and four decades of research. In K. H. Rubin & R. J. Coplan (Eds.), *The development of shyness and social withdrawal* (pp. 23–41). New York, NY: Guilford.

Schmidt, L. A., Fox, N. A., Rubin, K. H., Sternberg, E. M., Gold, P. W., Smith, C., & Schulkin, J. (1997). Behavioral and neuroendocrine responses in shy children. *Developmental Psychobiology, 30*, 127–140.

Schneider, B. H. (2009). An observational study of the interactions of socially withdrawn/anxious early adolescents and their friends. *Journal of Child Psychology and Psychiatry, 50*, 799–806.

Schneider, B. H., Richard, J. F., Younger, A. J., & Freeman, P. (2000). A longitudinal exploration of the continuity of children's social participation and social withdrawal across socioeconomic status levels and social settings. *European Journal of Social Psychology, 30*, 497–519.

Schneider, B. H., & Tessier, N. G. (2007). Close friendship as understood by socially withdrawn, anxious early adolescents. *Child Psychiatry and Human Development, 38*, 339–351.

Schwartz-Mette, R. A., & Rose, A. J. (2009). Conversational self-focus in adolescent friendships: observational assessment of an interpersonal process and relations with internalizing symptoms and friendship quality. *Journal of Social and Clinical Psychology, 28*, 1263–1297. https://doi.org/10.1521/jscp.2009.28.10.1263

Stewart, S. L., & Rubin, K. H. (1995). The social problem-solving skills of anxious-withdrawn children. *Development and Psychopathology, 7*, 323–336. https://doi.org/10.1017/s0954579400006532

Sullivan, H. S. (1953). *The interpersonal theory of psychiatry*. New York, NY: Norton.

Sussman, S., Pokhrel, P., Ashmore, R. D., & Brown, B. B. (2007). Adolescent peer group identification and characteristics: A review of the literature. *Addictive Behaviors, 32*, 1602–1627.

Suway, J. G., Degnan, K. A., Sussman, A. L., & Fox, N. A. (2012). The relations among theory of mind, behavioral inhibition, and peer interactions in early childhood. *Social Development, 21*, 331–342.

Tarullo, A. R., Mliner, S., & Gunnar, M. R. (2011). Inhibition and exuberance in preschool classrooms: Associations with peer social experiences and changes in cortisol across the preschool year. *Developmental Psychology, 47*, 1374–1388.

Turiel, E. (1983). *The development of social knowledge: Morality and convention*. Cambridge, England: Cambridge University Press.

Vanhalst, J., Luyckx, K., & Goossens, L. (2014). Experiencing loneliness in adolescence: A matter of individual characteristics, negative peer experiences, or both? *Social Development, 23*, 100–118.

Walker, O. L., Henderson, H. A., Degnan, K. A., Penela, E. C., & Fox, N. A. (2014). Associations between behavioral inhibition and children's social problem-solving behavior during social exclusion. *Social Development, 23*, 487–501.

Wang, J., McDonald, K. L., Rubin, K. H., & Laursen, B. (2012). Peer rejection as a social antecedent to rejection sensitivity in youth: The role of relational valuation. *Personality and Individual Differences, 53*, 939–942. https://doi.org/10.1016/j.paid.2012.07.007

Wichmann, C., Coplan, R. J., & Daniels, T. (2004). The social cognitions of socially withdrawn children. *Social Development, 13*, 377–392.

Yang, F., Chen, X., & Wang, L. (2015). Shyness-sensitivity and social, school, and psychological adjustment in urban Chinese children: A four-wave longitudinal study. *Child Development, 86*, 1848–1864. https://doi.org/10.1111/cdev.12414

Younger, A. J., & Daniels, T. (1992). Children's reasons for nominating their peers as withdrawn: Passive withdrawal versus active isolation. *Developmental Psychology, 28*, 955–960.

The Temperamentally Shy Child as the Social Adult: An Exemplar of Multifinality

Kristie L. Poole, Alva Tang, and Louis A. Schmidt

Abstract Does child temperament predict adult personality and social behavior? We argue that the antecedent and foundation of temperamental shyness observed in childhood and adulthood is rooted in temperamental inhibition first observed in early infancy, particularly inhibition to social novelty, which has a strong biological basis. With development, we believe the temperamental shyness phenotype becomes more intricate with the emergence of self-concept and the person now positioned within multiple contexts, each of which exerts different influences on shaping personality development. In this chapter, we review the developmental course and socioemotional outcomes of temperamental shyness. We first propose a developmental model of temperamental shyness that we have been developing over the last two decades.

The model illustrates links to temperamental inhibition, the multiple influences on temperamentally shy children across development, and how different types of temperamental shyness may develop over time and lead to multiple socioemotional outcomes in adulthood. Using this model, we then address three questions: (1) What is the developmental course of temperamental shyness from childhood to adulthood? (2) What factors alter the stability of temperamental shyness across development? (3) How are different types of shyness linked to distinct outcomes across development? We conclude with a discussion of some of the future avenues that are needed for research examining the developmental course of temperamental shyness across the lifespan.

The Child Is Father to The Man

—Wordsworth (1802)

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The Temperamentally Shy Child as the Social Adult: An Exemplar of Multifinality

Does child temperament predict adult personality and social behavior? Although this question has been a central tenet of the field of personality development for decades (Allport, 1937; Frenkel et al., 2015; Halverson, Kohnstamm, & Martin, 1994; Kagan & Moss, 1962), we only recently have been in a position to reliably answer this long-standing question. Possible reasons for this are at least threefold. First, birth cohorts that have been systematically investigated and followed prospectively and longitudinally are now reaching adulthood. Second, there have been advances in the development and refinement of statistical approaches to analyze and interpret longitudinal datasets. Third, repeated assessments of behaviors across time and context via direct observations in controlled laboratory settings and in the individual's everyday environments have improved the description, characterization, and definition of temperament and personality phenotypes. As illustrated in the many chapters in this volume, the prospective, longitudinal, and systematic study of the phenomenon of behavioral inhibition (a well-characterized temperamental phenotype derived from direct behavioral observations) and more complex statistical modeling of human development than in the past have now positioned us well to address the long-standing question of whether child temperament predicts adult personality and social behavior.

Behavioral inhibition is a temperamental construct that comprises both social and nonsocial components (García-Coll & Kagan, 1984; Kagan, Reznick, Clarke, Snidman, & García-Coll, 1984; Kagan, Reznick, & Snidman, 1987), each of which is unique from each other (Dyson, Klein, Olino, Dougherty, & Durbin, 2011; Kochanska, 1991; Neal, Edelmann, & Glachan, 2002; Schofield, Coles, & Gibb, 2009). However, much of the research examining the association between behavioral inhibition in childhood and later social behavioral tendencies (e.g., shyness, social anxiety, sociability) has not fully differentiated the specificity of social versus nonsocial behavioral inhibition in these relations between early behavioral inhibition and later social behavior. The social component of behavioral inhibition comprises wariness in response to unfamiliar social situations (e.g., stranger fear). There is evidence to suggest that *social* fearfulness and inhibition in early life may have particularly strong links with the development and maintenance of shyness and social anxiety given its strong social basis (Brooker, Kiel, & Buss, 2016; Chronis-Tuscano et al., 2009; Hayward, Killen, Kraemer, & Taylor, 1998; Kochanska, 1991; Mick & Telch, 1998; Miskovic & Schmidt, 2012; Schmidt & Schulkin, 1999; Schofield et al., 2009).

The specificity for social contexts highlights the importance of considering different types of behavioral inhibition in childhood (i.e., social versus nonsocial) when examining associations with later shyness and socioemotional outcomes (for animal models, see the chapter "Behavioral Inhibition in Nonhuman Primates: The Elephant in the Room" by Capitanio and the chapter "Behavioral Inhibition in Rodents: A Model to Study Causes and Health Consequences of Temperament" by

Cavigelli). Nonsocial inhibition refers to inhibition to novel toys, places, or events not involving people, while social inhibition refers to inhibition to unfamiliar people. In this chapter, we focus on the social component of behavioral inhibition (i.e., shyness). Shyness is defined as fear and inhibition in novel social situations and/or under conditions of perceived social evaluation (Kagan et al., 1987; Rubin, Coplan, & Bowker, 2009) and has its roots in temperamental inhibition for some children (see the chapter "The History and Theory of Behavioral Inhibition" by Kagan). These children we describe as temperamentally shy (Schmidt & Fox, 1999; Schmidt & Miskovic, 2013).

This chapter discusses the developmental course and socioemotional outcomes of temperamental shyness. We first propose a developmental model of temperamental shyness that we have been developing over the last two decades (e.g., Schmidt & Buss, 2010; Schmidt & Fox, 1999; Schmidt & Miskovic, 2013). Here we illustrate the links between temperamental inhibition and temperamental shyness, the multiple influences on temperamentally shy children across development, and how different types of temperamental shyness may develop over time and lead to different socioemotional outcomes in adulthood. Using this developmental model to highlight some of these issues, we then address three specific questions: (1) What is the developmental course of temperamental shyness from childhood to adulthood? (2) What factors alter the stability of temperamental shyness across development? (3) How are different types of shyness linked to distinct outcomes across development? We conclude with a discussion of some of the future avenues that are needed for research examining the developmental course of temperamental shyness across the lifespan.

Development of Temperamental Shyness

One of the limitations of previous and extant work on shyness has been that researchers have largely studied shyness as a homogenous phenomenon (see the chapter "Psychobiological Processes in the Development of Behavioral Inhibition" by Buss and Qu). Over the last two decades, we have proposed and refined a developmental model of shyness that suggests there may be at least two shyness subtypes (conflicted and avoidant) which are rooted in early temperament (Schmidt & Buss, 2010; Schmidt & Fox, 1999; Schmidt & Miskovic, 2013, 2014; Schmidt, Polak, & Spooner, 2001, 2005). The most recent iteration of our model is presented in Fig. 1.

As shown in Fig. 1, the x-axis represents developmental age or time, and the y-axis reflects the conceptualization of shyness, which ranges from temperament to self-concept and the relative weight given to each reflected in the color gradients. Temperament refers to early appearing individual differences in reactivity and regulation. In contrast to temperament, self-concept refers to later developing cognitive processes reflecting the beliefs one holds about the self and others. Here, $y = f(x)$ such that with increasing developmental age (x), the relative balance of temperament to self-concept to the conceptualization of shyness changes (y). With increasing age, self-concept (red and warmer colors) becomes a defining feature of

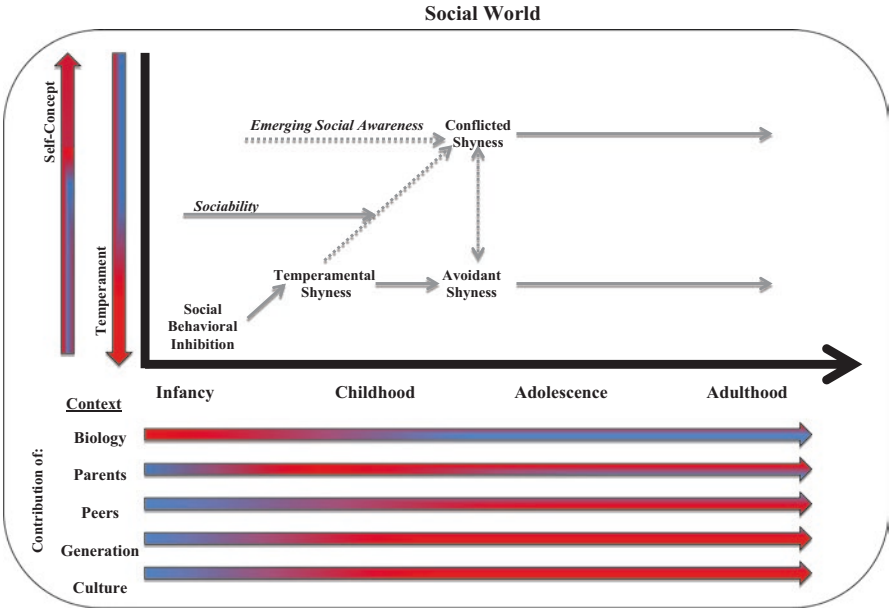

Fig. 1 Developmental model of temperamental shyness from early childhood to adulthood (from Schmidt & Poole, 2018). Note: In the colored gradients, red and warmer colors reflect relatively greater influence, while blue and cooler colors reflect relatively less influence

shyness relative to temperament (blue and cooler colors). It is also important to note that the two shyness subtypes differ on the temperament-self-concept continuum as a function of developmental age. Below the x-axis represents the different contexts and multiple influences on personality development over time, and the weight given to each over time reflected in the color gradients.

Heterogeneity

There is substantial heterogeneity in the phenomenon of temperamental shyness, and some of these differences have been hypothesized to emerge as a result of individual differences in sociability (Asendorpf, 1990; Asendorpf & Meier, 1993; Cheek & Buss, 1981). For several decades, researchers have provided evidence that shyness and sociability are conceptually and empirically independent personality dimensions. Shyness and sociability have unique motivational underpinnings, with shyness constituting a motivation for social avoidance and sociability a motivation for social approach (Asendorpf, 1990; Cheek & Buss, 1981; Schmidt & Buss, 2010). According to the conceptual framework proposed by Asendorpf (1990), some shy individuals have little motivation to interact with others (i.e., low on sociability) and comprise a shy subtype referred to as *avoidant*. In contrast, some shy

individuals have a strong motivation to approach and interact with others (i.e., high on sociability) but feel too fearful and inhibited to fulfill this desire. These shy, but sociable, individuals are presumed to experience a motivational approach-avoidance conflict (Asendorpf, 1990) and constitute a shy subtype referred to as *conflicted*. These two shyness subtypes are illustrated in Fig. 1, and hypothesized differences between the two subtypes are presented in Table 1.

Table 1 Hypothesized and empirical (*italicized text*) differences between avoidant and conflicted shyness (adapted and modified from Schmidt & Buss, 2010)

Psychological/ behavioral	Avoidant shyness	Conflicted shyness
Temperament	– Behaviorally inhibited to social novelty (necessary and sufficient)	– Behaviorally inhibited to social novelty (necessary but not sufficient)
	– (*Low*) *sociability*	– (*Relatively higher*) *sociability*
	– Sensitivity to punishment	– Sensitivity to reward
	– High avoidance/low approach	– High avoidance/high approach
Emotion	– Primary and negative emotions: Fear, distress (to social novelty)	– Primary and secondary emotions blending: *fear*, *distress* (*to social and self-evaluations*), embarrassment, shame
		– Some positive emotions: Interest, reward
Cognitive	– Automatic, bottom-up processes	– Controlled, top-down processes
	– Hot systems	– Cool systems
Physiological	– CNS: *right* frontal brain hyperarousal	– CNS: *left and right frontal brain hyperarousal*
	– ANS: *sympathetic*	– ANS: *parasympathetic*
First appearance	– Almost a year	– *3–4 years to adolescence*
Immediate causes	– Biology	– Biology, parents
	– Stranger interaction	– Peers (familiar and unfamiliar)
	– Novel social settings	– Social presentation and evaluation
Enduring causes	– Heredity	– Parents, peers
	– Chronic fear/anxiety	– Public self-consciousness
	– Low sociability	– Relatively higher sociability
	– Sensitivity to punishment	– Sensitivity to reward
	– Temperament	– Sensitivity to generational and cultural influences
Outcomes	– *Social withdrawal*, *depression*, GAD, SAD	– *Subsyndromal social anxiety*, *SAD substance use and abuse*
	– *Risk aversive*	– *Risk taking*
	– *Negative life course and social outcomes* (e.g., fewer friends, committed relationships; less likely to be married or parents; relatively lower educational, income and occupational attainment)	– *Negative life course and social outcomes* (e.g., relatively more friends, committed relationships; delays in marriage and parenthood; relatively higher educational, income, and occupational attainment)

Tenets of the Model

There are five main tenets of the model. We argue the following:

1. Shyness emerges in one's social world across development as a result of interactions between the child's early temperament and experiences, within multiple and different contexts. There are relative differences in the contributions of these contextual influences to shyness, depending on developmental age and the individual.
2. The conceptualization of shyness can range from temperament to self-concept, with relative differences in "conceptual" weightings also depending on developmental age of the individual.
3. Temperamental inhibition is a necessary, but not a sufficient, condition for the development of different types of shyness across development.
4. There is an early developing shyness linked to temperamental fear and a later developing shyness which may (or may not) be directly linked to temperamental inhibition and sociability. The later developing shyness is heavily dependent on one's social-cognitive-affective development, such as the self-concept, self-conscious emotions, and various social contexts.
5. Although these two types of shyness are dynamic and can overlap during development, they are largely distinct from each other with unique behavioral, psychophysiological, and psychiatric correlates and outcomes across development.

Developmental Periods

Infancy

The infancy period is characterized by reactivity and regulation of biological systems and the experience of basic emotions. During the first year of postnatal life, temperamental antecedents of shyness emerge in the form of behavioral inhibition to social novelty. The infant's social behavior is largely determined by individual differences in biological reactivity and regulation to sensory stimuli. Some infants have a temperamental bias to an inability with regulating their behavior in response to novel stimuli used to elicit fear (Kagan, 1994).

Childhood

Early childhood is characterized by an increase in cognitive development and social awareness. By early childhood (i.e., the second to third years of postnatal life), we see the development of temperamental shyness, with the emergence of self-awareness and the ability to experience self-conscious emotions. Here, we also begin to see more influence of parents and peers in shaping self-concept of the child. It is also

around this time (i.e., the third to fourth years of postnatal life) that the divergence in two types of temperamental shyness is observed. One type of temperamental shyness, early developing fearful shyness, continues to be defined by temperament and is maintained by fear to unfamiliar people throughout development. A second type of shyness, a later developing self-conscious shyness, is proposed to begin at ages 3–4 years (Buss, 1986) but also may emerge anytime after the preschool years.

This avoidant type of shyness emerges in concert with the increase in social-cognitive development occurring at this age. While this type of shyness may also be rooted in temperamental inhibition and an increase need for social affiliation (sociability) and increased opportunities to interact with peers occurring at this developmental age, it is not solely dependent on temperament as reflected in the dotted line in Fig. 1. That is, it is possible to develop self-conscious shyness during the preschool years—likely due to negative social influences and experiences, such as peers, family, and ridicule—without having been temperamentally inhibited as an infant (see the chapter "The History and Theory of Behavioral Inhibition" by Kagan). Accordingly, temperamental inhibition is a necessary, but not sufficient, condition for developing self-conscious and conflicted shyness as it is possible for self-conscious shyness to emerge exclusively from social experiences. As noted by the dotted line in the figure, the two subtypes may also overlap and influence each other at this age. We argue that fearful and self-conscious shyness in childhood are the precursors of avoidant and conflicted shyness, respectively, that begin to fully emerge in adolescence and adulthood.

It is also important to point out at this point that others have recently described two types of shyness from an emotion perspective that we believe are linked to our conceptualization of shyness from a temperament perspective and the two shyness types we describe, avoidant and conflicted shyness. Specifically, Colonnesi and her colleagues have conceptualized shyness as an emotion that can be delineated into "negative" and "positive" expressions of shyness (Colonnesi, Napoleone, & Bögels, 2014). Negative shyness refers in part to negative and withdrawal-related emotions experienced in social situations and which underlies and maintains avoidance behavior. On the other hand, positive expressions of shyness refer in part to positive and approach-related emotions during social situations in the face of the experience of competing negative emotions to these social encounters. We recently found that positive shy children displayed higher approach-related behaviors (i.e., higher sociability) than negative shy children (Poole & Schmidt, 2018). We believe that negative and positive shyness are conceptually and empirically related to our temperamental description of avoidant and conflicted shyness, respectively.

Adolescence

Adolescence is a period of significant changes, characterized by (1) the onset of puberty, (2) more advanced cognitive development (e.g., formal operations), and (3) the saliency of peer relationships and acceptance (Cheek, Carpentieri, Smith, Rierdan, & Koff, 1986; see also the chapter "Peer Relations and the Behaviorally Inhibited Child" by Rubin et al.). Past research has suggested that some types of

shyness peak in adolescence due to these three factors (Cheek et al., 1986). Personality development in general and shyness in particular also appear to be highly malleable in adolescence (Tang, Lahat, Crowley, Wu, & Schmidt, 2018). By adolescence, the two types of shyness from childhood are still distinguishable, but we now characterize the shyness subtypes as "avoidant" and "conflicted" to reflect their behavioral and psychological meanings and expressions at this developmental period. The avoidant type is still defined and maintained by temperament, while the conflicted type may be defined and maintained by some combination of temperament, self-concept and need for social affiliation, and the rewards of social interaction (i.e., sociability). As noted in the figure, adolescence is accompanied by increased influences of peers, culture, and generation in shaping the developmental course of these two types of shyness into adulthood. The shyness subtypes are dynamic, and as noted by the dotted line in the figure, the two subtypes may also overlap and influence each other in adolescence and adulthood.

Adulthood

The transition to adulthood presents with a series of new life stressors, including independence and autonomy from parents, higher education, career establishment, marriage, and parenthood. In adulthood, the two shyness subtypes are still distinguishable, but as was the case from childhood, the subtypes are dynamic and might overlap. We also see in adulthood that peers, generation, and culture are still important influences on shaping the developmental course of shyness. The unique influences of generation and culture on development are described in further detail later in the chapter.

Table 1 presents a summary of the features that distinguish avoidant and conflicted shyness phenotypes across different domains as well as the hypothesized age of onset, causes, and their outcomes in adulthood. Note that empirical differences are italicized, and there are some similar features that characterize both subtypes, which also might be reflected in the hypothesized overlap between the two phenotypes across development as noted earlier.

What Is the Developmental Course of Shyness and Related Constructs from Childhood to Adulthood?

Lifespan developmental theories (e.g., Baltes, 1987) suggest that personality and psychological functioning are not fixed at a certain age and continuous processes of growth and decline are evident even in middle and older adulthood (see Harris, Brett, Johnson, & Deary, 2016; Roberts, Walton, & Viechtbauer, 2006). This assertion is consistent with the finding that there are normative changes in the mean level

of shyness in the population across the lifespan from ages 4–86 represented by an inverted "U"-shape function, with marked increases in shyness during adolescence followed by gradual decreases across later development (Brook & Schmidt, 2018).

The notion that shyness and related constructs are not fixed is also supported by longitudinal studies examining trait consistency or temporal stability. For example, across childhood, behavioral inhibition is modestly stable (Pérez-Edgar & Fox, 2005). Similarly, social withdrawal has been reported to be moderately stable from early to middle childhood (Asendorpf, 1990; Fordham & Stevenson-Hinde, 1999; Hymel, Rubin, Rowden, & LeMare, 1990; Pedlow, Sanson, Prior, & Oberklaid, 1993; Rubin, Chen, McDougall, Bowker, & McKinnon, 1995; Sanson, Pedlow, Cann, Prior, & Oberklaid, 1996) and during late childhood to adolescence (Schneider, Younger, Smith, & Freeman, 1998). In adulthood, approximately 50% of non-shy college students reported being shy during early adolescence (Bruch, Giordano, & Pearl, 1986), and 90% of the general population reported being shy at one point in their lives (Zimbardo, Pilkonis, & Norwood, 1975). Together, these findings suggest that while these individual differences show some continuity across time, there is also much individual plasticity for growth and decline.

The potential importance of considering patterns of temporal stability and subgroups of shy individuals in the examination of personality development is to obtain specific outcome predictions for different children. Indeed, developmental psychologists have accounted for changes in time by assessing shyness at multiple time points to delineate developmental trajectories and heterogeneous subgroups of shy or socially withdrawn individuals. One study examining stranger fear across infancy and early toddlerhood (6–36 months) found four trajectories of social fear, characterized by stable high, decreasing, slow increasing, and steep increasing levels (Brooker et al., 2013). The infants in the high stable trajectory exhibited the highest levels of behavioral inhibition at 36 months. Further, one study examining developmental trajectories of social reticence found three pathways in early childhood in children ages 2–5 (Degnan et al., 2014): a low and increasing trajectory, a high and decreasing trajectory, and a high and increasing trajectory. Similarly, two other studies examining developmental trajectories of social withdrawal found three pathways in children from grades 1 to 6 (Booth-LaForce & Oxford, 2008) and from grades 5 to 8 (Oh et al., 2008): a normative consistently low and stable nonsocially withdrawn trajectory consisting of the majority of children, a decreasing trajectory that begins with high levels of social withdrawal that gradually attenuates, and an increasing trajectory that begins with moderate levels of social withdrawal that gradually increases. These studies also converge on identifying that individuals in an increasing trajectory, but not decreasing trajectory, are particularly at risk for internalizing problems (depressive and anxiety symptoms), and loneliness, relative to a low-stable trajectory (Booth-LaForce & Oxford, 2008; Degnan et al., 2014; Oh et al., 2008). Perhaps the stable high fear groups in these studies are temperamentally shy children who later become the avoidant shy individuals, and the slow and increasing trajectories reflect the later developing shyness who later become the conflicted shy individuals described in Fig. 1 earlier.

In examining longer-term trajectories, Tang, Van Lieshout, et al. (2018) recently found three developmental trajectories of shyness using shyness measures obtained from childhood to adulthood (ages 8, 12–16, 22–26, 30–35). There was a normative trajectory of low-stable non-shy individuals and two shyness trajectories: one that was characterized by increases and one characterized by decreases in shyness beginning in adolescence. Each trajectory predicted a host of mental health, socioemotional, and sociodemographic outcomes at ages 30–35. Relative to the low-stable non-shy trajectory, the increasing, but not the decreasing, shy trajectory was at higher risk for social anxiety, mood, and substance-use disorders and was hypervigilant to angry faces as indexed using an attention bias task. Furthermore, relative to the low-stable non-shy trajectory, the increasing, but not decreasing, shy trajectory had lower socioemotional and sociodemographic functioning and engaged in risk-taking behaviors (Schmidt et al., 2017). The increasing shy trajectory also reported greater loneliness, lower self-esteem, family functioning, and personal income and were less likely to hold a full-time job and own their own home. Also, they were more likely to have contact with the police and a criminal conviction. This increasing trajectory may represent the conflicted shy phenotype.

These results extend findings from longer-term longitudinal studies that found associations between shyness measured at one time point in middle childhood and delays in marriage, parenthood, career establishment (Caspi, Elder, & Bem, 1988; Kerr, Lambert, & Bem, 1996), and lower social competence (Grose & Coplan, 2015), when these individuals reached their 30s. Similarly, shy and "overcontrolled" children were slower to obtain part-time jobs, to leave their parents' home, and to find a romantic partner compared to their non-shy and "resilient" counterparts at age 23 (Hutteman, Denissen, Asendorpf, & Van Aken, 2009). Additionally, the different developmental pathways of shyness (Tang et al., 2017) suggest that not all shy children continue to be shy nor do they all experience these unfavorable outcomes in adulthood—it is particularly individuals with increases, but not decreases, in shyness. Given these descriptions of different developmental trajectories and their associations with starkly different outcomes, the logical extension is to elaborate on the factors that modify different developmental pathways.

What Factors Alter the Stability of Shyness across Development?

While the shapes of developmental trajectories provide a descriptive model on change and continuity in shyness across the life course and outcomes in different individuals, they do not explain *how* and *why* there is change/continuity, nor do they explain the link between specific developmental pathways and corresponding outcomes, particularly psychopathology. The current model for understanding social adjustment outcomes and psychopathology in the development of shyness emphasizes the transactions of interdependent processes at multiple levels in the social

(e.g., peers and families), biological, cultural, and generational contexts (Rubin et al., 2009). These factors may also exert differential influences during different developmental periods as represented by the color gradient in Fig. 1. Transactions are defined as the continuous dynamic interactions between an individual and his/her environment, and the development of a child is the product of such transactions (Sameroff, 2014). Understanding transactional interactions would yield a more complete picture of the development and maintenance of personality, as well as insight into how we can alter adverse developmental pathways. Accordingly, this section focuses on understanding the available literature identifying moderating or mediating contextual factors involved in the maintenance of shyness across childhood and adulthood.

Social Context

Research has illustrated the influential role of social experiences on the development and maintenance of inhibition and shyness across time (see the chapter "The Social World of Behaviorally Inhibited Children: A Transactional Account" by Henderson et al.). Although temperamental biases, such as behavioral inhibition, confer risk for the continuation of a shy personality style across development, the expression of these traits are influenced by the social context (e.g., familial and peer influences). For example, behaviorally inhibited toddlers who are placed into non-parental child-care services in early life are less likely to display shyness and social reticence as preschoolers, relative to behaviorally inhibited toddlers who were exclusively in the care of familiar parents (Fox, Henderson, Rubin, Calkins, & Schmidt, 2001). Furthermore, certain parenting styles, such as maternal overcontrol and intrusive parenting behaviors, promote the continuation of inhibition and social reticence into preschool (Rubin, Burgess, & Hastings, 2002) and social anxiety in adolescence (Lewis-Morrarty et al., 2012). In preschool-aged children, shy children were less likely to display social maladjustment if they had supportive mothers who were agreeable and exercised authoritative parenting, as opposed to non-supportive mothers who were overprotective or neurotic (Coplan, Arbeau, & Armer, 2008). Furthermore, early fearful temperament has been linked to prospective anxious tendencies if these children had mothers who were less supportive (Crockenberg & Leerkes, 2006).

In addition to maternal-child interactions and parenting styles influencing child shyness, parental personality and psychopathology are likely to influence the stability of children's inhibition, shyness, and social anxiety. Shyness has been shown to aggregate in families, which may reflect influences from genetic heritability, a shared environment, or both (Lieb et al., 2000; Smith et al., 2012). High-risk samples of mothers with social anxiety and shyness provide an interesting research design to examine how parental social modeling may influence the stability of children's shyness across time.

From a social learning perspective, it has been proposed that mothers with high levels of shyness and/or social anxiety may transmit tendencies of social inhibition as early as infancy via social modeling, a process by which children passively observe the parent's socially anxious responses, and consequently model their own behavior with increased displays of inhibition (Aktar, Majdandžić, Vente, & Bögels, 2014; De Rosnay, Cooper, Tsigaras, & Murray, 2006; Murray et al., 2008; Murray, Cooper, Creswell, Schofield, & Sack, 2007). Further, it has been hypothesized that shy mothers may inadvertently convey expectations of negative social evaluation to their child, resulting in transmission of information processing biases (Bögels, Stevens, & Majdandžić, 2011; Ollendick & Hirshfeld-Becker, 2002). These shy parents may also facilitate fewer socialization experiences for their children given their own social anxieties (Ollendick & Hirshfeld-Becker, 2002; Spence & Rapee, 2016). Collectively, the social tendencies expressed by socially anxious parents may perpetuate social avoidance not only in the parent but also in the child and contribute to the continuity of shyness across time.

When children start school, they increase social interactions with their peers and decrease social interactions with adults. In school years, children and adolescents are concerned about being accepted by and fitting in with peers. Peers also influence each other by modeling behaviors and reinforcing or punishing each other's behaviors. Indeed, shy and socially withdrawn children often exhibit lower social competence and have more adverse peer experiences (Rubin et al., 2009; see the chapter "Peer Relations and the Behaviorally Inhibited Child" by Rubin et al.). In particular, peer victimization plays a central role in the persistent cycle of internalizing problems and further victimization (Reijntjes, Kamphuis, Prinzie, & Telch, 2010) that is particularly problematic among shy and socially withdrawn children and adolescents. For example, shy and socially withdrawn children and adolescents who are socially excluded have a higher risk for internalizing problems and social avoidance (Boivin, Hymel, & Bukowski, 1995; Gazelle & Ladd, 2003; Gazelle & Rudolph, 2004; Ladd, 2006).

Studies of shyness or social withdrawal trajectories suggest that peer victimization and poor friendship quality may reinforce an increasing shy or socially withdrawn pathway. From grades 5–8, children who experienced more peer exclusion and victimization and unstable friendships were more likely to be categorized in the increasing social withdrawal trajectory, whereas children who experienced less peer exclusion and victimization were more likely to be in the decreasing social withdrawal trajectory (Oh et al., 2008). Peer victimization and peer exclusion also reinforce an increasing shy trajectory from childhood to early adolescence (Booth-Laforce et al., 2012; Booth-Laforce & Oxford, 2008). These findings are consistent with longer-term longitudinal studies that report individuals in an increasing shy trajectory from middle childhood to adulthood experienced more verbal bullying before age 16 compared to individuals in a stable non-shy trajectory (Tang, Van Lieshout, et al., 2017). Moreover, more adverse peer experiences in adolescence moderate the risk for anxiety disorders among young adults characterized by a history of child behavioral inhibition (Frenkel et al., 2015).

Recent studies have begun employing laboratory-based tasks of social rejection and exclusion to examine how shy (Howarth, Guyer, & Pérez-Edgar, 2013; Jarcho et al., 2016; Tang, Lahat et al., 2018) and behaviorally inhibited (Guyer et al., 2014; Lahat et al., 2014; Walker, Henderson, Degnan, Penela, & Fox, 2014) individuals process and cope with peer interactions as these events unfold (see the chapter "The Neural Mechanisms of Behavioral Inhibition" by Jarcho and Guyer). Understanding how shy individuals process and cope with adverse peer interactions may yield insight into whether maladaptive processing or coping strategies portend their socioemotional problems and maintain their shyness.

In social evaluation tasks, participants typically view pictures of peers and rate whether they would like to interact with that peer, and in turn, rate whether the peer would like to interact with him/herself. Shy children, particularly boys, report greater negative emotions when they are rejected but greater positive emotions when they are accepted (Howarth et al., 2013). In terms of neural responses, adolescents characterized by a history of childhood inhibition and social reticence show greater activation of the striatum (i.e., a brain region that is sensitive to rewards), when they received positive feedback from peers that they wanted to interact with compared to adolescents without a history of behavioral inhibition (Guyer et al., 2014). They also show greater activity in the dorsal anterior cingulate and insula (i.e., regions for processing social distress and uncertainty) and negative functional neural connectivity between the insula and ventromedial prefrontal cortex (i.e., region involved in emotion regulation) when they received unpredictable versus predictable feedback (Jarcho et al., 2016). These findings suggest that shy and behaviorally inhibited individuals show intense emotional responses to both positive and negative peer interactions and recruit brain regions that underlie social distress and uncertainty during peer interactions relative to their non-shy and behaviorally uninhibited counterparts.

In the Cyberball task, the participant plays a ball-tossing game with two others who are real or virtual players who ultimately exclude the participant, inducing feelings of social exclusion. During Cyberball, behaviorally inhibited children showed more socially withdrawn and less assertive behaviors (Walker et al., 2014). Specifically, behaviorally inhibited children with lower cognitive control (indexed by the N2 ERP to a cognitive control task) showed less assertiveness during Cyberball (Lahat et al., 2014). Likewise, across samples of children, adolescents, and adults, shy individuals reported higher fear of negative evaluation during Cyberball and displayed greater theta EEG response to ambiguous events, in which they did not receive the ball and waited for their turn to play (Tang, Lahat et al., 2018). Also, a combination of high shyness and high theta power to outright exclusion events was related to higher levels of social anxiety, across age groups. Together, these results extend the previous findings and suggest that heightened responses to social exclusion and ambiguous situations that signal potential social exclusion may reinforce the hallmark behaviors (i.e., social withdrawal, unassertiveness), cognitive biases (fear of negative evaluation), and outcome (i.e., social anxiety) associated with shyness.

Biological Context

Aside from external social influences, it is also important to consider factors endogenous to the individual. Previous research has illustrated that different biological factors may be associated with early developmental pathways of social reticence. For example, toddlers who were more behaviorally inhibited were more likely to be categorized in either high-increasing or high-decreasing trajectories, as opposed to the low-increasing trajectory (Degnan et al., 2014). This suggests that behavioral inhibition is a temperamental antecedent to socially reticent behaviors in early childhood.

Furthermore, individual differences in the biological systems underlying stress vulnerability represent biological correlates linked to the susceptibility to environmental influences on psychosocial development in childhood, including shyness. The extant literature has primarily examined biological correlates of stress vulnerability (e.g., cortisol responses and resting frontal EEG asymmetry) as *outcomes* or *correlates* of a fearful and shy temperament, but few studies have examined these biological vulnerabilities as *moderators* on the relation between a behaviorally inhibited temperament and a shy personality across time. As a result, the role of biological context in moderating the stability of shyness and related phenomena is not clearly understood beyond childhood.

The hypothalamic-pituitary-adrenal (HPA) axis is, for example, one physiological system that has been thought to play an important role in the development and maintenance of fear responses, including social fears linked to shyness (Schulkin, Morgan, & Rosen, 2005). Shy children display high cortisol levels under both stressed (e.g., Kagan et al., 1987) and nonstressed (e.g., Schmidt et al., 1997) conditions, which may be reflective of a hyperactive HPA axis (Kagan et al., 1987; Schmidt et al., 1997; Schmidt, Fox, Schulkin, & Gold, 1999). Increased HPA axis activity may be an underlying biobehavioral process predisposing individuals to avoid and withdraw from normative social contexts in everyday life, whereas lower activation of the HPA axis may reflect the tendency to approach social encounters.

In a cross-sectional study among early school-aged children, cortisol has been shown to moderate the association between mother-reported shyness and socially reticent behavior in children. Specifically, maternal-reported shyness was related to socially reticent behavior among children who had poor cortisol regulation (defined as lack of recovery to baseline cortisol levels following a social stressor), but was unrelated to socially reticent behavior when children had good cortisol regulation (recovery to baseline cortisol levels following social stressor) (Davis & Buss, 2012). Further, in a prospective study, high cortisol in preschool-aged boys predicted withdrawal behaviors among participants who had a negative reactive temperament in infancy (Pérez-Edgar, Schmidt, Henderson, Schulkin, & Fox, 2008).

Using a longitudinal study design, we recently demonstrated that cortisol reactivity in response to a self-presentation task predicted trajectories of social anxiety in children ages 4–11 across 3 years (Poole, Van Lieshout, McHolm, Cunningham, & Schmidt, 2018). Among children with heightened cortisol reactivity, participants

who had a socially anxious parent persistently manifested the highest and clinically significant levels of social anxiety across visits. We also recently examined whether self-reported history of childhood behavioral inhibition and concurrent baseline cortisol affected shyness levels in adults (Poole, Jetha, & Schmidt, 2017). Results revealed that a reported history of childhood *social* behavioral inhibition predicted higher shyness among female adults who also had high levels of cortisol output. However, among women with low cortisol levels, there was no relation between childhood social behavioral inhibition and adult shyness levels (Poole, Jetha, & Schmidt, 2017). Of note, these associations were not consistent when examining a history of *non*social behavioral inhibition. Given that these findings relied on retrospective self-reports and a cross-sectional design, future research should use objective measures of both social and nonsocial fear in early childhood and prospectively examine the influence of neuroendocrine functioning on the stability of these traits into adulthood.

In addition to neuroendocrine influences, which possibly maintain shy tendencies, a further biological vulnerability is the neural context (e.g., Beaton et al., 2008; Schwartz, Wright, Shin, Kagan, & Rauch, 2003). One relatively easily obtained and noninvasive measure of brain activity that is linked to underlying affective and behavioral profiles is reflected in the lateralization of electroencephalographic (EEG) activity in the frontal cortex. Davidson (1993, 2000) and Fox (1991, 1994) proposed activity in the left frontal brain region is presumed to be involved in the processing and experience of positive emotions (e.g., happiness) and facilitation of approach-related behaviors such as sociability. Conversely, activity in the right frontal brain is thought to underlie negative emotion (e.g., fear) and has been implicated in the development and maintenance of avoidance-related behaviors such as shyness. In a study of young adults, Schmidt (1999) reported that, although avoidant and conflicted shy subtypes were both characterized by right frontal EEG asymmetry at rest, the two subtypes differed in the absolute frontal EEG activity: the conflicted shy subtype exhibited higher activity in the left frontal region than the avoidant shy subtype. Schmidt argued that the pattern of right frontal EEG asymmetry (avoidance) due to hyper left frontal activity (approach) at rest might be a biological correlate of the approach-avoidance conflict presumed to underlie this particular shy subtype.

Right frontal EEG asymmetry appears to be a correlate of behavioral inhibition and shyness during different developmental periods including toddlerhood (Calkins, Fox, & Marshall, 1996; Fox et al., 2001), childhood (Fox, 1994; Schmidt et al., 1999; Theall-Honey & Schmidt, 2006), and adulthood (Beaton, Schmidt, Schulkin, & Hall, 2013; Schmidt, 1999; Schmidt & Fox, 1994) in cross-sectional designs. However, little is known about how right frontal EEG asymmetry may act as a biological diathesis to the *prospective* stability or change in shyness across several repeated assessments.

In one study, frontal EEG asymmetry moderated the association between negative reactivity in infancy and social wariness at age 4, such that this relation was stronger for infants with right frontal EEG asymmetry (Henderson, Fox, & Rubin, 2001). Recently, we have found that among 6-year-olds, children with right frontal

EEG asymmetry prior to grade school entry exhibited linear increases in shyness from grades 1–3 (Poole, Santesso, Van Lieshout, & Schmidt, 2018). We hypothesized that the early school age years (i.e., ages 6–8) demand interactions with new social peers and social expectations (Crozier & Burnham, 1990) that may serve as a natural gradient of increasing social stress that exacerbates the influence of underlying biological diatheses.

Cultural Context

Cross-cultural studies broaden the scope of personality development and psychological functioning of shy individuals and contribute to the generalizability of the literature that is often conducted in Western societies. Given the differences in values and attitudes in the individual-oriented Western versus group-oriented Eastern cultures, researchers have compared differences in the psychological adjustment and psychophysiological responses of shy children in China and North America (see Chen & Schmidt, 2015 and Khan, Schmidt, & Chen, 2017, for recent reviews).

Unlike Western cultures which primarily view shyness as a negative trait linked to unassertiveness, the traditional Chinese culture values shyness and sensitivity in children; children with these traits are perceived as mature, understanding, and accomplished (Chen, Cen, Li, & He, 2005). Chinese children accept peers who are shy. In contrast, Canadian children tend to reject shy children (Chen & Tse, 2008; Chen, Wang, & Wang, 2009). But even among older children and adolescents in China, shy children tend to be rejected, because they do not live up to the expectation that they should become more assertive as they grow up (Chen et al., 2005). Since shyness is viewed as a positive trait in China, it is interesting to note that a subtype of shyness characterized by high self-control, rather than by anxiety, exists (Xu, Farver, Yu, & Zhang, 2009). Shy children with high self-control did not exhibit anxiety during task performance or physiological reactivity, even though they showed less approach behaviors when confronted with strangers (Xu et al., 2009).

Recent economic transformation in China has been accompanied by shifts in values in the Chinese culture. These shifts may also influence personality development at a group level, in that the Chinese began valuing assertiveness and related behaviors that are valued in Western settings. This change is captured by the finding that school-aged children and preadolescents accepted shyness in their peers in the 1990s, but not in the 2000s (Chen et al., 2005; Liu, Chen, Li, & French, 2012). However, in more rural areas of China, shyness was still associated with better psychological, social, and school adjustment (Chen et al., 2009; Chen, Wang, & Cao, 2011). In contrast to shyness, unsociability was not tolerated in rural (Chen et al., 2011) or urban (Liu et al., 2014) areas of China, as preadolescents who are unsociable have more socioemotional and school difficulties. The association between unsociability and adjustment difficulties in China is also stronger than that observed in a Canadian sample (Liu et al., 2015). Together, these findings suggest that the meaning of the trait and individuals' personality development and psychological adjustment are shaped by the cultural settings, which need to be considered when examining the development of shyness.

Generational Context

The previous section described the changes in the historical context of China and how those changes transformed the values and attitudes attributed to trait shyness and shy children's psychological adjustment in cross-sectional studies. Though longitudinal designs can eliminate the differences in historical experiences between age groups inherent in cross-sectional research, cohort differences are still apparent when comparing cohorts born in different generations in longitudinal research. In a series of studies, Twenge and her colleagues, [Twenge, Campbell, Hoffman, and Lance (2010), Twenge, Campbell, and Freeman (2012), and Twenge et al. (2010)] have shown that generational differences might account for significant statistical variance in understanding personality development, social behavior, and psychopathology. As well, in longer-term longitudinal studies examining childhood shyness and adult outcomes, different generational and cultural contexts may influence different results. Recent findings from studies of shy children born to more recent generations who are now adults are challenging earlier findings of negative life course outcomes for some shy children (e.g., Schmidt et al., 2017; Van Zalk, Lamb, & Jason Rentfrow, 2017), raising the possibility of subtle generational and birth cohort influences.

For instance, in Caspi et al. (1988), the American cohort that was followed between the 1920s and 1940s (*the Silent Generation*) lived in a relatively rigid patriarchal society, in which women endorsed reserved traditional roles, such as being homemakers, whereas men endorsed more dominant roles, such as being breadwinners. Such values might have contributed to observed gender differences, in which shy boys delayed their career establishment in their 30s (Caspi et al., 1988). In contrast, shy children's career prospects were not affected in a Swedish cohort examined in the 1950s to 1970s (*the Baby Boomers*) (Kerr et al., 1996), because shy and reserved behaviors were viewed as valuable, and socially assertive behaviors were not demanded in that country. In a more recent Canadian cohort followed from the 1980s to 2010s (*the Millennials*), Schmidt et al. (2017) also found no gender differences in whether shy boys and girls held jobs in their 30s.

As described in the previous and current section, historical and societal events are not constant. In each generation, there are new events and challenges that demand different behavioral adaptations that may contribute to personality development. Of note, Millennials are exposed to technological advances in health practices, social media communication, and increased values for education. These historical changes are likely to influence the personality development of the cohort at a group level and at the individual level.

For example, among a national sample of adolescents residing in the United States from 1976 to 2016, a smaller proportion of adolescents engage in adult activities, including dating, having sex, drinking alcohol, working for pay, and driving, compared to adolescents raised in earlier years (Twenge & Park, 2017). Since life expectancy is increasing, the life course may be prolonged for recent generations: people may live longer and delay retirement, they may take longer to fully develop their personality, and their shyness and social inhibition may be lower and extended in adulthood as the work settings may present with novel social situations requiring

self-directed behavior and assertiveness. Also, emergent adulthood and career development are both delayed and extended by post-secondary education compared to previous generations. Additionally, shy individuals may adapt to and seek out the new remote social media interactions to meet friends and romantic partners and obtain online education. These settings may reinforce social avoidance and a shy personality over time. Finally, because longer-term longitudinal studies examining the development of shyness are rare and may employ different methods, it remains an empirical question to systematically examine how different generations of shy children grow up and how current technological advance may serve to alter the stability of shyness across time.

How Are Different Types of Shyness Linked to Distinct Outcomes across Development?

As noted earlier, there are several factors that may alter the trajectory of shyness across development, as well as distinct outcomes associated with different trajectories of shyness. In addition to examining how various contexts (e.g., social, biological, cultural, generational) may influence the stability of shyness, it is it is also important to account for individual differences in approach-related motivations among shy individuals across development that may alter shyness and its associated consequences.

As mentioned earlier, some heterogeneity in the phenomenon of temperamental shyness may emerge as a result of individual differences in sociability (Asendorpf, 1990; Asendorpf & Meier, 1993; Cheek & Buss, 1981). Specifically, some shy individuals are characterized by low levels of sociability and comprise a shy subtype we refer to as *avoidant.* In contrast, some shy individuals are characterized by high levels of sociability and are presumed to experience a motivational approach-avoidance conflict (Asendorpf, 1990) and constitute a shy subtype we refer to as *conflicted*. These two shyness subtypes were described earlier and illustrated in Fig. 1. Hypothesized differences between the two subtypes were presented in Table 1.

Conflicted Shyness across Development

Despite the existence of different subtypes of shyness, shyness is often times treated as a homogeneous construct when examining its implications on development and adaptive functioning. This is potentially problematic, given the hypothesized differences in adjustment based on subtypes of shyness. Specifically, it has been proposed that conflicted shyness (i.e., high on shyness *and* sociability) may be a particularly maladaptive form of shyness, given the distressing social motivation conflicts that these individuals experience. This internal conflict may result in an inability to perform goal-directed behavior and a cascade of secondary negative outcomes.

Indeed, the maladaptive nature of conflicted shyness has been demonstrated in several studies during different developmental periods up until the fourth decade of life.

In preschool and school-aged children, conflicted shyness is associated with early socioemotional difficulties including low self-competence, few prosocial behaviors, negative emotionality, and anxiety (Coplan et al., 2013; Coplan, Findlay, & Nelson, 2004; Coplan, Prakash, O'Neil, & Armer, 2004). Recently, a longitudinal study by Kopala-Sibley and Klein (2017) found that conflicted shyness in preschool-aged children was predictive of internalizing and externalizing behaviors in later childhood. Further, conflicted shyness has been linked to loneliness, emotional instability, lower self-worth, and social anxiety during childhood and into adolescence (Crozier, 1995; Eisenberg, Shepard, Fabes, Murphy, & Guthrie, 1998; Tang, Santesso, Segalowitz, Schulkin, & Schmidt, 2016). In addition, adolescents (Page, 1990), young adults (Santesso, Schmidt, & Fox, 2004), and adults (Poole, Van Lieshout, & Schmidt, 2017a) with conflicted shyness are more likely to engage in risky behaviors and use and abuse illicit substances compared with their non-shy peers.

Conflicted shyness during emerging adulthood has been shown to be distinguishable from avoidant shyness on autonomic (Schmidt & Fox, 1994), electrocortical (Schmidt, 1999; Schmidt & Fox, 1994; Tang, Santesso, Segalowitz, Schulkin, & Schmidt, 2016), and neural (Tang, Beaton, Schulkin, Hall, & Schmidt, 2014) measures and is associated with increased social distress, increased fear of negative evaluations, and more social comparisons with peers (Nelson, 2013) relative to the avoidant shyness subtype (i.e., high on shyness, but low on sociability). We have also demonstrated that beyond emerging adulthood, adults in their 30s with conflicted shyness are at an increased risk for experiencing the cognitive, behavioral, and somatic symptoms underlying social anxiety disorder (Poole, Van Lieshout, & Schmidt, 2017a). We have also found that adults characterized by conflicted shyness exhibited a higher incidence of mixed handedness (a risk factor for psychopathology; Spere, Schmidt, Riniolo, & Fox, 2005) and poorer adjustment in adulthood across demographic, psychological, social, and health domains of adaptive functioning (Poole, Van Lieshout, & Schmidt, 2017b).

Although the majority of the extant studies of shyness and sociability utilize cross-sectional designs, they still provide important insights into the implications of conflicted shyness across development. Interestingly, through examining the consequences of conflicted shyness across time, it is evident that this shy subtype may be linked to the emergence of distinct maladaptive behaviors during different developmental periods as demands, experiences, expectations, and unique stressors and supports shift with age. However, cross-sectional research designs fail to answer several important questions. Important empirical questions that remain are whether different subtypes of shyness in childhood persist into adulthood and whether there is plasticity in shyness subtypes across development. It remains unknown whether these different shyness subtypes in childhood have *predictive* utility for adult social behaviors and socioemotional functioning. It would be important for future studies to assess the interaction of shyness *and* sociability using a longitudinal study design in order to examine the stability of a conflicted shyness phenotype and to explore the trajectory of functional impairment over time in socially conflicted individuals.

Conclusions and Future Directions

The development of human personality is undoubtedly complex and multi-determined. Although longitudinal data are well-suited for tracking personality development, changes, and outcomes across the lifespan, the literature lacks studies that examine an integrative model that acknowledges interdependent effects from the biological, social, and behavioral domains. In the context of shyness, several factors have been described as being *independently* involved in the development and maintenance of shyness, including temperamental factors (e.g., behavioral inhibition), parental influences (e.g., over control, psychopathology), peer influences (e.g., exclusion), cognitive variables (e.g., information processing biases), biological risk factors (e.g., genes, physiological regulation, brain activity), culture, and generational influences (see e.g., Chen & Schmidt, 2015; Chronis-Tuscano et al., 2009; Clauss & Blackford, 2012; Ollendick & Hirshfeld-Becker, 2002; Schmidt, 1999; Schmidt et al., 2017; Spence & Rapee, 2016).

Despite the identification of factors predisposing children to shyness and social anxiety, the extant literature has not fully investigated risk factors from multiple interacting systems internal and external to the child. Doing so would establish a clearer picture as to how these factors are acting in a complex, transactive manner to affect the emergence and reinforcement of shyness in children over time. In this chapter, we have proposed a developmental model of temperamental shyness that takes into account the multiple contexts in which the shy child develops and the multiple influences on the shy child across development that might help direct future research in the area. One of the limitations of the extant literature on shyness is that researchers have treated shyness as a homogeneous phenomenon which can potentially limit predictive utility as we know that not all people who are shy are alike.

It is also important to point out that researchers are challenged by the problem of taxonomy and definition, since different measures and constructs are used to measure and characterize the trait at different developmental periods. In order to attribute true changes in a construct, in practice, the *same* variable(s) tapping a construct should be repeatedly assessed from infancy to adulthood. However, it remains a challenge for researchers to investigate the underlying coherence between early behavioral inhibition and later shyness and use a common and conceptually linked measure across time. To illustrate this problem, measuring fearful and reactive behaviors during confrontations with strangers and novel objects is appropriate in infancy. These behaviors would not appropriately capture the phenotype in adulthood. Yet, in practice, researchers are expected to use the same measures in their analyses.

Future studies would need to provide comprehensive transactional models to look at interdependent changes in the same variables/concepts for developmental change and continuity. This can be achieved by testing cross-lagged models using multivariate statistical techniques (e.g., structural equation modeling). Additionally, future studies will need to examine and identify the importance of different developmental stages that may be "sensitive" to or contribute a great degree of change in personality. For example, lifespan stage theorists (e.g., Erikson, 1982) suggest that each developmental stage provides problems for individuals to which they need to solve and

adapt. For the development of shyness, adolescence may be a significant period that involves greater awareness and values of peer relationships and increases in social fears that may induce increases of shyness at the population level. For example, adolescence is correlated with greater increases in this shyness (Brook & Schmidt, 2018). At the individual level, trajectory studies have also demonstrated that an increasing shy trajectory begins increasing in shyness by early adolescence (Oh et al., 2008; Tang, Van Lieshout, et al., 2018). These findings suggest that at certain developmental periods, attention should be placed on relevant and age-specific tasks that tap the individual's cognitive, behavioral, social, and affective changes. For example, in adolescence, there should be emphasis placed on the influence of social relationships when examining the development and maintenance of shyness.

An additional remaining question pertains to the longer-term implications of shyness at a biological and molecular level. For example, allostatic load refers to the cost exacted by chronic stress and its resultant physiological "wear and tear" (McEwen, 1998). In samples of socially anxious adults (Beaton et al., 2006, 2013) and some shy children (Schmidt, Santesso, Schulkin, & Segalowitz, 2007), patterns of low cortisol reactivity have been observed and was hypothesized to reflect a recalibration of the HPA axis due to a prolonged history of shyness and social anxiety (Fries, Hesse, Hellhammer, & Hellhammer, 2005). It will be interesting to examine biomarkers of biological breakdown in individuals with chronic shyness, as well as examine how these physiological alterations may mediate psychiatric, social, and health outcomes into later adulthood in shy individuals.

Finally, although emerging research has been useful in identifying short-term patterns of stability in shyness and related constructs, as well as the socioemotional and functional implication of shyness across development, very little attention has been devoted to later developmental periods including older adulthood. Thus, it remains unclear whether there may be unique patterns of shyness (i.e., growth, decline) into older adulthood (e.g., Brook & Schmidt, 2018) and whether the experience of shyness poses unique consequences and challenges during this developmental period characterized by instability and changing social roles. Given the increasing number of baby boomers entering late adulthood, it will be valuable for future research to examine the prevalence, developmental course, and implications of shyness into later adulthood.

Returning to our original question, does child temperament predict adult personality and social behavior? The evidence reviewed in the present chapter would suggest that the answer to this question is yes. Temperamental shyness is rooted in behavioral inhibition in early childhood and shaped by multiple influences over development leading to continuity and modifications of the phenotype and multiple outcomes in adulthood and who we ultimately become as adults. To that end, Wordsworth's musings, "the child is father to the man" (i.e., we retain features of our childhood into adulthood), rings true.

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References

Aktar, E., Majdandžić, M., Vente, W., & Bögels, S. M. (2014). Parental social anxiety disorder prospectively predicts toddlers' fear/avoidance in a social referencing paradigm. *Journal of Child Psychology and Psychiatry, 55*, 77–87.

Allport, G. W. (1937). *Personality: A psychological interpretation*. London, UK: Constable & Ltd..

Asendorpf, J. B. (1990). Beyond social withdrawal: Shyness, unsociability, and peer avoidance. *Human Development, 33*, 250–259.

Asendorpf, J. B., & Meier, G. H. (1993). Personality effects on children's speech in everyday life: Sociability-mediated exposure and shyness-mediated reactivity to social situations. *Journal of Personality and Social Psychology, 64*, 1071–1083.

Baltes, P. B. (1987). Theoretical propositions of life-span developmental psychology: On the dynamics between growth and decline. *Developmental Psychology, 23*, 611–626.

Beaton, E. A., Schmidt, L. A., Ashbaugh, A. R., Santesso, D. L., Antony, M. M., McCabe, R. E., … Schulkin, J. (2006). Low salivary cortisol levels among socially anxious young adults: Preliminary evidence from a selected and a non-selected sample. *Personality and Individual Differences, 41*, 1217–1228.

Beaton, E. A., Schmidt, L. A., Schulkin, J., Antony, M. M., Swinson, R. P., & Hall, G. B. (2008). Different neural responses to stranger and personally familiar faces in shy and bold adults. *Behavioral Neuroscience, 122*, 704.

Beaton, E. A., Schmidt, L. A., Schulkin, J., & Hall, G. B. (2013). Repeated measurement of salivary cortisol within and across days among shy young adults. *Personality and Individual Differences, 55*, 705–710.

Bögels, S., Stevens, J., & Majdandžić, M. (2011). Parenting and social anxiety: Fathers' versus mothers' influence on their children's anxiety in ambiguous social situations. *Journal of Child Psychology and Psychiatry, 52*, 599–606.

Boivin, M., Hymel, S., & Bukowski, W. M. (1995). The roles of social withdrawal, peer rejection, and victimization by peers in predicting loneliness and depressed mood in childhood. *Development and Psychopathology, 7*, 765–785.

Booth-LaForce, C., Oh, W., Kennedy, A. E., Rubin, K. H., Rose-Krasnor, L., & Laursen, B. (2012). Parent and peer links to trajectories of anxious withdrawal from grades 5 to 8. *Journal of Clinical Child & Adolescent Psychology, 41*, 138–149.

Booth-LaForce, C., & Oxford, M. L. (2008). Trajectories of social withdrawal from grades 1 to 6: Prediction from early parenting, attachment, and temperament. *Developmental Psychology, 44*, 1298–1313.

Brook, T. A., & Schmidt, L. A. (2018). Shyness across the lifespan from ages 4 to 86 years: A study of mean level age differences and measurement invariance. *Manuscript submitted for publication*

Brooker, R. J., Buss, K. A., Lemery-Chalfant, K., Aksan, N., Davidson, R. J., & Goldsmith, H. H. (2013). The development of stranger fear in infancy and toddlerhood: Normative development, individual differences, antecedents, and outcomes. *Developmental Science, 16*, 864–878.

Brooker, R. J., Kiel, E. J., & Buss, K. A. (2016). Early social fear predicts kindergarteners' socially anxious behaviors: Direct associations, moderation by inhibitory control, and differences from nonsocial fear. *Emotion, 17*, 997–1110.

Bruch, M. A., Giordano, S., & Pearl, L. (1986). Differences between fearful and self-conscious shy subtypes in background and current adjustment. *Journal of Research in Personality, 20*, 172–186.

Buss, A. H. (1986). A theory of shyness. In W. H. Jones, J. M. Cheek, & S. R. Briggs (Eds.), *Shyness: Perspectives on research and treatment* (pp. 39–46). New York, NY: Plenum Press.

Calkins, S. D., Fox, N. A., & Marshall, T. R. (1996). Behavioral and physiological antecedents of inhibited and uninhibited behavior. *Child Development, 67*, 523–540.

Caspi, A., Elder, G. H., Jr., & Bem, D. J. (1988). Moving away from the world: Life-course patterns of shy children. *Developmental Psychology, 24*, 824–831.

Cheek, J. M., & Buss, A. H. (1981). Shyness and sociability. *Journal of Personality and Social Psychology, 41*, 330–339.

Cheek, J. M., Carpentieri, A. M., Smith, T. G., Rierdan, J., & Koff, E. (1986). Adolescent shyness. In W. H. Jones, J. M. Cheek, & S. R. Briggs (Eds.), *Shyness: Perspectives on research and treatment* (pp. 105–115). New York, NY: Plenum Press.

Chen, X., Cen, G., Li, D., & He, Y. (2005). Social functioning and adjustment in Chinese children: The imprint of historical time. *Child Development, 76*, 182–195.

Chen, X., & Schmidt, L.A. (2015). Temperament and personality development. In R. Lerner (Editor-in-Chief), *Handbook of Child Psychology and Developmental Science* (7th ed.), In M. Lamb & C. García-Coll (Section Editors), Vol. 3, *Social and Emotional Development* (pp. 152–200). Hoboken, NJ: Wiley.

Chen, X., & Tse, H. C. H. (2008). Social functioning and adjustment in Canadian-born children with Chinese and European backgrounds. *Developmental Psychology, 44*, 1184–1189.

Chen, X., Wang, L., & Cao, R. (2011). Shyness-sensitivity and unsociability in rural Chinese children: Relations with social, school, and psychological adjustment. *Child Development, 82*, 1531–1543.

Chen, X., Wang, L., & Wang, Z. (2009). Shyness-sensitivity and social, school, and psychological adjustment in rural migrant and urban children in China. *Child Development, 80*, 1499–1513.

Chronis-Tuscano, A., Degnan, K. A., Pine, D. S., Pérez-Edgar, K., Henderson, H. A., Diaz, Y., … Fox, N. A. (2009). Stable early maternal report of behavioral inhibition predicts lifetime social anxiety disorder in adolescence. *Journal of the American Academy of Child & Adolescent Psychiatry, 48*, 928–935.

Clauss, J. A., & Blackford, J. U. (2012). Behavioral inhibition and risk for developing social anxiety disorder: A meta-analytic study. *Journal of the American Academy of Child & Adolescent Psychiatry, 51*, 1066–1075.

Colonnesi, C., Napoleone, E., & Bögels, S. M. (2014). Positive and negative expressions of shyness in toddlers: Are they related to anxiety in the same way? *Journal of Personality and Social Psychology, 106*, 624–637.

Coplan, R. J., Arbeau, K. A., & Armer, M. (2008). Don't fret, be supportive! Maternal characteristics linking child shyness to psychosocial and school adjustment in kindergarten. *Journal of Abnormal Child Psychology, 36*, 359–371.

Coplan, R. J., Findlay, L. C., & Nelson, L. J. (2004). Characteristics of preschoolers with lower perceived competence. *Journal of Abnormal Child Psychology, 32*, 399–408.

Coplan, R. J., Prakash, K., O'Neil, K., & Armer, M. (2004). Do you "want" to play? Distinguishing between conflicted shyness and social disinterest in early childhood. *Developmental Psychology, 40*, 244–258.

Coplan, R. J., Rose-Krasnor, L., Weeks, M., Kingsbury, A., Kingsbury, M., & Bullock, A. (2013). Alone is a crowd: Social motivations, social withdrawal, and socio- emotional functioning in later childhood. *Developmental Psychology, 49*, 861–875.

Crockenberg, S. C., & Leerkes, E. M. (2006). Infant and maternal behavior moderate reactivity to novelty to predict anxious behavior at 2.5 years. *Development and Psychopathology, 18*, 17–34.

Crozier, W., & Burnham, M. (1990). Age-related differences in children's understanding of shyness. *British Journal of Developmental Psychology, 8*, 179–185.

Crozier, W. R. (1995). Shyness and self-esteem in middle childhood. *British Journal of Educational Psychology, 65*, 85–95.

Davidson, R. J. (1993). The neuropsychology of emotion and affective style. In M. Lewis & J. M. Haviland (Eds.), *Handbook of emotion* (pp. 143–154). New York, NY: Guilford.

Davidson, R. J. (2000). Affective style, psychopathology, and resilience: Brain mechanisms and plasticity. *American Psychologist, 55*, 1196–1214.

Davis, E. L., & Buss, K. A. (2012). Moderators of the relation between shyness and behavior with peers: Cortisol dysregulation and maternal emotion socialization. *Social Development, 21*, 801–820.

De Rosnay, M., Cooper, P. J., Tsigaras, N., & Murray, L. (2006). Transmission of social anxiety from mother to infant: An experimental study using a social referencing paradigm. *Behaviour Research and Therapy, 44*, 1165–1175.

Degnan, K. A., Almas, A. N., Henderson, H. A., Hane, A. A., Walker, O. L., & Fox, N. A. (2014). Longitudinal trajectories of social reticence with unfamiliar peers across early childhood. *Developmental Psychology, 50*, 2311–2323.

Dyson, M. W., Klein, D. N., Olino, T. M., Dougherty, L. R., & Durbin, C. E. (2011). Social and non-social behavioral inhibition in preschool-age children: Differential associations with parent-reports of temperament and anxiety. *Child Psychiatry and Human Development, 42*, 390–405.

Eisenberg, N., Shepard, S. A., Fabes, R. A., Murphy, B. C., & Guthrie, I. K. (1998). Shyness and children's emotionality, regulation, and coping: Contemporaneous, longitudinal, and across-context relations. *Child Development, 69*, 767–790.

Erikson, E. (1982). *The life cycle completed*. New York, NY: Norton.

Fordham, K., & Stevenson-Hinde, J. (1999). Shyness, friendship quality, and adjustment during middle childhood. *The Journal of Child Psychology and Psychiatry and Allied Disciplines, 40*(5), 757–768.

Fox, N. A. (1991). If it's not left, it's right: Electroencephalogram asymmetry and the development of emotion. *American Psychologist, 46*, 863–872.

Fox, N. A. (1994). Dynamic cerebral processes underlying emotion regulation. The development of emotion regulation: Behavioral and biological considerations. *Monographs of the Society for Research in Child Development, 59*(2–3), 152–166.

Fox, N. A., Henderson, H. A., Rubin, K. H., Calkins, S. D., & Schmidt, L. A. (2001). Continuity and discontinuity of behavioral inhibition and exuberance: Psychophysiological and behavioral influences across the first four years of life. *Child Development, 72*, 1–21.

Frenkel, T. I., Fox, N. A., Pine, D. S., Walker, O. L., Degnan, K. A., & Chronis-Tuscano, A. (2015). Early childhood behavioral inhibition, adult psychopathology and the buffering effects of adolescent social networks: A twenty-year prospective study. *Journal of Child Psychology and Psychiatry, 56*, 1065–1073.

Fries, E., Hesse, J., Hellhammer, J., & Hellhammer, D. H. (2005). A new view on hypocortisolism. Psychoneuroendocrinology, 30(10), 1010-1016.

Garcia-Coll, C. G., Kagan, J., & Reznick, J. S. (1984). Behavioral inhibition in young children. Child Development, 1005–1019.

Gazelle, H., & Ladd, G. W. (2003). Anxious solitude and peer exclusion: A diathesis-stress model of internalizing trajectories in childhood. *Child Development, 74*, 257–278.

Gazelle, H., & Rudolph, K. D. (2004). Moving toward and away from the world: Social approach and avoidance trajectories in anxious solitary youth. *Child Development, 75*, 829–849.

Grose, J., & Coplan, R. J. (2015). Longitudinal outcomes of shyness from childhood to emerging adulthood. *Journal of Genetic Psychology, 176*, 408–413.

Guyer, A. E., Benson, B., Choate, V. R., Bar-Haim, Y., Pérez-Edgar, K., Jarcho, J. M., … Nelson, E. E. (2014). Lasting associations between early-childhood temperament and late-adolescent reward-circuitry response to peer feedback. *Development and Psychopathology, 26*, 229–243.

Halverson, C. F., Kohnstamm, G. A., & Martin, R. P. (Eds.). (1994). *The developing structure of temperament and personality from infancy to adulthood*. Hillsdale, NJ: Erlbaum.

Harris, M. A., Brett, C. E., Johnson, W., & Deary, I. J. (2016). Personality stability from age 14 to age 77 years. *Psychology and Aging, 31*, 862.

Hayward, C., Killen, J. D., Kraemer, H. C., & Taylor, C. B. (1998). Linking self-reported childhood behavioral inhibition to adolescent social phobia. *Journal of the American Academy of Child & Adolescent Psychiatry, 37*, 1308–1316.

Henderson, H. A., Fox, N. A., & Rubin, K. H. (2001). Temperamental contributions to social behavior: The moderating roles of frontal EEG asymmetry and gender. *Journal of the American Academy of Child & Adolescent Psychiatry, 40*, 68–74.

Howarth, G. Z., Guyer, A. E., & Pérez-Edgar, K. (2013). Young children's affective responses to acceptance and rejection from peers: A computer-based task sensitive to variation in temperamental shyness and gender. *Social Development, 22*, 146–162.

Hutteman, R., Denissen, J. J., Asendorpf, J. B., & Van Aken, M. A. (2009). Changing dynamics in problematic personality: A multiwave longitudinal study of the relationship between shyness and aggressiveness from childhood to early adulthood. *Development and Psychopathology, 21*, 1083–1094.

Hymel, S., Rubin, K. H., Rowden, L., & LeMare, L. (1990). Children's peer relationships: Longitudinal prediction of internalizing and externalizing problems from middle to late childhood. *Child Development, 61*, 2004–2021.

Jarcho, J. M., Davis, M. M., Shechner, T., Degnan, K. A., Henderson, H. A., Stoddard, J., … Nelson, E. E. (2016). Early-childhood social reticence predicts brain function in preadolescent youths during distinct forms of peer evaluation. *Psychological Science, 27*, 821–835.

Kagan, J. (1994). *Galen's prophecy: Temperament in human nature*. New York, NY: Basic Books.

Kagan, J., & Moss, H. A. (1962). *Birth to maturity: A study in psychological development*. New Haven, CT: Yale University Press.

Kagan, J., Reznick, J. S., Clarke, C., Snidman, N., & García-Coll, C. (1984). Behavioral inhibition to the unfamiliar. *Child Development, 55*, 2212–2225.

Kagan, J., Reznick, J. S., & Snidman, N. (1987). The physiology and psychology of behavioral inhibition in children. *Child Development, 58*, 1459–1473.

Kerr, M., Lambert, W. W., & Bem, D. J. (1996). Life course sequelae of childhood shyness in Sweden: Comparison with the United States. *Developmental Psychology, 32*, 1100–1105.

Khan, A., Schmidt, L. A., & Chen, X. (2017). Cultural neuroscience of emotion: Toward a developmental framework. *Psychology & Neuroscience, 10*, 11–40.

Kochanska, G. (1991). Patterns of inhibition to the unfamiliar in children of normal and affectively ill mothers. *Child Development, 62*, 250–263.

Kopala-Sibley, D. C., & Klein, D. N. (2017). Distinguishing types of social withdrawal in children: Internalizing and externalizing outcomes of conflicted shyness versus social disinterest across childhood. *Journal of Research in Personality, 67*, 27–35.

Ladd, G. W. (2006). Peer rejection, aggression or withdrawn behavior, and psychological maladjustment from ages 5 to 12: An examination of four predictive models. *Child Development, 77*, 822–846.

Lahat, A., Walker, O. L., Lamm, C., Degnan, K. A., Henderson, H. A., & Fox, N. A. (2014). Cognitive conflict links behavioural inhibition and social problem solving during social exclusion in childhood. *Infant and Child Development, 23*, 273–282.

Lewis-Morrarty, E., Degnan, K. A., Chronis-Tuscano, A., Rubin, K. H., Cheah, C. S., Pine, D. S., … Fox, N. A. (2012). Maternal over-control moderates the association between early childhood behavioral inhibition and adolescent social anxiety symptoms. *Journal of Abnormal Child Psychology, 40*, 1363–1373.

Lieb, R., Wittchen, H. U., Höfler, M., Fuetsch, M., Stein, M. B., & Merikangas, K. R. (2000). Parental psychopathology, parenting styles, and the risk of social phobia in offspring: A prospective-longitudinal community study. *Archives of General Psychiatry, 57*, 859–866.

Liu, J., Chen, X., Coplan, R. J., Ding, X., Zarbatany, L., & Ellis, W. (2015). Shyness and unsociability and their relations with adjustment in Chinese and Canadian children. *Journal of Cross-Cultural Psychology, 46*, 371–386.

Liu, J., Chen, X., Li, D., & French, D. (2012). Shyness sensitivity, aggression, and adjustment in urban Chinese adolescents at different historical times. *Journal of Research on Adolescence, 22*, 393–399.

Liu, J., Coplan, R. J., Chen, X., Li, D., Ding, X., & Zhou, Y. (2014). Unsociability and shyness in Chinese children: Concurrent and predictive relations with indices of adjustment. *Social Development, 23*, 119–136.

McEwen, B. S. (1998). Stress adaptation, and disease: Allostasis and allostatic load. *Annals of the New York Academy of Sciences, 840*, 33–44.

Mick, M. A., & Telch, M. J. (1998). Social anxiety and history of behavioral inhibition in young adults. *Journal of Anxiety Disorders, 12*, 1–20.

Miskovic, V., & Schmidt, L. A. (2012). Social fearfulness in the human brain. *Neuroscience & Biobehavioral Reviews, 36*(1), 459–478.

Murray, L., Cooper, P., Creswell, C., Schofield, E., & Sack, C. (2007). The effects of maternal social phobia on mother–infant interactions and infant social responsiveness. *Journal of Child Psychology and Psychiatry, 48*, 45–52.

Murray, L., De Rosnay, M., Pearson, J., Bergeron, C., Schofield, E., Royal-Lawson, M., & Cooper, P. J. (2008). Intergenerational transmission of social anxiety: The role of social referencing processes in infancy. *Child Development, 79*, 1049–1064.

Neal, J. A., Edelmann, R. J., & Glachan, M. (2002). Behavioural inhibition and symptoms of anxiety and depression: Is there a specific relationship with social phobia? *British Journal of Clinical Psychology, 41*, 361–374.

Nelson, L. J. (2013). Going it alone: Comparing subtypes of withdrawal on indices of adjustment and maladjustment in emerging adulthood. *Social Development, 22*, 522–538.

Oh, W., Rubin, K. H., Bowker, J. C., Booth-LaForce, C., Rose-Krasnor, L., & Laursen, B. (2008). Trajectories of social withdrawal from middle childhood to early adolescence. *Journal of Abnormal Child Psychology, 36*, 553–566.

Ollendick, T. H., & Hirshfeld-Becker, D. R. (2002). The developmental psychopathology of social anxiety disorder. *Biological Psychiatry, 51*, 44–58.

Page, R. M. (1990). Shyness and sociability: A dangerous combination for illicit substance use in adolescent males? *Adolescence, 25*, 803–806.

Pedlow, R., Sanson, A., Prior, M., & Oberklaid, F. (1993). Stability of maternally reported temperament from infancy to 8 years. *Developmental Psychology, 29*(6), 998.

Pérez-Edgar, K., & Fox, N. A. (2005). Temperament and anxiety disorders. *Child and Adolescent Psychiatric Clinics of North America, 14*, 681–706.

Pérez-Edgar, K., Schmidt, L. A., Henderson, H. A., Schulkin, J., & Fox, N. A. (2008). Salivary cortisol levels and infant temperament shape developmental trajectories in boys at risk for behavioral maladjustment. *Psychoneuroendocrinology, 33*, 916–925.

Poole, K. L., Jetha, M. K., & Schmidt, L. A. (2017). Linking child temperament, physiology, and adult personality: Relations among retrospective behavioral inhibition, salivary cortisol, and shyness. *Personality and Individual Differences, 113*, 68–73.

Poole, K. L., Santesso, D. L., Van Lieshout, R. J., & Schmidt, L. A. (2018). Frontal brain asymmetry and the trajectory of shyness across the early school age years. *Manuscript submitted for publication*

Poole, K. L., & Schmidt, L. A. (2018). Smiling through the shyness: The adaptive function of positive affect in shy children. Emotion.

Poole, K. L., Van Lieshout, R. J., McHolm, A. E., Cunningham, C. E., & Schmidt, L. A. (2018). Trajectories of social anxiety in children: Influence of child cortisol reactivity and parental social anxiety. *Journal of Abnormal Child Psychology, 46*(6), 1309–1319.

Poole, K. L., Van Lieshout, R. J., & Schmidt, L. A. (2017a). Exploring relations between shyness and social anxiety disorder: The role of sociability. *Personality and Individual Differences, 110*, 55–59.

Poole, K. L., Van Lieshout, R. J., & Schmidt, L. A. (2017b). Shyness and sociability beyond emerging adulthood: Implications for understanding the developmental sequelae of shyness subtypes. *Journal of Social and Clinical Psychology, 36*, 316–334.

Reijntjes, A., Kamphuis, J. H., Prinzie, P., & Telch, M. J. (2010). Peer victimization and internalizing problems in children: A meta-analysis of longitudinal studies. *Child Abuse & Neglect, 34*, 244–252.

Roberts, B. W., Walton, K. E., & Viechtbauer, W. (2006). Patterns of mean-level change in personality traits across the life course: A meta-analysis of longitudinal studies. *Psychological Bulletin, 132*, 1–25.

Rubin, K. H., Burgess, K. B., & Hastings, P. D. (2002). Stability and social–behavioral consequences of toddlers' inhibited temperament and parenting behaviors. *Child Development, 73*, 483–495.

Rubin, K. H., Chen, X., McDougall, P., Bowker, A., & McKinnon, J. (1995). The waterloo longitudinal project: Predicting internalizing and externalizing problems in adolescence. *Development and Psychopathology, 7*, 751–764.

Rubin, K. H., Coplan, R. J., & Bowker, J. C. (2009). Social withdrawal in childhood. *Annual Review of Psychology, 60*, 141–171.

Sanson, A. (1996). Shyness ratings: Stability and correlates in early childhood. *International Journal of Behavioral Development, 19*(4), 705–724.

Sameroff, A. J. (2014). A dialectic integration of development for the study of psychopathology. In M. Lewis & K. D. Rudolph (Eds.), *Handbook of developmental psychopathology* (pp. 25–43). New York, NY: Springer.

Santesso, D. L., Schmidt, L. A., & Fox, N. A. (2004). Are shyness and sociability still a dangerous combination for substance use? Evidence from a U.S. and Canadian sample. *Personality and Individual Differences, 37*, 5–17.

Schmidt, L. A. (1999). Frontal brain electrical activity in shyness and sociability. *Psychological Science, 10*, 316–320.

Schmidt, L. A., & Buss, A. H. (2010). Understanding shyness: Four questions and four decades of research. In K. R. Rubin & R. J. Coplan (Eds.), *The development of shyness and social withdrawal* (pp. 23–41). New York, NY: Guildford Publications.

Schmidt, L. A., & Fox, N. A. (1994). Patterns of cortical electrophysiology and autonomic activity in adults' shyness and sociability. *Biological Psychology, 38*, 183–198.

Schmidt, L. A., & Fox, N. A. (1999). Conceptual, biological, and behavioral distinctions among different categories of shy children. In L. A. Schmidt & J. Schulkin (Eds.), *Extreme fear, shyness, and social phobia: Origins, biological mechanisms, and clinical outcomes* (pp. 47–66). New York, NY: Oxford University Press.

Schmidt, L. A., Fox, N. A., Rubin, K. H., Sternberg, E. M., Gold, P. W., Smith, C. C., & Schulkin, J. (1997). Behavioral and neuroendocrine responses in shy children. *Developmental Psychobiology, 30*, 127–140.

Schmidt, L. A., Fox, N. A., Schulkin, J., & Gold, P. W. (1999). Behavioral and psychophysiological correlates of self-presentation in temperamentally shy children. *Developmental Psychobiology, 35*, 119–135.

Schmidt, L. A., & Miskovic, V. (2013). A new perspective on temperamental shyness: Differential susceptibility to endoenvironmental influences. *Social and Personality Psychology Compass, 7*, 141–157.

Schmidt, L. A., & Miskovic, V. (2014). Shyness and the electrical activity of the brain: On the interplay between theory and method. In R. J. Coplan & J. C. Bowker (Eds.), *The handbook of solitude: Psychological perspectives on social isolation, social withdrawal, and being alone* (pp. 51–70). Malden, MA: John Wiley & Sons,.

Schmidt, L. A., Polak, C. P., & Spooner, A. L. (2001). Biological and environmental contributions to childhood shyness: A diathesis-stress model. In W. R. Crozier & L. E. Alden (Eds.), *International handbook of social anxiety: Concepts, research and interventions relating to the self and shyness* (pp. 29–51). London, UK: John Wiley & Sons.

Schmidt, L. A., Polak, C. P., & Spooner, A. L. (2005). Biological and environmental contributions to childhood shyness: A diathesis-stress model. In W. R. Crozier & L. E. Alden (Eds.), *The essential handbook of social anxiety for clinicians* (pp. 33–55). London, UK: John Wiley & Sons.

Schmidt, L. A., & Poole, K. L. (2018). On the bifurcation of temperamental shyness: Development, context, and neoteny. *New Ideas in Psychology*

Schmidt, L. A., Santesso, D. L., Schulkin, J., & Segalowitz, S. J. (2007). Shyness is a necessary but not sufficient condition for high salivary cortisol in typically developing 10 year-old children. *Personality and Individual Differences, 43*, 1541–1551.

Schmidt, L. A., & Schulkin, J. (Eds.). (1999). *Extreme fear, shyness, and social phobia: Origins, biological mechanisms, and clinical outcomes*. New York, NY: Oxford University Press.

Schmidt, L. A., Tang, A., Day, K. L., Lahat, A., Boyle, M. H., Saigal, S., & Van Lieshout, R. J. (2017). Personality development within a generational context: Life course outcomes of shy children. *Child Psychiatry and Human Development, 48*, 632–641.

Schneider, B., Younger, A., Smith, T., & Freeman, P. A. (1998). A longitudinal exploration of the cross-context stability of social withdrawal in early adolescence. *Journal of Early Adolescence, 18*, 374–396.

Schofield, C. A., Coles, M. E., & Gibb, B. E. (2009). Retrospective reports of behavioral inhibition and young adults' current symptoms of social anxiety, depression, and anxious arousal. *Journal of Anxiety Disorders, 23*, 884–890.

Schulkin, J., Morgan, M. A., & Rosen, J. B. (2005). A neuroendocrine mechanism for sustaining fear. *Trends in Neurosciences, 28*, 629–635.

Schwartz, C. E., Wright, C. I., Shin, L. M., Kagan, J., & Rauch, S. L. (2003). Inhibited and uninhibited infants "grown up": Adult amygdalar response to novelty. *Science, 300*, 1952–1953.

Smith, A. K., Rhee, S. H., Corley, R. P., Friedman, N. P., Hewitt, J. K., & Robinson, J. L. (2012). The magnitude of genetic and environmental influences on parental and observational measures of behavioral inhibition and shyness in toddlerhood. *Behavior Genetics, 42*(5), 764–777.

Spence, S. H., & Rapee, R. M. (2016). The etiology of social anxiety disorder: An evidence-based model. *Behaviour Research and Therapy, 86*, 50–67.

Spere, K. A., Schmidt, L. A., Riniolo, T. C., & Fox, N. A. (2005). Is a lack of cerebral hemisphere dominance a risk factor for social "conflictedness"? Mixed handedness in shyness and sociability. *Personality and Individual Differences, 39*, 271–281.

Tang, A., Beaton, E. A., Schulkin, J., Hall, G. B., & Schmidt, L. A. (2014). Revisiting shyness and sociability: A preliminary investigation of hormone-brain-behavior relations. *Frontiers in Psychology, 5*, 1430.

Tang, A., Lahat, A., Crowley, M. J., Wu, J., & Schmidt, L. A. (2018). Shyness, social exclusion, and socioemotional functioning: An event-related neural oscillation study of children, adolescents, and adults: An event-related brain oscillation study. Manuscript submitted for publication

Tang, A., Santesso, D. L., Segalowitz, S. J., Schulkin, J., & Schmidt, L. A. (2016). Distinguishing shyness and sociability in adults: An event-related electrocortical- neuroendocrine study. *Biological Psychology, 119*, 200–209.

Tang, A., Van Lieshout, R. J., Lahat, A., Duku, E., Boyle, M. H., Saigal, S., & Schmidt, L. A. (2018). Shyness trajectories across the first four decades predict mental health outcomes. *Journal of Abnormal Child Psychology, 45*, 1621–1633.

Theall-Honey, L. A., & Schmidt, L. A. (2006). Do temperamentally shy children process emotion differently than non-shy children? Behavioral, psychophysiological, and gender differences in reticent preschoolers. *Developmental Psychobiology, 48*, 187–196.

Twenge, J. M., Campbell, S. M., Hoffman, B. J., & Lance, C. E. (2010). Generational differences in work values: Leisure and extrinsic values increasing, social and intrinsic values decreasing. *Journal of Management, 36*, 1117–1142.

Twenge, J. M., Campbell, W. K., & Freeman, E. C. (2012). Generational differences in young adults' life goals, concern for others, and civic orientation, 1966–2009. *Journal of Personality and Social Psychology, 102*, 1045–1062.

Twenge, J. M., & Park, H. (2017). The decline in adult activities among US adolescents, 1976–2016. *Child Development*.

Van Zalk, N., Lamb, M. E., & Jason Rentfrow, P. (2017). Does shyness vary according to attained social roles? Trends across age groups in a large British sample. *Journal of Personality, 85*, 830–840.

Walker, O. L., Henderson, H. A., Degnan, K. A., Penela, E. C., & Fox, N. A. (2014). Associations between behavioral inhibition and children's social problem-solving behavior during social exclusion. *Social Development, 23*, 487–501.

Xu, Y., Farver, J. A. M., Yu, L., & Zhang, Z. (2009). Three types of shyness in Chinese children and the relation to effortful control. *Journal of Personality and Social Psychology, 97*, 1061–1073.

Zimbardo, P. G., Pilkonis, P., & Norwood, R. (1975). The social disease called shyness. *Psychology Today, 8*, 69–72.

Relations between Behavioral Inhibition, Cognitive Control, and Anxiety: Novel Insights Provided by Parsing Subdomains of Cognitive Control

George A. Buzzell, Sonya V. Troller-Renfree, Santiago Morales, and Nathan A. Fox

Abstract The temperament of behavioral inhibition (BI) is classically defined based on behavioral observations of a child's fear and avoidance of novelty. Such behavioral observations have proven powerful in identifying individual differences in temperament, and such differences have been shown to be predictive of later developmental outcomes, particularly levels of shyness or anxiety. However, behavioral observations alone leave open several questions, including: (1) How does the brain of a child high in behavioral inhibition differ from a child low in behavioral inhibition? (2) Which domains of cognition are directly related to variation in behavioral inhibition? (3) For domains of cognition not directly related to behavioral inhibition, how do individual differences interact with behavioral inhibition to predict later risk for anxiety? Examining these questions, research has demonstrated that individual differences in the child's ability to monitor and control their behaviors when trying to complete a goal, a set of processes known as "cognitive control," may change the likelihood of a child high in behavioral inhibition developing later anxiety. However, relations between behavioral inhibition and cognitive control have been inconsistent across studies. Here, we leverage a cognitive neuroscience framework to review studies that have investigated the interrelations between behavioral inhibition, cognitive control, and anxiety. Critically, we separate cognitive control into the subdomains of "monitoring" and "control instantiation" as well as further parse control instantiation based on domain and time course. In making these distinctions, we show that there is consistent evidence that the behavioral inhibition phenotype is directly related to increased monitoring, but not levels of control instantiation. However, behavioral inhibition is related to the

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time course of control, and both monitoring and control interact with behavioral inhibition to predict increased risk for the development of anxiety. We suggest that continued progress in understanding the interrelations between behavioral inhibition and cognitive control will require a similar framework that separates cognitive control into subdomains.

Behavioral inhibition (BI) is an early childhood temperament, grounded in biology (Fox, Henderson, Marshall, Nichols, & Ghera, 2005), characterized by negative reactivity and avoidance within new situations or in the presence of strangers (Fox et al., 2005; Kagan, Reznick, & Snidman, 1988). Behavioral inhibition is a known risk factor for the later development of anxiety (Chronis-Tuscano et al., 2009; Frenkel et al., 2015), particularly social anxiety (Clauss & Blackford, 2012). However, not all children with a history of behavioral inhibition develop anxiety, and there is substantial interest in identifying what individual and environmental factors influence the relations between behavioral inhibition and anxiety.

Individual differences in behavioral inhibition ultimately reflect individual differences at a neurocognitive level. Therefore, adopting a cognitive neuroscience approach in the study of behavioral inhibition can provide unique information about this temperament. Indeed, advances in neuroimaging techniques, and their application to the study of development, have led to considerable advances in our understanding of the behavioral inhibition phenotype and its relation to later anxiety. The present chapter integrates these recent findings and sketches the emerging neurocognitive picture of behavioral inhibition and how this temperament relates to the development of anxiety (see also Blackford et al. in chapter "The Neurobiology of Behavioral Inhibition as a Developmental Mechanism").

Children with behavioral inhibition have been shown to cognitively process the world differently than children without behavioral inhibition. Children high in behavioral inhibition pay attention to different things in their environment (Pérez-Edgar et al., 2010), process threatening or novel stimuli differently (Schwartz, Wright, Shin, Kagan, & Rauch, 2003), and monitor and control their behavior differently (McDermott et al., 2009), compared to children low in behavioral inhibition. In this chapter, we focus on this last set of differences, outlining how children high in behavioral inhibition differ from children low in behavioral inhibition in terms of their ability to monitor and control behavior, a set of processes generally referred to as "cognitive control." We take a cognitive neuroscience perspective and focus on two main questions: (1) What aspects of cognitive control are related to variations in the behavioral inhibition phenotype? (2) What aspects of cognitive control interact with the behavioral inhibition temperament to predict later anxiety?

To foreshadow our answers to these questions, the literature seems to support the notion that behavioral inhibition is directly associated with hypersensitive monitoring of behavior. That is, children with high levels of behavioral inhibition spend more energy paying attention to their behaviors and environment. Moreover, this increased monitoring of behavior appears to increase risk for children high in behavioral inhibition to later develop anxiety. Similarly, control processes also

appear to exacerbate the risk for later anxiety in children high in behavioral inhibition. However, unlike monitoring, increased control processes do not appear integral to the behavioral inhibition phenotype. We end this chapter with a discussion of outstanding research questions and the need for additional research to further clarify relations between behavioral inhibition, cognitive control, and anxiety.

The Behavioral Inhibition Phenotype

Before discussing the neuroscience of behavioral inhibition, and its relations with anxiety, it is important to provide a more detailed sketch of the behavioral inhibition phenotype and related concepts. Kagan, Reznick, Clarke, Snidman, and Garcia-Coll (1984) first described behavioral inhibition, referring to children exhibiting high levels of this temperament as displaying "inhibition to the unfamiliar" (see the chapter "The History and Theory of Behavioral Inhibition" by Kagan). These children display an aversion and negative reactivity toward strangers, novel toys, or new situations (Fox, Henderson, Rubin, Calkins, & Schmidt, 2001; Kagan & Snidman, 1991). In general, it is believed that these children exhibit increased reactivity of fear circuitry, a theory supported by more recent neuroimaging findings (Schwartz et al., 2003).

It should be noted that Kagan and Snidman (2004) prefer to denote early infant reactivity as the actual temperament, with observed behaviors in toddlerhood as one of the outcomes of the temperament. In contrast, we define the behavioral inhibition temperament as a set of inhibited behaviors observed during toddlerhood. Our basis for denoting the behavioral inhibition temperament as a phenotype observed in toddlerhood grows out of a series of studies finding that fear-related behavior (e.g., avoidance and freezing) in toddlerhood was related to and predicted biological differences (e.g., heart rate, cortisol, EEG) measured during toddlerhood and later (Fox et al., 2005). It is also worth noting that a related behavioral profile, social reticence, emerges in the early school years (Coplan, Rubin, Fox, Calkins, & Stewart, 1994). Social reticence is characterized by the avoidance of peer interactions while maintaining vigilance and attention toward these peers (see the chapter "Peer Relations and the Behaviorally Inhibited Child" by Rubin et al.). While behavioral inhibition in toddlerhood is predictive of *later* social reticence (Degnan et al., 2014), and behavioral inhibition is predicted by *prior* infant reactivity (Fox, Snidman, Haas, Degnan, & Kagan, 2015), we believe these phenomena reflect three related, but distinct, constructs. Thus, we reserve the term "behavioral inhibition" for the behavioral phenotype observed during toddlerhood and focus on this phenotype throughout the chapter.

Here, it is also worth noting related work by Rothbart (1981) and Rothbart and Bates (2006), which defines temperament within a dimensional structure. Briefly, this model of temperament classifies infants and young children in terms of "reactivity," reflecting both positive and negative reactivity, and "regulation," reflecting the ability of infants and children to self-sooth and control their own behavior

(Rothbart, 1981; Rothbart & Bates, 2006). We note here that our conceptualization of behavioral inhibition and relations with cognitive control exhibit strong similarities to the prior conceptualization put forth by Rothbart (1981) and Rothbart and Bates (2006). Whereas prior work by Kagan et al. (1984) largely treated behavioral inhibition as a categorical variable (i.e., presence vs. absence of behavioral inhibition), we tend to explore behavioral inhibition as a continuous variable and treat the behavioral inhibition temperament as such within this chapter. Moreover, a key contribution of the Rothbart model was the conceptualization of self-regulation as an aspect of temperament (Rothbart, 1981; Rothbart & Bates, 2006). We continue this theoretical tradition here by investigating the relations between behavioral inhibition and cognitive control, with cognitive control reflecting strong similarities to the "regulation" dimension of Rothbart's model (Rothbart, 1981; Rothbart & Bates, 2006).

Cognitive Control: Monitoring and Control Instantiation

Cognitive control refers to the set of neurocognitive processes allowing individuals to monitor and flexibly adapt their behavior in an effort to achieve a goal (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Holroyd & Coles, 2002). A goal can be anything from a child riding their new bicycle along the sidewalk to performing well on a computer-based laboratory task. Although the distinction is sometimes made in the literature, researchers do not frequently enough define and study the various constructs that make up "cognitive control." In this chapter, we argue that distinguishing among different components of cognitive control helps explain seemingly paradoxical findings between behavioral inhibition and cognitive control and highlights avenues for future research. While multiple taxonomies are possible (e.g., Nigg, 2017; Shenhav, Botvinick, & Cohen, 2013) and often useful, here we rely primarily on a simple distinction between the constructs of "monitoring" and "control instantiation." We further parse control instantiation where appropriate but maintain a monolithic treatment of monitoring throughout the chapter.[1]

We use the term "monitoring" to refer to the neurocognitive processes associated with detecting when something goes wrong or noticing when changes occur that will impair the ability to achieve a goal. In the example of safely riding a bicycle down the street, monitoring would refer to noticing deviations from this goal, like accidentally swerving into the street or seeing objects on the sidewalk obstructing

[1] In this chapter, for simplicity, we treat monitoring as a singular construct. Indeed, while extensive research has investigated the multifaceted nature of control instantiation, little research has investigated parsing of monitoring along additional dimensions. Nonetheless, parsing monitoring into relevant sub-constructs may be meaningful and useful. One possibility is that the neurocognitive process of monitoring differs based on the type of task that is being monitored, or the type of goal that one is trying to achieve. Another possibility is that monitoring may meaningfully be defined in terms of its time course, that is, whether monitoring occurs before or after an event of interest, and the duration for which monitoring is sustained.

the path. In contrast, we reserve the term "control instantiation" for changes made to behavior (along with associated neural correlates) to increase the likelihood of achieving a goal. In the bicycle example, control instantiation would refer to the child changing their course direction or paying more attention after they detect themselves swerving into the street. Thus, monitoring and control instantiation are two complementary, but distinct, constructs of the broader concept of cognitive control.

In this chapter, we first review approaches to studying monitoring, relations with the behavioral inhibition phenotype, and ultimately, how interactions between monitoring and behavioral inhibition predict risk for later anxiety. Next, we turn to a description of control instantiation and the interrelations with behavioral inhibition and anxiety. Finally, we integrate findings across the monitoring and control domains and outline the emerging picture of relations between behavioral inhibition, cognitive control, and anxiety. We end this chapter with a discussion of outstanding questions and future research directions that should be pursued.

Monitoring

Within the laboratory, behavioral tasks and physiological recordings are often used to study monitoring. While monitoring is difficult to study directly at the behavioral level, one approach taken is to observe how behavior changes after participants make an error on a computer-based task (Danielmeier & Ullsperger, 2011). It is assumed that when the brain's performance monitoring system detects a mistake, individuals slow down or improve their accuracy on the following trial. This way, researchers can indirectly assess whether the participant detected the mistake (i.e., whether the participant was monitoring their behavior or not). A problem with this approach, however, is that such behavioral measures are heavily confounded by control instantiation. Presumably, if an individual detects a mistake, then they will instantiate control in some way (e.g., increasing attention) to prevent future mistakes. Thus, the most direct approach to studying monitoring processes in children is to use neuroimaging techniques.

In adults, a substantial literature has identified a network of neural regions, centered around the cingulate cortex, which forms the performance monitoring system (Ullsperger, Danielmeier, & Jocham, 2014). Activation of this system can be reliably indexed using either functional magnetic resonance imaging (fMRI) or electroencephalography (EEG). For example, when participants make an error on a computer-based task, fMRI reveals increased activation within the medial frontal cortex (MFC), including the cingulate cortex (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). Similarly, EEG recordings demonstrate a characteristic pattern of event-related potential (ERP) activity following errors: a negative voltage deflection over frontocentral scalp locations, termed the error-related negativity (ERN; Gehring, Liu, Orr, & Carp, 2012), followed by a slower, positive voltage

deflection over centroparietal scalp locations, termed the error positivity (Pe; Overbeek, Nieuwenhuis, & Ridderinkhof, 2005; Steinhauser & Yeung, 2010).

Source localization estimates of the ERN and Pe have localized these ERPs to a network of neural regions centered on the cingulate cortex (i.e., the performance monitoring system; Buzzell et al., 2017; Debener et al., 2005; Herrmann, Römmler, Ehlis, Heidrich, & Fallgatter, 2004). Additionally, time-frequency analyses focusing on theta-band EEG oscillations can be employed as a reliable index of performance monitoring system activation in response to errors (Cavanagh, Zambrano-Vazquez, & Allen, 2012). However, errors need not occur for the performance monitoring system to become activated, with increased activity having been observed for conflict (Buzzell, Roberts, Baldwin, & McDonald, 2013), uncertainty (Buzzell et al., 2016), external feedback about a task (Holroyd & Coles, 2002), or changes in task difficulty (Petersen & Posner, 2012). In sum, the performance monitoring system monitors for any situation that might signal the need for a participant to stop performing a task in an automatic fashion and, instead, instantiate control.

Monitoring and Behavioral Inhibition

Leveraging neuroimaging techniques, the literature consistently demonstrates that the behavioral inhibition phenotype is integrally linked to increased monitoring. The first evidence for a link between behavioral inhibition and neural measures of monitoring came from the study by McDermott et al. (2009). This study examined ERN magnitude in adolescence within a longitudinal cohort of children assessed for levels of behavioral inhibition in childhood, as a neural index of monitoring. Children with a history of behavioral inhibition had a significantly larger ERN, suggesting increased monitoring in these children (McDermott et al., 2009). Subsequent work in a separate cohort of children replicated this effect even earlier, at age 7 (Lahat et al., 2014).

In this second cohort, the ERN was assessed again in adolescence, both while the children believed they were being observed by others and also while alone (Buzzell et al., 2017). This social manipulation was done to capture the effects of social context on monitoring. The social context is thought to be particularly relevant for behavioral inhibition, as early behavioral inhibition is most evident in novel social situations and predicts both social reticence (Degnan et al., 2014) and social anxiety later in development (Chronis-Tuscano et al., 2009; Clauss & Blackford, 2012). Critically, increases in the ERN while under social observation were greatest for children with a history of behavioral inhibition (Buzzell, Troller-Renfree, et al., 2017). This more recent study demonstrates that beyond general increases in monitoring for children high in behavioral inhibition, monitoring in social contexts is particularly elevated (see the chapter "The Neural Mechanisms of Behavioral Inhibition" by Jarcho and Guyer and the chapter "The Social World of Behaviorally Inhibited Children: A Transactional Account" by Henderson et al.).

Beyond increased error monitoring, research also consistently reveals that children with a history of being high in behavioral inhibition exhibit increased activation of the performance monitoring system in response to a variety of events. For example, compared to children lower in behavioral inhibition, children higher in behavioral inhibition display heightened fMRI activity within the cingulate cortex—a key region of the performance monitoring system—for trials with high levels of stimulus conflict (i.e., for incongruent trials on an emotional Stroop task; Jarcho et al., 2013).

Moreover, similar findings were found when the N2 ERP component was employed as an index of monitoring (Lahat et al., 2014). Using a flanker task, 7-year-old children with a history of high behavioral inhibition exhibited a larger N2 to incongruent (high conflict) flanker stimuli (Lahat, Walker, et al., 2014). When these same children performed a go/no-go task, children with higher behavioral inhibition again demonstrated a larger N2, this time in response to infrequent "no-go" stimuli that require control (Lamm et al., 2014). This latter study also applied a source localization approach to estimate the neural source of the increased N2 component. Analyses revealed that children with higher behavioral inhibition had increased activity, in part, within the cingulate cortex (Lamm et al., 2014). To summarize, substantial evidence using fMRI, ERP, or EEG source localization approaches are consistent with the notion that the behavioral inhibition phenotype is associated with increased monitoring.

Monitoring, Behavioral Inhibition, and Anxiety

Parallel to the finding that behavioral inhibition is directly associated with increased monitoring, substantial research in adults and adolescents demonstrate that anxiety is also associated with increased monitoring, particularly in response to errors. Indeed, two reviews and a meta-analysis have linked increases in the ERN and frontal-midline theta oscillations of the EEG—both indices of error monitoring—to anxiety (Cavanagh & Shackman, 2015; Meyer, 2017; Moser, Moran, Schroder, Donnellan, & Yeung, 2013). However, it is also important to note that relations between the ERN and anxiety in *children* are mixed, at least when assessed at subclinical levels (for a review, see Meyer, 2017).

Recently, it has been suggested that relations between the ERN and subclinical anxiety changes direction as a function of age, with such a shift tracking normative development of fear and anxiety (Meyer, 2017). In very young children, anxiety associated with self-monitoring and the ERN may be limited, and instead anxious cognition may be associated with more external sources of fear (e.g., a strange developmental psychologist looking on as EEG is recorded). However, as children become older, sources of anxiety may shift toward an internal focus on one's mistakes, and a concomitant increase in the ERN (Meyer, 2017). However, Meyer (2017) also notes that for children with *clinical levels of anxiety*, the typical relation

between the ERN and anxiety is still observed, where a larger ERN is related to increased anxiety.

Alternatively, the theoretical framework put forth by Moser et al. (2013) suggests that the ERN is not a *risk marker* for later anxiety, but rather a *symptom* of anxiety. These authors suggest that the increased ERN observed in adolescents or adults with anxiety is the result of anxious cognition causing distraction and a shift toward a more in-the-moment style of cognitive control termed "reactive control." One index for the shift toward a reactive strategy is increased effort (i.e., a larger ERN) at the monitoring stage of task processing (Moser et al., 2013). However, no evidence to date has ruled conclusively in favor of either the theoretical framework put forth by Moser et al. (2013) or the hypothesis suggested by Meyer (2017). To summarize, what remains clear in the literature is that consistent and robust relations between anxiety and a larger ERN are present in both adults and adolescents, whereas findings in young children have been mixed and theoretical explanations remain debated.

It is important to note that while relations between the ERN and anxiety in children have been mixed, the relations between behavioral inhibition and the ERN have been remarkably consistent. Studies reliably find that behavioral inhibition is predictive of an enhanced ERN in childhood (Lahat, Lamm, et al., 2014), late childhood to early adolescence (Buzzell, Troller-Renfree, et al., 2017), or mid-to-late adolescence (McDermott et al., 2009). Perhaps more striking, longitudinal relations between early behavioral inhibition and later anxiety are also consistently *moderated* by the level of monitoring that these children display, with increased monitoring—as measured by the ERN—amplifying the strength of longitudinal relations between behavioral inhibition and anxiety (Lahat, Lamm, et al., 2014; McDermott et al., 2009).

It should also be noted that a third study by Buzzell, Beatty, Paquette, Roberts, and McDonald (2017) reports on a mediation model in which ERN examined at age 12, specifically within social contexts, *mediates* relations between early behavioral inhibition and later social anxiety, but only when behavioral measures (post-error response time) are also included in the model. This more nuanced *mediation* model suggests one possible mechanism that takes into account social influences on brain and behavior and directly links behavioral inhibition to the development of social anxiety. Later in the chapter, we detail this mechanism outlined by Buzzell, Richards, et al. (2017).

However, it is important to note here that additional, unpublished analyses of the data reported by Buzzell, Troller-Renfree, et al. (2017) demonstrate that when the social context of the ERN is ignored, the ERN at age 12 also *moderates* the relation between behavioral inhibition and anxiety. That is, consistent with prior work (Lahat, Lamm, et al., 2014; McDermott et al., 2009), behavioral inhibition predicted later social anxiety only for children with a large ERN in this dataset as well. In this new analysis, social context was ignored, and the ERN was calculated as a difference wave (delta-ERN) based on all trials in the experiment. Thus, in all three of these studies (Buzzell, Troller-Renfree, et al., 2017; Lahat, Lamm, et al., 2014; McDermott et al., 2009), which span two longitudinal cohorts and three separate

assessment ages, behavioral inhibition was predictive of later anxiety only for children with a relatively larger ERN.

Given that direct relations between the behavioral inhibition phenotype and an enhanced ERN also exists, these moderation analyses suggest that the monitoring component of behavioral inhibition plays a critical role in the development of later anxiety. Of course, we do not suggest that increased monitoring for children high in behavioral inhibition is the sole mechanism through which anxiety develops; indeed we contend that there are many developmental pathways through which anxious cognition may emerge. For instance, behavioral inhibition is also known to be associated with heightened reactivity of fear circuitry within the brain (Schwartz et al., 2003), a mechanism that undoubtedly plays a crucial role in the development of later anxiety. Nonetheless, increased monitoring, which appears to be an inherent feature of the behavioral inhibition phenotype, seems to play a critical role in the development of later anxiety.

Why would increased monitoring, which is commonly thought to be a useful and adaptive cognitive process, predispose an individual to develop clinical levels of anxiety? To answer this question, it is important to reflect on the phenotype of anxiety, and more specifically, social anxiety. Symptoms of social anxiety include rumination, worry, and self-focus, specifically within social contexts or while under social evaluation (Clark & Wells, 1995; Rapee & Heimberg, 1997). While worry or self-focus may be adaptive when maintained at normative levels, excessive worry or self-focus can drain attentional resources and lead to distraction (Eysenck, Derakshan, Santos, & Calvo, 2007; Moser et al., 2013; Rapee & Heimberg, 1997). Similarly, recent research has shown that monitoring can also sometimes lead to distraction (Buzzell, Beatty, et al., 2017; der Borght, Schevernels, Burle, & Notebaert, 2016), as opposed to control (Botvinick et al., 2001).

That is, it may be that monitoring is only adaptive when it leads to control instantiation. If you recognize that you are doing something wrong, but don't do anything about it, that is not an adaptive process. If monitoring does not translate into control instantiation, or if excessive monitoring actually leads to impaired performance (Buzzell, Beatty, et al., 2017; Buzzell, Troller-Renfree, et al., 2017), then such a process becomes *maladaptive* and even pathological. Indeed, Moran, Bernat, Aviyente, Schroder, and Moser (2015) have shown that while anxious adults exhibit increased monitoring, as measured by a larger ERN, they also demonstrate a reduced ability to instantiate control following error detection, as measured by reduced interchannel phase synchrony (a measure of functional connectivity between medial and later prefrontal cortices). Thus, at least one reason why increases in monitoring might be associated with increased risk for anxiety is the propensity for excessive monitoring to cause distraction.

Given that behavioral inhibition is most strongly predictive of developing social anxiety as opposed to other subtypes of anxiety (e.g., generalized, specific phobia), the question remains as to why a relatively general neural response to error monitoring relates to behavioral inhibition and the development of a highly specified, and social-specific, disorder. One hypothesis is that within the majority of lab-based EEG studies, participants might believe that the experimenters are evaluating their

performance to some degree. This is likely true even when the experimenters remain outside the room while the participant performs the task. Therefore, many of the studies investigating the ERN may, at least indirectly, reflect the measurement of error monitoring *while under social observation*.

Critically, the phenotypes of social anxiety (Clark & Wells, 1995; Rapee & Heimberg, 1997) and behavioral inhibition (Fox et al., 2005; Kagan et al., 1984) are most prevalent under social evaluation, or social settings in general. Therefore, it may be the presence of increased monitoring *while under social observation* that is most closely related to behavioral inhibition and social anxiety. In line with this hypothesis, three studies in adults have shown that not only does explicit manipulation of social evaluation increase the ERN magnitude (Hajcak, Moser, Yeung, & Simons, 2005) but that such increases are greatest for those with social (Barker, Troller-Renfree, Pine, & Fox, 2015) or performance (Masaki, Maruo, Meyer, & Hajcak, 2017) anxiety.

Similarly, a longitudinal study of children that were previously assessed for behavioral inhibition found that such social-specific increases in the ERN were directly predicted by behavioral inhibition levels measured approximately 10 years prior (Buzzell, Troller-Renfree, et al., 2017). More importantly, longitudinal relations between behavioral inhibition and social anxiety were explained by social-specific ERN increases, along with a maladaptive response to errors: post-error response time slowing (Buzzell, Troller-Renfree, et al., 2017). This most recent finding provides strong evidence for the hypothesis that excessive monitoring, *particularly within social contexts*, is one aspect of the behavioral inhibition phenotype that plays a critical role in the development of social anxiety later in life. Moreover, these data provide evidence that it is the maladaptiveness of such excessive error monitoring that leads to pathological levels of social anxiety: error monitoring only explained relations between behavioral inhibition and social anxiety insofar as greater slowing after errors in the social condition—with no improvement in accuracy—was observed (Buzzell, Troller-Renfree, et al., 2017). These findings open up an intriguing new line of research, though additional studies are needed.

Control Instantiation

Although the notion of monitoring is relatively monolithic, control instantiation can be meaningfully parsed into subdimensions. First, the type of control instantiation is important to specify. For example, two common types of control instantiation include, but are not limited to, inhibiting responses (inhibitory control) and switching between different tasks (task switching). Briefly, inhibitory control refers to the suppression of a stimulus representation, motor command, or other neural process, typically through suppression of motor-related neural activity (Aron, 2007). Task switching refers to the ability to flexibly switch between two (or more) sets of maintained information, task rules, or other neural ensembles, each of which is associated with alternative task goals (Braver, Reynolds, & Donaldson, 2003).

Additionally, control instantiation can be divided into whether it is deployed before or after a cognitively demanding event (e.g., conflict). Proactive control refers to the instantiation of control in an anticipatory manner, *before* the cognitive demand (Braver, 2012). In contrast, reactive control refers to the instantiation of control in a "just-in-time" manner, as it is needed, *after* the conflict occurs (Braver, 2012). In the example of a child riding their bike, if the child were to pay extra attention to the sidewalk and their steering, in an effort to *prevent* veering into the street, this would be an example of proactive control. In contrast, if the child were simply to wait until they accidently veered into the street, *reacting* to this event with corrective behavior, this would be an example of reactive control. It is worth noting that both proactive and reactive control can be adaptive, depending on the context, and healthy human behavior is associated with the use of both proactive and reactive control.

Similar to the construct of monitoring, control instantiation can be assessed using behavioral metrics, although not perfectly. Simply put, if a task is designed such that it requires control instantiation to be performed well, then a child's control instantiation abilities can be *indirectly* inferred from how accurately (and quickly) they perform the task. For example, in order to measure inhibitory control, a "go/no-go" task can be employed, which requires participants to frequently respond to "go" stimuli while infrequently inhibiting responses to "no-go" stimuli (Bokura, Yamaguchi, & Kobayashi, 2001). Using such a task, accuracy on no-go trials can be measured as an index of control instantiation, more specifically inhibitory control. Alternatively, in order to test whether children instantiate control following a mistake, accuracy rates on trials that follow errors can be assessed (Danielmeier & Ullsperger, 2011).

However, the same problem that plagues behavioral measures of monitoring applies to the assessment of control instantiation. That is, behavioral measures of control instantiation are heavily confounded with monitoring, as control instantiation is rarely implemented without monitoring processes first detecting the need for control instantiation. Moreover, a given task that is designed to putatively measure a specific type of control is often confounded by other types of control that are also required to perform the task. For example, in a go/no-go task, not only is inhibitory control needed, but also attentional control directed toward the go and no-go stimuli is required (Schröger, 1993). Fortunately, control instantiation can be readily assessed using neural measures, allowing for selective measurement of brain regions known to be associated with a given control process.

The neural correlates of control instantiation are dependent on the type of control that is being instantiated. For example, if a task requires increased attentional allocation, then this will be observed in fMRI recordings as increased activity within a frontoparietal network, thought to be the source of attentional control (Corbetta & Shulman, 2002), along with amplification of the attended stimuli within the relevant sensory cortex. In contrast, if a task requires the inhibition of motor responses, activity within prefrontal and motor cortices will be observed (Aron, 2007). Evidence for control instantiation can also be observed using EEG, by assessing whether sensory processing is enhanced as the result of attention control (Roberts, Fedota, Buzzell, Parasuraman, & McDonald, 2014), or oscillations within the motor

cortex are altered as the result of inhibitory control (Bengson, Mangun, & Mazaheri, 2012). In relation to determining proactive vs. reactive control instantiation, the location of neural activity does not typically differ, but the time course of activation does (Braver, 2012). That is, proactive control is associated with increased and sustained activation prior to the need for control, whereas reactive control is associated with increased neural activity closer in time, or following, when the control is needed.

Control Instantiation and Behavioral Inhibition

Evidence for relations between control instantiation and behavioral inhibition have been sparse and mixed. A relatively early study found that increases in control instantiation, particularly inhibitory control, was directly related to the behavioral inhibition phenotype (Thorell, Bohlin, & Rydell, 2004). In particular, Thorell et al. (2004) found that laboratory-based assessments of behavioral inhibition at age 5 were positively correlated with performance on go/no-go task, designed to assess inhibitory control. More recently, Lamm et al. (2014) also demonstrated that behavioral inhibition might be directly related to inhibitory control, finding that behavioral inhibition in toddlerhood was predictive of increased accuracy on a go/no-go task at age 7.

Despite these results, a number of studies have failed to identify a direct relation between the behavioral inhibition phenotype and inhibitory control (Jarcho et al., 2013, 2014; Lahat, Lamm, et al., 2014; Lahat, Walker, et al., 2014; Troller-Renfree et al., 2018; White, McDermott, Degnan, Henderson, & Fox, 2011). Additionally, the only study investigating relations between behavioral inhibition and attentional shifting found no relation between these constructs (White et al., 2011). Based on the results of these studies, it does not appear that there is strong evidence for a direct link between the behavioral inhibition phenotype and overall levels of control instantiation. However, in the section entitled "Control instantiation, behavioral inhibition, and anxiety," we discuss substantial work suggesting that while the overall level of control instantiation may not relate directly to the behavioral inhibition phenotype, such control processes do seem to influence the strength of the relations between behavioral inhibition and later anxiety.

A recent study suggests that prior questions surrounding the direct relations between behavioral inhibition and control instantiation may have been ill posed. Instead of asking whether *increased* control is associated with behavioral inhibition, it might be better to ask whether the *time course* of control instantiation is what directly relates to behavioral inhibition. That is, perhaps a distinguishing feature of the behavioral inhibition phenotype is whether control is instantiated in a proactive vs. reactive manner, regardless of the overall *intensity* of control. Adopting this perspective, a recent study by Troller-Renfree, Buzzell, Pine, Henderson, and Fox (in press) employed the AX-CPT (Braver, 2012) to investigate whether the behavioral inhibition phenotype is directly related to a relatively stronger reactive control strategy, as opposed to a proactive control strategy.

The AX-CPT requires individuals to attend to one stimulus, the "cue," and then respond to a second stimulus, "the probe," based on the identity of both the cue and probe. Briefly, there are certain cue stimuli that are highly predictive of the probe, such that if proactive control is being used, performance should be most accurate on these trials. In contrast, there are also infrequent cue-probe pairings in which a different probe follows this cue. Here, performance will be impaired by the over-reliance on a proactive control strategy. Thus, by analyzing behavioral data from this task, it is possible to determine the degree to which a child relies relatively more on a proactive vs. reactive control strategy.

Using the AX-CPT, Troller-Renfree, Buzzell, Pine, et al. (in press) found that children with a history of increased behavioral inhibition have a tendency to not proactively deploy control in an effort to prevent mistakes. Rather, they seem to rely on employing control in a reactive and "just-in-time" manner.

While this recent finding is only the first step in probing whether the time course of control instantiation directly relates to the behavioral inhibition phenotype, these data suggest an intriguing possibility: prior work identifying a relation between behavioral inhibition and inhibitory control intensity (Lamm et al., 2014; Thorell et al., 2004) may have actually been driven by a stronger reactive control strategy in children with behavioral inhibition. The reason for this thinking is that tasks designed to test inhibitory control are often set up in such a way that inhibitory control cannot be deployed in a proactive manner; instead, these tasks seem to measure *reactive* inhibitory control. For example, in either a go/no-go or Stroop task, the most efficient method of performing these tasks well is to wait until the need for control is detected via monitoring processes and to then apply inhibitory control only at that point (i.e., to use a reactive control strategy). Thus, the occasional observations of a direct relation between behavioral inhibition and inhibitory control, at least at the behavioral level, may actually reflect the tendency for children with behavioral inhibition to adopt a reactive control strategy.

Control Instantiation, Behavioral Inhibition, and Anxiety

As previously mentioned, a review of the literature provides minimal evidence that increased control instantiation is an inherent component of the behavioral inhibition phenotype. Nonetheless, although control instantiation ability may reflect a developmentally distinct neurocognitive process that is orthogonal to the behavioral inhibition phenotype, control instantiation could still interact with behavioral inhibition to predict risk for anxiety. Additionally, at least one study to date has demonstrated that it is not the *intensity* of control instantiation but individual differences in the *time course* of control instantiation (i.e., proactive vs. reactive control) that is directly related to the behavioral inhibition phenotype (Troller-Renfree, Buzzell, Pine, et al., in press). Here, we review studies investigating whether the level of control instantiation, or the time course of control instantiation, interact with the behavioral inhibition phenotype to predict the development of later anxiety.

In both adults and children without a history of behavioral inhibition, increased levels of inhibitory control are typically associated with *reduced* anxiety symptoms (Eysenck et al., 2007; Kertz, Belden, Tillman, & Luby, 2015; Lengua, 2003). The fact that anxiety in either adults or children is associated with reduced levels of inhibitory control is a relatively intuitive connection: inhibitory control broadly reflects the ability to inhibit or control behavior, which might include the control or suppression of anxiety-provoking thoughts. Based on this logic, one might hypothesize that for children with a history of behavioral inhibition, *lower* levels of inhibitory control would exacerbate risk for developing later anxiety.

However, three studies, from two independent research groups, have actually demonstrated the opposite pattern: children with a history of behavioral inhibition and *increased* levels of inhibitory control are at greater risk of developing anxiety (Thorell et al., 2004; Troller-Renfree, Buzzell, Bowers, et al., 2018; White et al., 2011). In the first study, Thorell et al. (2004) found that 5-year-old children with high levels of behavioral inhibition and inhibitory control (assessed using a go/no-go task) were more likely to be rated as high in social anxiety by their teachers 3 years later. In a separate study by White et al. (2011), behavioral inhibition in early childhood (ages 2 and 3) was predictive of anxiety symptoms later in childhood (ages 4 and 5), but only for children with high levels of inhibitory control (as assessed using two Stroop tasks designed for children). Finally, in perhaps the most extensive investigation of relations between behavioral inhibition, inhibitory control, and later anxiety, Troller-Renfree, Buzzell, Bowers, et al. (2018) also found that higher levels of inhibitory control exacerbated later risk for anxiety, but only for children high in behavioral inhibition.

In this study, Troller-Renfree, Buzzell, Bowers, et al. (2018) analyzed the same cohort of children as White et al. (2011) but over a wider span of time (ages 2–12) and employed a go/no-go task to measure inhibitory control. Specifically, these authors had children perform a go/no-go task in the laboratory at ages 5, 7, and 9 and then modeled developmental slopes of inhibitory control ability across these time points, yielding initial estimates of the children's inhibitory control ability at age 5, as well as estimates of how their inhibitory control ability changed over this 4-year period (e.g., an increasing, decreasing, or level slope). Troller-Renfree, Buzzell, Bowers, et al. (2018) found that behavioral inhibition predicted later social anxiety symptoms, but only for children with a steeper slope of inhibitory control development in the intervening years. This study not only provides additional evidence that high levels of inhibitory control ability increase risk for later anxiety in children with behavioral inhibition but also illustrates the importance of considering developmental trajectories in inhibitory control ability.

Given prior findings that increased levels of inhibitory control are protective against anxiety when behavioral inhibition is not measured or considered (Eysenck et al., 2007; Kertz et al., 2015; Lengua, 2003), why would the analyses involving behavioral inhibition show a categorically different set of relations? Some insight into this question comes from additional analyses in the study by White et al. (2011). In this study, children not only performed the Stroop task as a way to assess inhibitory control but also performed a Dimensional Change Card Sort Task, designed to

assess task-switching ability (White et al., 2011). Recall that task switching reflects the ability to flexibly shift between various thoughts or behaviors based on task goals. Critically, White et al. (2011) found that for children high in behavioral inhibition, improved task-switching ability was indeed associated with a *reduced* risk for later anxiety.

Collectively, the study by White et al. (2011) suggests that not all forms of control instantiation are associated with increased risk for later anxiety for children with a history of behavioral inhibition. In fact, the only type of control instantiation that has been shown to increase risk for developing anxiety in children high in behavioral inhibition is inhibitory control. One possibility is that increased levels of inhibitory control leads to an "over controlled" and less flexible style of responding and interacting with others (Henderson, Pine, & Fox, 2015).

The studies to date support the notion that inhibitory control is a risk factor for later anxiety development in children with behavioral inhibition. However, it is important to note that extant research investigating these relations have relied solely on behavioral measures of inhibitory control. As mentioned above, inferences that can be drawn from behavioral measures of inhibitory control are limited—these measures are almost always confounded by monitoring. Because of this, an improved ability to monitor one's behavior would lead to improved task performance even if the intensity of inhibitory control ability were held constant.

In order to rule out this alternative explanation, neural measures of both inhibitory control ability and monitoring would need to be assessed concurrently in the same children and controlled for. Thus, while the current literature suggests inhibitory control increases risk for later anxiety, neural evidence supporting this claim is needed. Using the AX-CPT, Troller-Renfree, Buzzell, Pine, et al. (in press) demonstrated that not only is behavioral inhibition (at ages 2 and 3) predictive of a more reactive control strategy at age 12 but that this control strategy moderates longitudinal relations between behavioral inhibition and social anxiety. Specifically, children with a history of behavioral inhibition only developed social anxiety symptoms if they also exhibited a more reactive control strategy (Troller-Renfree, Buzzell, Pine, et al., in press). Such findings are consistent with the fact that behavioral measures of increased inhibitory control also increase the likelihood that children with behavioral inhibition will develop anxiety, given that studies used to investigate inhibitory control often encourage a reactive control strategy. However, additional investigations of how behavioral inhibition and anxiety relate to both the *intensity* and *time course* of control instantiation, at both the behavioral and neural level, are needed.

The Emerging Picture

In surveying the existing literature on relations between behavioral inhibition and cognitive control, a coherent picture begins to emerge. An inherent aspect of the behavioral inhibition phenotype appears to be excessive monitoring, especially while under social evaluation, along with the adoption of a more reactive control

strategy. In contrast, the majority of the evidence suggests that behavioral inhibition is not directly related to levels of control instantiation (inhibitory control or task switching).

That is, when placed within situations that require control, children with behavioral inhibition do not plan ahead, nor flexibly adapt their behavior. Instead, these children appear to excessively monitor their own behavior and such monitoring does not appear to be adaptive for children with behavioral inhibition as they are more likely to develop anxiety. These findings are largely in agreement, as behavioral tasks that assess inhibitory control often encourage a reactive control strategy, and increased monitoring is necessary to adopt such a reactive control strategy. It is worth noting that this generalization of behavioral inhibition and later risk for anxiety is not without limitations. An improved understanding of how cognitive control relates to behavioral inhibition and risk for anxiety will require additional longitudinal research that incorporates assessment of cognitive control using multiple tasks and neuroimaging techniques. Below, we outline unresolved issues and suggestions for future research within this domain.

Unresolved Questions and Future Directions

Need for More Longitudinal Research

It is worth noting that the majority of studies investigating relations between behavioral inhibition and cognitive control come from two longitudinal cohorts, studied by the same research group. An astounding degree of internal consistency has been observed in the results of several distinct experimental tasks assessing cognitive control within these two cohorts. However, strong scientific theory not only requires replication but also replication by independent researchers. While research by some independent research groups have corroborated the findings outlined here (Thorell et al., 2004), other work appears to conflict with these findings (Torpey et al., 2013). Thus, additional research into the relations between behavioral inhibition and cognitive control, preferably within a longitudinal context, is critically needed.

Does Inhibitory Control Relate to Behavioral Inhibition and Later Anxiety?

Throughout this chapter, we have asked which aspects of cognitive control are inherent to the behavioral inhibition phenotype, as well as which processes interact with behavioral inhibition to predict later risk for anxiety. Some evidence that inhibitory control is inherent to the behavioral inhibition phenotype has been published (Lamm et al., 2014; Thorell et al., 2004), though the majority of work suggests that

inhibitory control is a developmentally distinct process (Jarcho et al., 2013, 2014; Lahat, Lamm, et al., 2014; Lahat, Walker, et al., 2014; Troller-Renfree, Buzzell, Bowers, et al., 2018; White et al., 2011). Inhibitory control does appear to consistently increase risk for later anxiety in children with a history of behavioral inhibition. However, such findings have relied exclusively on behavioral measures.

Given that tasks measuring inhibitory control are often confounded with monitoring and a reactive control strategy, other explanations are possible. A simple solution to this issue is to employ neural measures of inhibitory control to isolate this process from monitoring. For example, synchronized EEG oscillations between electrodes located over the frontal and motor cortices, or fMRI-based measures (e.g., increased correlation in the blood flow within frontal and motor regions), could both be taken as direct evidence of inhibitory control. Moreover, concurrent measurement of proactive vs. reactive control strategy could be assessed and controlled for. Such an approach would allow for a direct test of (1) whether inhibitory control is an inherent aspect of the behavioral inhibition phenotype and (2) whether increased inhibitory control exacerbates risk for later anxiety.

Why Does Increased Monitoring Increase Anxiety Risk?

Monitoring is typically viewed as an adaptive process, allowing for the detection of situations that require control, allowing us to reach our goals. Within this context, why is excessive monitoring a risk factor for anxiety? Recent cognitive neuroscience research demonstrates that monitoring can sometimes cause distraction (Buzzell, Beatty, et al., 2017; der Borght et al., 2016; Purcell & Kiani, 2016) and that such a mechanism may help to explain why excessive monitoring is associated with anxiety (Buzzell, Troller-Renfree, et al., 2017). However, the boundary conditions of this effect are unknown.

Is the relation between monitoring and controlling an inverted "U" with a moderate amount of monitoring beneficial and an excessive amount maladaptive? Or, alternatively, is it that individuals with anxiety simply lack an additional mechanism that translates monitoring into control instantiation? If anxious individuals simply lack this secondary process, excessive monitoring could be a way to boost a "leaky signal" that connects monitoring and control instantiation in anxious individuals. Relatedly, what are the contexts within which excessive monitoring may or may not be maladaptive for anxious individuals? It appears that excessive monitoring is maladaptive within social situations, at least for children with a history of high behavioral inhibition (Buzzell, Troller-Renfree, et al., 2017). However, future work will be needed to directly test the alternative theories of maladaptive error monitoring in these children. Does the arousal from social situations simply push their monitoring toward the extreme end of an inverted "U," overloading the cognitive system and causing distraction? Or does social situation impair the effectiveness of a separate mechanism linking monitoring and control?

Does the Time Course of Cognitive Control Matter?

To date, there has only been one study that investigates the time course of control instantiation in children with a history of behavioral inhibition (Troller-Renfree, Buzzell, Pine, et al., in press). It is critical that this finding be replicated but also that similar relations are evaluated at younger ages and in conjunction with neuroimaging approaches. Moreover, it would be helpful to test whether the control strategy adopted by children with behavioral inhibition changes based on the type of control being assessed, such as attentional control compared to inhibitory control. Finally, assessing the time course of control, and perhaps even monitoring, at much longer timescales (i.e., hours and days) could also be informative. For example, does anticipatory anxiety reflect excessive monitoring or control instantiation prior to an anxiety-provoking event? To summarize, the recent study by Troller-Renfree, Buzzell, Pine, et al. (in press) presents an exciting new line of research to pursue in terms of understanding of behavioral inhibition and relations to later anxiety; however, much more work is needed within this domain.

Need for Multidimensional Assessments of Cognitive Control

Throughout this chapter, we have reviewed a series of studies that each focus on one, or at most two, aspects of cognitive control. However, performing even simple laboratory tasks requires a coordinated effort across the brain, involving multiple neural systems and subsystems. Thus, to what extent are the findings of a study reporting on a given construct (e.g., inhibitory control), confounded by another construct (e.g., monitoring or control strategy)?

To answer such a question, multidimensional approaches that concurrently measure and analyze two or more constructs of cognitive control, on the same participants, are needed. At the most basic level, such an approach would allow for isolating a given construct of interest by statistically controlling for variability in other measured constructs. However, perhaps of greater interest would be to take a latent profile approach, identifying what profiles of cognitive control are associated with behavioral inhibition, anxiety, or their interaction. While such methods will require considerably larger samples sizes, we believe such approaches will provide invaluable insight into the nature of behavioral inhibition and the etiology of anxiety. Ultimately, such insight could inform novel approaches to treating anxiety, or early intervention strategies for children identified with high levels of behavioral inhibition and control profiles that place them at heightened risk for developing anxiety problems.

Conclusions

In conclusion, studying cognitive control in relation to behavioral inhibition provides unique insights into both the phenotype of behavioral inhibition, as well as the later development of anxiety. However, critical insights are provided when cognitive control is separated into the subdomains of monitoring and control instantiation. In doing so, the literature appears to support the view that monitoring is not only directly related to behavioral inhibition but also interacts with behavioral inhibition to predict later development of anxiety. In contrast, control instantiation does not appear to directly relate to behavioral inhibition, though this construct does seem to interact with behavioral inhibition to predict the later development of anxiety. Nonetheless, the complete set of interrelations between behavioral inhibition, cognitive control, and anxiety are not fully understood. Future longitudinal research, employing both behavioral and cognitive neuroscience methods, will be needed to arrive at a more complete understanding of how behavioral inhibition relates to cognitive control and predicts risk for later anxiety.

References

Aron, A. R. (2007). The neural basis of inhibition in cognitive control. *The Neuroscientist, 13*(3), 214–228. https://doi.org/10.1177/1073858407299288

Barker, T. V., Troller-Renfree, S., Pine, D. S., & Fox, N. A. (2015). Individual differences in social anxiety affect the salience of errors in social contexts. *Cognitive, Affective, & Behavioral Neuroscience, 15*(4), 723–735. https://doi.org/10.3758/s13415-015-0360-9

Bengson, J. J., Mangun, G. R., & Mazaheri, A. (2012). The neural markers of an imminent failure of response inhibition. *NeuroImage, 59*(2), 1534–1539.

Bokura, H., Yamaguchi, S., & Kobayashi, S. (2001). Electrophysiological correlates for response inhibition in a go/NoGo task. *Clinical Neurophysiology, 112*(12), 2224–2232.

Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., & Cohen, J. D. (2001). Conflict monitoring and cognitive control. *Psychological Review, 108*(3), 624.

Braver, T. S. (2012). The variable nature of cognitive control: A dual mechanisms framework. *Trends in Cognitive Sciences, 16*(2), 106–113.

Braver, T. S., Reynolds, J. R., & Donaldson, D. I. (2003). Neural mechanisms of transient and sustained cognitive control during task switching. *Neuron, 39*(4), 713–726. https://doi.org/10.1016/S0896-6273(03)00466-5

Buzzell, G. A., Beatty, P. J., Paquette, N. A., Roberts, D. M., & McDonald, C. G. (2017). Error-induced blindness: Error detection leads to impaired sensory processing and lower accuracy at short response-stimulus intervals. *Journal of Neuroscience, 37*, 2895–2903.

Buzzell, G. A., Richards, J. E., White, L. K., Barker, T. V., Pine, D. S., & Fox, N. A. (2017). Development of the error-monitoring system from ages 9–35: Unique insight provided by MRI-constrained source localization of EEG. *NeuroImage, 157*, 13–26. https://doi.org/10.1016/j.neuroimage.2017.05.045

Buzzell, G. A., Roberts, D. M., Baldwin, C. L., & McDonald, C. G. (2013). An electrophysiological correlate of conflict processing in an auditory spatial Stroop task: The effect of individual differences in navigational style. *International Journal of Psychophysiology, 90*(2), 265–271. https://doi.org/10.1016/j.ijpsycho.2013.08.008

Buzzell, G. A., Roberts, D. M., Fedota, J. R., Thompson, J. C., Parasuraman, R., & McDonald, C. G. (2016). Uncertainty-dependent activity within the ventral striatum predicts task-related changes in response strategy. *Cognitive, Affective, & Behavioral Neuroscience, 16*(2), 219–233.

Buzzell, G. A., Troller-Renfree, S. V., Barker, T. V., Bowman, L. C., Chronis-Tuscano, A., Henderson, H. A., … Fox, N. A. (2017). A neurobehavioral mechanism linking behaviorally inhibited temperament and later adolescent social anxiety. *Journal of the American Academy of Child & Adolescent Psychiatry, 56*(12), 1097–1105. https://doi.org/10.1016/j.jaac.2017.10.007

Cavanagh, J. F., & Shackman, A. J. (2015). Frontal midline theta reflects anxiety and cognitive control: Meta-analytic evidence. *Journal of Physiology - Paris, 109*(1), 3–15.

Cavanagh, J. F., Zambrano-Vazquez, L., & Allen, J. J. (2012). Theta lingua franca: A common mid-frontal substrate for action monitoring processes. *Psychophysiology, 49*(2), 220–238.

Chronis-Tuscano, A., Degnan, K. A., Pine, D. S., Perez-Edgar, K., Henderson, H. A., Diaz, Y., … Fox, N. A. (2009). Stable early maternal report of behavioral inhibition predicts lifetime social anxiety disorder in adolescence. *Journal of the American Academy of Child and Adolescent Psychiatry, 48*(9), 928–935. https://doi.org/10.1097/CHI.0b013e3181ae09df

Clark, D. M., & Wells, A. (1995). A cognitive model of social phobia. *Social Phobia: Diagnosis, Assessment, and Treatment, 41*(68), 00022–00023.

Clauss, J. A., & Blackford, J. U. (2012). Behavioral inhibition and risk for developing social anxiety disorder: A meta-analytic study. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*(10), 1066.e1–1075.e1. https://doi.org/10.1016/j.jaac.2012.08.002

Coplan, R. J., Rubin, K. H., Fox, N. A., Calkins, S. D., & Stewart, S. L. (1994). Being alone, playing alone, and acting alone: Distinguishing among reticence and passive and active solitude in young children. *Child Development, 65*(1), 129–137.

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews. Neuroscience, 3*(3), 201.

Danielmeier, C., & Ullsperger, M. (2011). Post-error adjustments. *Frontiers in Psychology, 2*, 233.

Debener, S., Ullsperger, M., Siegel, M., Fiehler, K., Von Cramon, D. Y., & Engel, A. K. (2005). Trial-by-trial coupling of concurrent electroencephalogram and functional magnetic resonance imaging identifies the dynamics of performance monitoring. *Journal of Neuroscience, 25*(50), 11730–11737.

Degnan, K. A., Almas, A. N., Henderson, H. A., Hane, A. A., Walker, O. L., & Fox, N. A. (2014). Longitudinal trajectories of social reticence with unfamiliar peers across early childhood. *Developmental Psychology, 50*(10), 2311–2323. https://doi.org/10.1037/a0037751

der Borght, L. V., Schevernels, H., Burle, B., & Notebaert, W. (2016). Errors disrupt subsequent early attentional processes. *PLoS One, 11*(4), e0151843. https://doi.org/10.1371/journal.pone.0151843

Eysenck, M. W., Derakshan, N., Santos, R., & Calvo, M. G. (2007). Anxiety and cognitive performance: Attentional control theory. *Emotion, 7*(2), 336.

Fox, N. A., Henderson, H. A., Marshall, P. J., Nichols, K. E., & Ghera, M. M. (2005). Behavioral inhibition: Linking biology and behavior within a developmental framework. *Annual Review of Psychology, 56*, 235–262.

Fox, N. A., Henderson, H. A., Rubin, K. H., Calkins, S. D., & Schmidt, L. A. (2001). Continuity and discontinuity of behavioral inhibition and exuberance: Psychophysiological and behavioral influences across the first four years of life. *Child Development, 72*(1), 1–21.

Fox, N. A., Snidman, N., Haas, S. A., Degnan, K. A., & Kagan, J. (2015). The relations between reactivity at 4 months and behavioral inhibition in the second year: Replication across three independent samples. *Infancy, 20*(1), 98–114. https://doi.org/10.1111/infa.12063

Frenkel, T. I., Fox, N. A., Pine, D. S., Walker, O. L., Degnan, K. A., & Chronis-Tuscano, A. (2015). Early childhood behavioral inhibition, adult psychopathology and the buffering effects of adolescent social networks: A twenty-year prospective study. *Journal of Child Psychology and Psychiatry, and Allied Disciplines, 56*(10), 1065–1073. https://doi.org/10.1111/jcpp.12390

Gehring, W. J., Liu, Y., Orr, J. M., & Carp, J. (2012). The error-related negativity (ERN/ne). In S. J. Luck & E. S. Kappenman (Eds.), *Oxford library of psychology. The Oxford handbook of event-related potential components* (pp. 231–291). New York, NY: Oxford University Press.

Hajcak, G., Moser, J. S., Yeung, N., & Simons, R. F. (2005). On the ERN and the significance of errors. *Psychophysiology, 42*(2), 151–160.

Henderson, H. A., Pine, D. S., & Fox, N. A. (2015). Behavioral inhibition and developmental risk: A dual-processing perspective. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology, 40*(1), 207–224. https://doi.org/10.1038/npp.2014.189

Herrmann, M. J., Römmler, J., Ehlis, A.-C., Heidrich, A., & Fallgatter, A. J. (2004). Source localization (LORETA) of the error-related-negativity (ERN/ne) and positivity (Pe). *Cognitive Brain Research, 20*(2), 294–299.

Holroyd, C. B., & Coles, M. G. H. (2002). The neural basis of human error processing: Reinforcement learning, dopamine, and the error-related negativity. *Psychological Review, 109*(4), 679–709. https://doi.org/10.1037/0033-295X.109.4.679

Jarcho, J. M., Fox, N. A., Pine, D. S., Etkin, A., Leibenluft, E., Shechner, T., & Ernst, M. (2013). The neural correlates of emotion-based cognitive control in adults with early childhood behavioral inhibition. *Biological Psychology, 92*(2), 306–314. https://doi.org/10.1016/j.biopsycho.2012.09.008

Jarcho, J. M., Fox, N. A., Pine, D. S., Leibenluft, E., Shechner, T., Degnan, K. A., … Ernst, M. (2014). Enduring influence of early temperament on neural mechanisms mediating attention–emotion conflict in adults. *Depression and Anxiety, 31*(1), 53–62. https://doi.org/10.1002/da.22140

Kagan, J., Reznick, J. S., Clarke, C., Snidman, N., & Garcia-Coll, C. (1984). Behavioral inhibition to the unfamiliar. *Child Development, 55*(6), 2212–2225. https://doi.org/10.2307/1129793

Kagan, J., Reznick, S., & Snidman, N. (1988). Biological bases of childhood shyness. *Science, 240*(4849), 167.

Kagan, J., & Snidman, N. (1991). Infant predictors of inhibited and uninhibited profiles. *Psychological Science, 2*(1), 40–44.

Kagan, J., & Snidman, N. (2004). *The long shadow of temperament*. Cambridge, MA: Harvard University Press.

Kertz, S. J., Belden, A. C., Tillman, R., & Luby, J. (2015). Cognitive control deficits in shifting and inhibition in preschool age children are associated with increased depression and anxiety over 7.5 years of development. *Journal of Abnormal Child Psychology*. https://doi.org/10.1007/s10802-015-0101-0

Lahat, A., Lamm, C., Chronis-Tuscano, A., Pine, D. S., Henderson, H. A., & Fox, N. A. (2014). Early behavioral inhibition and increased error monitoring predict later social phobia symptoms in childhood. *Journal of the American Academy of Child and Adolescent Psychiatry, 53*(4), 447–455. https://doi.org/10.1016/j.jaac.2013.12.019

Lahat, A., Walker, O. L., Lamm, C., Degnan, K. A., Henderson, H. A., & Fox, N. A. (2014). Cognitive conflict links behavioral inhibition and social problem solving during social exclusion in childhood. *Infant and Child Development, 23*(3), 273–282. https://doi.org/10.1002/icd.1845

Lamm, C., Walker, O. L., Degnan, K. A., Henderson, H. A., Pine, D. S., McDermott, J. M., & Fox, N. A. (2014). Cognitive control moderates early childhood temperament in predicting social behavior in seven year old children: An ERP study. *Developmental Science, 17*(5), 667–681. https://doi.org/10.1111/desc.12158

Lengua, L. J. (2003). Associations among emotionality, self-regulation, adjustment problems, and positive adjustment in middle childhood. *Journal of Applied Developmental Psychology, 24*(5), 595–618. https://doi.org/10.1016/j.appdev.2003.08.002

Masaki, H., Maruo, Y., Meyer, A., & Hajcak, G. (2017). Neural correlates of choking under pressure: Athletes high in sports anxiety monitor errors more when performance is being evaluated. *Developmental Neuropsychology, 42*(2), 104–112. https://doi.org/10.1080/87565641.2016.1274314

McDermott, J. M., Perez-Edgar, K., Henderson, H. A., Chronis-Tuscano, A., Pine, D. S., & Fox, N. A. (2009). A history of childhood behavioral inhibition and enhanced response monitoring in adolescence are linked to clinical anxiety. *Biological Psychiatry, 65*(5), 445–448.

Meyer, A. (2017). A biomarker of anxiety in children and adolescents: A review focusing on the error-related negativity (ERN) and anxiety across development. *Developmental Cognitive Neuroscience, 27*(Supplement C), 58–68. https://doi.org/10.1016/j.dcn.2017.08.001

Moran, T. P., Bernat, E. M., Aviyente, S., Schroder, H. S., & Moser, J. S. (2015). Sending mixed signals: Worry is associated with enhanced initial error processing but reduced call for subsequent cognitive control. *Social Cognitive and Affective Neuroscience, 10*(11), 1548–1556.

Moser, J. S., Moran, T. P., Schroder, H. S., Donnellan, M. B., & Yeung, N. (2013). *On the relationship between anxiety and error monitoring: A meta-analysis and conceptual framework*. Retrieved from https://books.google.com/books?hl=en&lr=&id=TIWMCgAAQBAJ&oi=fnd&pg=PA40&dq=moran+moser+anxiety+review+2013&ots=lI_94R2AFf&sig=AlE6Zh6X1CxwxYPqHjuAKi5W0A4

Nigg, J. T. (2017). Annual research review: On the relations among self-regulation, self-control, executive functioning, effortful control, cognitive control, impulsivity, risk-taking, and inhibition for developmental psychopathology. *Journal of Child Psychology and Psychiatry, 58*(4), 361–383.

Overbeek, T. J., Nieuwenhuis, S., & Ridderinkhof, K. R. (2005). Dissociable components of error processing: On the functional significance of the Pe Vis-à-Vis the ERN/ne. *Journal of Psychophysiology, 19*(4), 319–329.

Pérez-Edgar, K., Bar-Haim, Y., McDermott, J. M., Chronis-Tuscano, A., Pine, D. S., & Fox, N. A. (2010). Attention biases to threat and behavioral inhibition in early childhood shape adolescent social withdrawal. *Emotion, 10*(3), 349–357. https://doi.org/10.1037/a0018486

Petersen, S. E., & Posner, M. I. (2012). The attention system of the human brain: 20 years after. *Annual Review of Neuroscience, 35*(1), 73–89. https://doi.org/10.1146/annurev-neuro-062111-150525

Purcell, B. A., & Kiani, R. (2016). Neural mechanisms of post-error adjustments of decision policy in parietal cortex. *Neuron, 89*(3), 658–671. https://doi.org/10.1016/j.neuron.2015.12.027

Rapee, R. M., & Heimberg, R. G. (1997). A cognitive-behavioral model of anxiety in social phobia. *Behaviour Research and Therapy, 35*(8), 741–756. https://doi.org/10.1016/S0005-7967(97)00022-3

Ridderinkhof, K. R., Ullsperger, M., Crone, E. A., & Nieuwenhuis, S. (2004). The role of the medial frontal cortex in cognitive control. *Science, 306*(5695), 443–447. https://doi.org/10.1126/science.1100301

Roberts, D. M., Fedota, J. R., Buzzell, G. A., Parasuraman, R., & McDonald, C. G. (2014). Prestimulus oscillations in the alpha band of the EEG are modulated by the difficulty of feature discrimination and predict activation of a sensory discrimination process. *Journal of Cognitive Neuroscience, 26*(8), 1615–1628. https://doi.org/10.1162/jocn_a_00569

Rothbart, M. K. (1981). Measurement of temperament in infancy. *Child Development, 52*, 569–578.

Rothbart, M. K., & Bates, J. E. (2006). Temperament. In N. Eisenberg (Ed.), *Handbook of child psychology*. New York, NY: Wiley Retrieved from http://onlinelibrary.wiley.com/doi/10.1002/9780470147658.chpsy0303/full

Schröger, E. (1993). Event-related potentials to auditory stimuli following transient shifts of spatial attention in a go/Nogo task. *Biological Psychology, 36*(3), 183–207. https://doi.org/10.1016/0301-0511(93)90017-3

Schwartz, C. E., Wright, C. I., Shin, L. M., Kagan, J., & Rauch, S. L. (2003). Inhibited and uninhibited infants "grown up": Adult amygdalar response to novelty. *Science, 300*(5627), 1952–1953. https://doi.org/10.1126/science.1083703

Shenhav, A., Botvinick, M. M., & Cohen, J. D. (2013). The expected value of control: An integrative theory of anterior cingulate cortex function. *Neuron, 79*(2), 217–240. https://doi.org/10.1016/j.neuron.2013.07.007

Steinhauser, M., & Yeung, N. (2010). Decision processes in human performance monitoring. *Journal of Neuroscience, 30*(46), 15643–15653.

Thorell, L. B., Bohlin, G., & Rydell, A.-M. (2004). Two types of inhibitory control: Predictive relations to social functioning. *International Journal of Behavioral Development, 28*(3), 193–203. https://doi.org/10.1080/01650250344000389

Torpey, D. C., Hajcak, G., Kim, J., Kujawa, A. J., Dyson, M. W., Olino, T. M., & Klein, D. N. (2013). Error-related brain activity in young children: Associations with parental anxiety and child temperamental negative emotionality. *Journal of Child Psychology and Psychiatry, 54*(8), 854–862.

Troller-Renfree, S., Buzzell, G. A., Bowers, M., Salo, V., Forman-Alberti, A., Smith, E., … Fox, N. A. (2018). Development of inhibitory control during childhood and its relations to early temperament and later social anxiety. https://doi.org/10.31234/osf.io/tj4hn

Troller-Renfree, S. V., Buzzell, G. A., Pine, D. S., Henderson, H., & Fox, N. A. (in press). Developmental consequences of not planning ahead: reduced proactive control moderates longitudinal relations between behavioral inhibition and anxiety. *Journal of the American Academy of Child & Adolescent Psychiatry*.

Ullsperger, M., Danielmeier, C., & Jocham, G. (2014). Neurophysiology of performance monitoring and adaptive behavior. *Physiological Reviews, 94*(1), 35–79. https://doi.org/10.1152/physrev.00041.2012

White, L. K., McDermott, J. M., Degnan, K. A., Henderson, H. A., & Fox, N. A. (2011). Behavioral inhibition and anxiety: The moderating roles of inhibitory control and attention shifting. *Journal of Abnormal Child Psychology, 39*(5), 735–747.

Attention Mechanisms in Behavioral Inhibition: Exploring and Exploiting the Environment

Koraly Pérez-Edgar

Abstract Attention mechanisms may play a pivotal role in the emergence of socio-emotional profiles. In the case of behavioral inhibition (BI), sensitivity to novelty, coupled with an attention bias to threat, may increase the risk for socially reticent behavior and anxiety. Early work suggests that behaviorally inhibited children may be more vigilant to novelty and threat in the environment, which then leads to behavioral avoidance. In addition, attention bias to threat, in particular, may moderate the relation between early behavioral inhibition and the later emergence of anxiety. However, we are only now examining how these early attentional processes act to shape observed outcomes. The current chapter speculates that attention mechanisms may lead behaviorally inhibited children to resort to habitual and inflexible repertoires for dealing with unfamiliar and unexpected environments. Thus, rather than explore new contexts, which may lead to new knowledge and reward, behaviorally inhibited children may instead exploit prior knowledge and behaviors, limiting their exposure to new experiences. The lack of new experiences, in turn, decreases the probability that behaviorally inhibited children will recognize that their initial fears and concerns are often unwarranted.

Attention is pivotal to development. By filtering the environment, attention acts as a developmental hub (Wass, Scerif, & Johnson, 2012), gating the acquisition of information and skills across domains and knitting together experiences across time and space. In addition, attention is a computational mechanism with the ultimate goal of selecting aspects of the environment for deep exploration, filtering out sources of information that are irrelevant to current goals or clash with affective motivation (Amso & Scerif, 2015). Idiosyncratic patterns of learning emerge for individuals through this iterative process, shaping working memory and knowledge transfer (Wass et al., 2012).

Attention can thus shape developmental trajectories across cognitive and socio-emotional domains. Central to the current chapter is the growing interest in the role

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attention (and attention biases) may play in shaping the life course of children who display early behavioral inhibition (BI). As infants, behaviorally inhibited children display signs of fear and wariness in response to unfamiliar stimuli (Schmidt et al., 1997), and this trait is marked by heightened vigilance, motor quieting, and withdrawal from novelty (García Coll, Kagan, & Reznick, 1984; Kagan, Reznick, & Snidman, 1987, see also the chapter "The Social World of Behaviorally Inhibited Children: A Transactional Account" by Henderson et al. and the chapter "Peer Relations and the Behaviorally Inhibited Child" by Rubin et al.). By elementary school, many behaviorally inhibited children fear social circumstances, displaying poorly regulated social behavior and social reticence (Coplan, Rubin, Fox, Calkins, & Stewart, 1994; Fox et al., 1995). This, in turn, increases the likelihood of peer rejection, low self-esteem, and poor social competence (Rubin, Chen, & Hymel, 1993; Schmidt, Fox, Schulkin, & Gold, 1999). Longitudinal studies of behavioral inhibition, and the broader construct of temperamental shyness, have found marked levels of anxiety, particularly social anxiety, by mid-adolescence and young adulthood (Chronis-Tuscano et al., 2009; Kagan, Snidman, McManis, & Woodward, 2001; see also the chapter "The Temperamentally Shy Child as the Social Adult: An Exemplar of Multifinality" by Poole et al.).

Despite the two- to threefold increase in risk for anxiety disorders (Clauss & Blackford, 2012), the majority of behaviorally inhibited children are not clinically anxious (Degnan & Fox, 2007). Clearly, there must be a number of moderating influences that shape the trajectory from temperament to disorder. Past work suggests that parenting styles (Williams et al., 2009), parental anxiety levels (Biederman et al., 2001), and early schooling environment (Almas et al., 2011) all play a role in exacerbating or ameliorating early risk (see also the chapter "Behavioural Inhibition and the Prevention of Internalising Distress in Early Childhood" by Rapee and Bayer). Recently, a great deal of attention (pun intended) has focused on the role systematic biases in early information processing patterns may play in shaping the emergence and course of anxiety (see the chapter "Relations Between Behavioral Inhibition, Cognitive Control and Anxiety: Novel Insights Provided by Parsing Subdomains of Cognitive Control" by Buzzell et al. and the chapter "Behavioral Inhibition and the Associative Learning of Fear" by Reynolds et al.)

Prior work has documented the phenotypic and developmental links between behavioral inhibition and anxiety (Pérez-Edgar & Guyer, 2014), emphasizing the descriptive associations with variations in attention and attention bias (Pérez-Edgar, Taber-Thomas, Auday, & Morales, 2014). However, less work has tried to explore the process by which attention patterns, day to day, year by year, come to shape behavior in the environment, which in turn shapes socioemotional profiles (Morales, Fu, & Pérez-Edgar, 2016). We are interested in how early biases or sensitivities unfold to lead to observed outcomes in behaviorally inhibited children (Anaya & Pérez-Edgar, in press).

The current chapter focuses on how attention is central to patterns of exploration and exploitation of the environment. From moment to moment, a child must decide if he/she should strike out into a novel context or engage in novel behaviors to solve a pressing challenge or reach a goal. Alternately, the child can rely on strategies and

repertoires already in place that have proven effective, or at the very least tolerable, in the past. The balance between exploration and exploitation, in turn, helps determine phenotypic profiles of socioemotional development. Attention can be an exploratory tool, or it can lock an individual into a narrow information channel. Understanding variation in attention-linked patterns of exploration and exploitation may help disentangle observed variation in behavioral profiles.

That is, although behaviorally inhibited children may share an initial bias to threat, a great deal of variability in their subsequent strategies and responses to threat may emerge. Here, our question of interest is: How does attention fuel how the child comes to learn from the environment, alternately *exploring* for new knowledge and *exploiting* already entrenched behavioral and social repertoires? Patterns of attention may mediate engagement with the environment, balancing between exploration and exploitation over time and contexts. The (more speculative) sections of this chapter borrow from the ethology literature to discuss how patterns of exploitation and exploration, supported by attentional and temperamental biases, may create the developmental tether between behavioral inhibition and anxiety.

Behavioral Inhibition, Anxiety, and Attention

Anxiety can be marked by concern for specific cues or contexts, or be pervasive across time and space with overwhelming and persistent fears and worries (Lau & Waters, 2017). For the behaviorally inhibited child, concerns often center on the social components of their daily lives. As such, behavioral inhibition is specifically linked with increased risk for social anxiety (Clauss & Blackford, 2012). The transition from behavioral inhibition to anxiety is one pathway for children, but not the only trajectory (Degnan & Fox, 2007). That is, Kagan (2012) suggested that early behavioral inhibition constrains the scope of possibilities for a child, such that a highly reticent toddler is highly unlikely to become an exuberant and gregarious leader among his peers. That is not to say, however, that the reticent toddler cannot become a thoughtful and soft-spoken child who moves with relative ease through the social world. The individual child's developmental arc builds on the foundation of behavioral inhibition, bringing together emerging cognitive and emotional processes with idiosyncratic experiences with the outside world.

Attention mechanisms, while not always explicitly examined in early behavioral inhibition research, are at the core of the behavioral or phenotypic profiles we have come to regard as "quintessentially" behaviorally inhibited. That is, children with high levels of behavioral inhibition have an in-born bias to attend to novel stimuli (Reeb-Sutherland et al., 2009). Over time, repeated cycles of attention, processing, and interpretation of discomforting stimuli may lead behaviorally inhibited children to make an association that equates novelty with threat. In response, the behaviorally inhibited child quite logically retreats in the face of novelty—and the associated threat—as a form of self-preservation.

Of course, the child's subjective sense of threat, and retreat to safety, may be viewed from an external lens as maladaptive retreat from a social world that actually provides a balance of risks and rewards. Our own work (Pérez-Edgar, McDermott, et al., 2010) suggests that early, global patterns of attention orienting are an associated characteristic of behavioral inhibition. That is, infants likely to be behaviorally inhibited later in life display a pattern of increased vigilance, repeatedly returning to visually "check" on a stimulus, long after other infants have presumably deemed the stimulus as uninteresting or benign. Attention patterns may act as daily mechanisms that help sustain high levels of behavioral inhibition over childhood and strengthen the link to anxiety.

The patterns of automatic threat detection and withdrawal idiosyncratic to behavioral inhibition are embedded within larger patterns of development that are seen in most children over time. Attention patterns linked to behavioral inhibition are embedded within larger mechanisms of development that are both experience expectant and experience dependent. Thus, a behaviorally inhibited child may expect to confront a host of novel objects, people, and situations in the social world. The initial response to retreat or engage will then color the type of information and experiences provided to higher-order mechanisms that shape the development of more controlled cognitive processes. These include response inhibition, error monitoring, and attention shifting. Each of these processes, in turn, has been associated with the transition from behavioral inhibition to anxiety (Henderson & Wilson, 2017). These data serve as initial evidence for the mechanisms that channel automatic attention to higher-order cognitive processes and on to anxiety.

Multiple individual differences factors are woven into this developmental trajectory. For example, individual differences in temperamental negative affect (Pérez-Edgar et al., 2017) and maternal anxiety (Morales et al., 2017) are linked with patterns of attention to emotion faces in the first 2 years of life. Both temperamental negative affect (Pérez-Edgar & Fox, 2005) and maternal anxiety (Degnan & Fox, 2007) are, in turn, associated with levels of behavioral inhibition. Later on, we see that the link between early behavioral inhibition and anxiety and social withdrawal is often only evident among behaviorally inhibited children who also show an attention bias to threat (Morales, Taber-Thomas, & Pérez-Edgar, 2017; Nozadi et al., 2016; Pérez-Edgar, Bar-Haim, et al., 2010; Pérez-Edgar et al., 2011; White et al., 2017).

Children present a mix of automatic and strategic stages of information processing after the initial deployment of attention via salience detection mechanisms. For example, many children may initially focus on a perceived threat due to automatic stimulus-driven attention. However, these same children may then willfully avoid the stimulus or context that captured their attention (Sylvester, Hudziak, Gaffrey, Barch, & Luby, 2016). Thus, anxiety may couple both attention bias and behavioral avoidance (Roy, Dennis, & Warner, 2015). Interestingly, the behavioral transition between bias and avoidance recapitulates the developmental progression from the initial emergence of orienting and vigilance processes to the later, slowly unfolding development of executive attention (Amso & Scerif, 2015).

Attention as a Developmental Force

There are two competing characterizations of attention mechanisms in behaviorally inhibited children. First, children high in behavioral inhibition may differ in their level of attention control relative to children low in behavioral inhibition. This is in line with the attention control theory (outlined below) that is typically seen in the adult clinical literature (Eysenck, Derakshan, Santos, & Calvo, 2007). Alternately, children high in behavioral inhibition may differ in the manner in which they deploy attentional resources across space and time, driven by unique sensitivities to salient cues (Henderson & Wilson, 2017).

To illustrate these alternate characterizations, we can build on Posner's broad sub-components of attention, which include orienting, vigilance, and executive control (Posner, Rothbart, Sheese, & Voelker, 2012). These three core areas of functioning allow a child moving through her busy environment to notice an important event (alerting), shift attention to the event (orienting), and then decide if she needs to act (executive). The alerting system is tasked with obtaining and maintaining an alert state, is subserved by midbrain structure with strong interconnectivity between frontal and parietal regions, and is linked to norepinephrine functioning.

The second, orienting system, is thought to select sensory events for further processing, is linked to inferior and superior parietal systems, and is linked to cholinergic activity. The orienting system plays an important role in early self-regulation through reactive control as it is evident in the first year of life and is a core tool in the infant's regulatory armament. Indeed, there is an evident overlap between the neural network for orienting and executive functions in infants (Gao et al., 2009).

Appearing later in development is the more adult-like executive attention system. This system is called in to resolve conflict among responses, is linked to prefrontal (including the anterior cingulate cortex, ACC) activity, and is closely aligned with dopaminergic functioning. This system is thought to reflect the effortful control behaviors researchers observe in older children. Indeed, poor executive attention is associated with lower levels of effortful control (Ellis, Rothbart, & Posner, 2004). Over time, initial attempts at reactive control supported by the orienting system are subsumed by effortful control mechanisms and the executive attention system. This transition provides the individual with greater flexibility in responding to environmental stimuli and a wider range of options when needing to regulate (Pérez-Edgar et al., 2014). Unlike infants and toddlers, the older child's orienting system can recruit the executive system to meet a challenge, *as needed* (Shulman et al., 2009).

Effortful control is often linked to the deployment of attention control, which encompasses the ability to systematically shift and focus attention. Developmentally, attention control emerges prior to more complex mechanisms of effortful control and need not have the volitional component of effortful control (Brooker et al., 2014). Thus, there is a slow shift in the relative balance between reactive and proactive controls (Eisenberg & Spinrad, 2004). Works from Munakata (Munakata, Snyder, & Chatham, 2012) and Rothbart (Rothbart, Sheese, Rueda, & Posner, 2011) both demonstrate that control processes do not replace automatic modes of

functioning. Rather, observed changes across development reflect the integration of both automatic and controlled processes, proceeding from the neural level to the behavioral phenotype. Daily experience helps tune top-down executive attention. Attention, in turn, supports learning from a currently attended location, typically based on task goals (Amso & Scerif, 2015). Thus, the process creates the informational and experiential pipeline for development.

The top-down executive attention system plays an important role in deciding between competing alternatives, particularly when confronting a novel course of action. Over time, however, consistent patterns of choice may create a habit which shifts selection activity to lower-level mechanisms, often centered on reward-sensitive areas of the striatum (Amso & Scerif, 2015). Thus, processes that are initially effortful and computationally taxing can, with repetition, become canalized, automatic, and habitual. This is a normative developmental process. The question that follows is whether individuals with, or at risk for, anxiety show (1) greater difficulty re-engaging the effortful control system as needed, (2) show systematic variations in the habitual patterns that are laid down (e.g., increased attention bias to threat), or (3) both.

The first proposal is that anxious individuals show a general deficit in attention processes. Attention control theory (ACT; Eysenck et al., 2007) posits that anxiety introduces competition between stimulus-driven processing and goal-directed attention processes. As such, an anxious individual may be biased to focus on salient stimuli or cues, even when they are irrelevant, or even detrimental to, overarching goals. Thus, the individual will have to recruit more control processes than their non-anxious peer in order to remain on task and achieve comparable levels of performance. In this way, complex or multifaceted tasks require more effort, more attention, and more core resources. The deployment of attention is thus less fluid and less efficient. This extended effort may lead to fatigue in the moment and reluctance to engage in the task again in the future. Indeed, this response is reminiscent of typical patterns seen in behavioral inhibition, which is often marked by withdrawal from tasks that are novel or are linked to prior negative feedback (Fox, Henderson, Marshall, Nichols, & Ghera, 2005; Kagan, 1997).

Importantly, ACT argues that anxiety-linked attentional inefficiencies are not limited to threatening or emotionally salient cues or tasks. Rather, anxiety impinges on tasks that are typically seen as emotionally neutral and low-threat (Pacheco-Unguetti, Acosta, Callejas, & Lupiáñez, 2010). The system favors bottom-up capture and increase processing of irrelevant stimuli (Rossi & Pourtois, 2017), "just in case" they prove threatening. This pattern is again reflected in the increased vigilance and "checking" seen in behavioral inhibition (Pérez-Edgar, McDermott, et al., 2010).

In addition to ACT-type theories, which point to general deficits in attention capacity, we may also find differences in how children deploy attention, even if attentional processes are equivalent in overall level of "efficacy." Affect-biased attention is marked by preferential perception, and processing, of stimuli based on relative affective salience (Morales et al., 2016; Todd, Cunningham, Anderson, & Thompson, 2012). To this extent all individuals display some form of affect-biased

attention, as we use salience to help filter the otherwise overwhelming stream of information permeating our environments. As with many developmental phenomena, salience, as defined via affect-biased attention, is both experience expectant and experience dependent. That is, there are normative preferences for specific perceptual patterns evident early in life (LoBue, Rakison, & DeLoache, 2010) that become differentiated and personalized over time with experience.

Biases emerge shortly after infants can make perceptual distinctions (Colombo, 2001), preferring, for example, contours and sharp borders. We can see subconscious detection mechanisms for conspecifics by the first half of the first year of life. These preferences, when brought together, help explain early biases for faces and face-like stimuli (Colombo & Salley, 2015). We can then layer on emotion as a source of salience, as emotional cues can signal both survival and motivational cues.

In the competition for limited attentional resources, infants prioritize objects that decrease danger and increase reward (Peltola, Leppanen, Palokangas, & Hietanen, 2008), and no other object is as closely tied to survival, punishment, and reward as the human face (Hoehl & Striano, 2010). Due to the coupling of perceptual cues, rewarding daily events (e.g., feeding), and long hours of exposure, infants quickly begin to show preferential looking to human faces (Leppänen & Nelson, 2009). This preference is magnified when the face also conveys an emotional threat signal. For example, a series of studies (Peltola et al., 2008; Peltola, Hietanen, Forssman, & Leppänen, 2013; Peltola, Leppanen, Maki, & Hietanen, 2009) has found that within the second half of the first year of life, infants are less likely to disengage from negative faces relative to happy and neutral faces.

Bias is evident across the attention spectrum, from alerting to orienting to executive attention, encompassing both fleeting stimuli and sustained patterns of goal-directed behavior (Amso & Scerif, 2015). Importantly affect-biased attention is a dynamic general functional state, and not solely a static trait-level marker. For example, in young children profiles of attention bias vary as a function of napping history (Cremone, Kurdziel, Fraticelli-Torres, McDermott, & Spencer, 2017) such that a lack of nap can lead to a reduction in "attentional sharpness" and an increase in attention biases to salient cues.

Profiles of affect-biased attention highlight stimuli that reflect past history and are relevant to current motivations. As such, they build on central cognitive mechanisms and are shaped by the specific concerns of the individual both at the trait level (e.g., behavioral inhibition) and in that moment in time when you encounter a novel social situation. Although research on affect-biased attention is still emerging, there are four general precepts that can be drawn from the available data (Morales et al., 2016; Todd et al., 2012).

First, affect-biased attention is an emergent system that builds on multiple attention systems (both automatic and controlled). Affect-biased attention reflects prior learning (Ehlers & Todd, 2017), guided by the individual's idiosyncratic concerns. Dudeney's (Dudeney, Sharpe, & Hunt, 2015) meta-analysis suggests that attentional biases are broader and more common in young children and then become more specific to the cue and the individual with age.

Second, affect-biased attention's role in shaping behavior changes with development as a function of both maturation and experience. Newly developed cognitive and social skills will refine the balance between automatic implicit biases and more effortful control processes. Normative development would provide the child with the flexibility to engage effortful mechanisms when needed, but otherwise efficiently rely on automatic, habitual mechanisms (Eisenberg & Spinrad, 2004; Pérez-Edgar, 2015).

Third, affect-biased attention is a domain general mechanism that is not limited to temperamental risk for anxiety or threat cues. Affect-biased attention has been linked to patterns of externalizing behaviors, food choices, prosocial behavior, and drug abuse, for example (Morales et al., 2016; Peltola, Yrttiaho, & Leppänen, 2018). Thus, we likely develop overlapping profiles of affect-biased attention that come to the fore as we move across functional domains.

Fourth, the relation between patterns of affect-biased attention and socioemotional functioning is reciprocal and not unidirectional. Shifts in social domains and the emergence of new developmental challenges will shift the inputs fed into the system, further refining patterns of affect-biased attention.

Altogether, salient day-to-day experiences can shape what stimuli a child is exposed to and what stimuli take on an acute importance in the life of the child. In this way, idiosyncratic and personalized patterns of affect-biased attention emerge in an experience-dependent manner. Thus, behaviorally inhibited children are not anxious simply because they show affect-biased attention. Rather, maladaptation may arise when attention patterns come to be driven by internal concerns and states rather than environmental parameters or specific goals. The behaviorally inhibited child may be at acute risk for anxiety when motivational targets can "hijack" attention and focus the child on non-goal-directed behavior (Hummel, Premo, & Kiel, 2017). Thus, the child is focused on specific components of the environment to the detriment of competing input that are more closely aligned with the task at hand. Instead, the child is engaged in an extended hunt for information that matches prior idiosyncratic concerns. If affect-biased attention creates a "habitual filtering process" that is inflexible (Morales et al., 2016; Todd et al., 2012), children may display a seemingly contradictory juxtaposition between attention narrowing and hypervigilance.

Bias arises from an evolving equation that couples the child's perception of the environment with their interpretation of the environment. In the context of behavioral inhibition, bias couples a lower threshold to perceive and process threat in the environment with the greater likelihood to assign a putatively neutral environmental signal as negative or threatening. In exploring the environment, children simultaneously draw from two forms of information processing, automatic and controlled, differing across individuals primarily in their relative balance and strength of the system (Henderson, Pine, & Fox, 2015).

The automatic form of information processing is stimulus driven and reflexive. With respect to the developmental trajectories associated with behavioral inhibition, much of the focus has been on novelty detection, attention bias to threat, and incentive processing. In contrast, controlled information processing is marked by attention

shifting and inhibitory control. It may be that in anxious individuals, the goal to search for threat is habitually active (Vogt, De Houwer, Crombez, & Van Damme, 2013; Wells & Matthews, 1996). As a result, differences in bias patterns across individuals are most evident when emotion is not relevant to the task at hand. It may help reveal the "background goals" ever present for individual with, or at risk for, anxiety (Dodd, Vogt, Turkileri, & Notebaert, 2017). With development, and increasing levels of neural and social sophistication, early orienting mechanisms should be engaged only as needed (Rothbart, Ellis, Rueda, & Posner, 2003). For the at-risk child, "as needed" becomes "ever present."

Distilling the available data, Henderson and colleagues (Henderson et al., 2015; Henderson & Wilson, 2017) outlined three potential models that could account for the association between attentional processes and BI-linked patterns of socioemotional development: the top-down model of control, the risk potentiation model, and the overgeneralized control model.

In the top-down model, effortful control processes moderate temperament-linked patterns of risk. In this formulation, automatic and effortful control processes are orthogonal, develop independently, and are therefore additive. For example, Susa (Susa, Pitică, Benga, & Miclea, 2012) found that children with anxiety showed attention biases to threat unless they also displayed high levels of effortful control. In this formulation, effortful control can place a "brake" on the automatic processes that lead anxious children and adults to privilege threatening input.

The risk potentiation model, in contrast, suggests that the child's initial reactive style of responding to environmental input becomes his or her default mode of response. When cognitive processes are called upon, they work to increase risk by allowing more time to focus on, elaborate, and respond to threat rather than reframing the threat or supporting disengagement. For example, Henderson (Henderson, 2010) found that shy children did not differ in a flanker task assessing inhibitory control, relative to non-shy peers. However, shyness was associated with poor socioemotional functioning particularly when coupled with an enhanced neural response (N2 amplitude) during the task. These data suggest that both reactive and self-regulatory components of temperament can come together to increase risk. Although the exact mechanisms for potentiated risk are still unclear, it may emerge from early regulatory processes that rely heavily on automatic attention mechanisms, such as orienting. Thus, it may be that early patterns of behavior and rapid reactive responses shape underlying neural networks, which in turn propagate forward to influence how children deploy higher-order control mechanisms as they come on line over the course of development (Auday, Taber-Thomas, & Pérez-Edgar, 2018).

Finally, with the overgeneralized control model, initial reactive tendencies lead to associative learning patterns that lower the threshold and exaggerate the consequences of potential threat cues. As a result, the child implements control strategies in contexts that do not require intervention. As such, these overgeneralized responses limit the flexibility with which children implement automatic and controlled processes. Here, behaviorally inhibited children do not differ in the overall level of control, as in the prior two models. Rather, risk emerges from responses to specific environmental cues.

Exploration and Exploitation of the Environment: Feeding Attentional Mechanisms of Development

If we embrace the proposition that individual variation in attention, particularly affect-biased attention, supports (but does not necessarily cause) the relation between behavioral inhibition and anxiety, we need to delineate how attention mechanisms *over time* shape profiles of behavior linked to behavioral inhibition.

A central goal of development is to acquire the ability to be in, and interact with, the environment. Borrowing from ethology, an organism, in this case the behaviorally inhibited child, must learn to toggle between exploring the environment to seek out new resources and exploiting the environment by deploying previously successful behavioral repertoires. That is, when facing a specific goal, such as acquiring food, the organism can branch out to explore new territory, opening the possibility of finding a rich bonanza or encountering only barren land. Alternately, the organism can stay in a well-tended location, trading the potential feast for a fairly predictable reward based on past experience. In the case of behavioral inhibition, we could extend this analogy by swapping out the hunt for food and substituting in social engagement, for example.

Organisms use internal and contextual cues to determine the net pay off of exploration versus exploitation (Reader, 2015). Across both species and individuals, there is variation in how fixed the demarcation line is and how flexibly the individual adjusts to prevailing conditions. Here, behaviorally inhibited children may vary in the extent to which they willingly move to new contexts and engage in new behaviors or remain within the context of a previously tested behavioral repertoire.

In the ethology literature, individuals are always under some level of uncertainty as they seek resources or meet survival goals. Searches can be guided by external cues or internal markers held in memory. Controlled searches call on set rules and biases that increase the likelihood of success and rely on prior information gathered from the environment and past experience to guide the search. Exploration, in contrast, is primarily an information-gathering activity (Reader, 2015). For exploration, the individual must be willing to neglect a more certain reward now to produce new knowledge and potential greater reward later (Kayser, Mitchell, Weinstein, & Frank, 2015). Exploration requires the willingness to probe new options with unknown outcomes that may be either punishing or rewarding (Humphreys et al., 2015). Exploitation, in contrast, selects from a relatively limited repertoire, in the hopes of attaining a more predictable, albeit potentially less rewarding, outcome. The decision for exploration versus exploitation is guided by past history plus an assessment of current events (Humphreys et al., 2015) that is essentially subjective (Kayser et al., 2015). That is, there is no strong algorithm that can predict the correct strategy for any one individual in a given context.

Verbeek, Drent, and Wiepkema (1994) suggest that exploratory behaviors are part of a correlated suite of behavioral traits that describe how an individual goes about engaging with the environment. At one end of the spectrum are fast, superficial explorers that may gather information across a wide territory but have a shallow

understanding of environmental permutations. On the end of the spectrum are slow, "thorough" explorers that methodically map out the parameters of a smaller region. The individual may then have a rich understanding of a specific environment. The question then becomes whether or not the individual is willing to test this knowledge in a new context. Exploration also often relies on the ability to gather information from others, building in a social component that saves the individual from repeating search or exploratory behaviors others have already engaged in (Reader, 2015; Toelch, Bruce, Meeus, & Reader, 2011). Turning to others for information can also have a broader impact on development and information gathering, as illustrated in studies highlighting vicarious fear learning in children (see the chapter "Behavioral Inhibition and the Associative Learning of Fear" by Reynolds et al.)

In the analogous case of behavioral inhibition, a child who is a "thorough" explorer that is unwilling to leverage existing knowledge for exploration may become overly reliant on an existing behavioral repertoire (Reader, 2015), which in turn limits the child's ability to develop and test new ways of engaging with the environment. Of course, exploration and exploitation are not all-or-nothing propositions. A child may engage in both activities across time and can toggle in a gray zone, often referred to as "low-cost sampling" (Reader, 2015). Vigilance may act as a form of low-cost sampling for the behaviorally inhibited child. The question then becomes: What does the child do when the novel target is detected—engage or retreat?

In the ethology literature, the highest levels of survival and adaptation are often seen in individuals that are high in both neophilia and neophobia. Indeed, these "skittish innovators" (Reader, 2015) move in and out of exploratory and exploitation modes, gathering relatively easily a wider range of information and experiences that can then be applied to future environments. These individuals also avoid the pitfalls of the two extremes of neophilia and neophobia. They do not have a limited, circumscribed behavioral repertoire nor do they sacrifice engaging in sustained learning by flitting in and out of the environment.

Cavigelli and colleagues have created a valid rodent model of behavioral inhibition, centered on naturally occurring variation in neophilia and neophobia (see the chapter "Behavioral Inhibition in Rodents: A Model to Study Causes and Health Consequences of Temperament" by Cavigelli). Based on observation, approximately 30% of a litter will be slow to approach social and nonsocial novel markers. Further, approximately 17% show a stable profile of neophobia over time. Strikingly, rats with a stable profile of "behavioral inhibition" die earlier than non-behaviorally inhibited rats (Cavigelli & McClintock, 2003). In addition, variance in exploratory behavior is associated with variance in behavioral inhibition profile and associated with levels of circulating glucocorticoids (Cavigelli et al., 2007). Thus, we may be able to link a behavioral inhibition profile to psychophysiological patterns associated with both exploration and long-term health consequences. Indeed, long-term studies of behavioral inhibition and shyness suggest increased levels of health concerns, even beyond our core interest in anxiety (see the chapter "The Temperamentally Shy Child as the Social Adult: An Exemplar of Multifinality" by Poole et al.).

As noted above, individuals must make the choice between exploration and exploitation when assessing the best path for goal attainment. The choice is "easier" when information levels are high and outcomes are more assured. Thus, there is a central question that emerges: To what extent is my environment predictable? The answer may allow us to see how individuals vary in their sensitivity to predictability and the extent to which predictability is a subjective determination. Based on the larger exploration vs exploitation literature, the "rational" expected response is that environmental uncertainty leads to more exploration. This is due to the fact that the individual's current environment cannot reliably provide the resources needed for survival and adaptive functioning.

However, this process presupposes that the individual is fairly comfortable with uncertainty, as they would need to abandon the information gathered from prior experience in an environment for the unknown contours of a new location or a new approach strategy. Systematic observation suggests that there is a naturally occurring stable variation in this computational process (Capitanio, 2017; Cavigelli & McClintock, 2003; Reader, 2015), which is reflected in animal models of behavioral inhibition (see the chapter "Behavioral Inhibition in Nonhuman Primates: The Elephant in the Room" by Capitanio and the chapter "Behavioral Inhibition in Rodents: A Model to Study Causes and Health Consequences of Temperament" by Cavigelli).

We can see the same question echoed in the literature focusing on temperament and temperamental risk for anxiety. Indeed, the clinical literature suggests that anxious individuals are driven by a heightened sensitivity, and outsized response, to uncertainty and the potential for threat, as reflected in the Uncertainty and Anticipation Model of Anxiety (UAMA) (Grupe & Nitschke, 2013). As such, you may expect less exploration in the face of an uncertain or unpredictable environment, even when exploitation is relatively detrimental.

The idiosyncratic tendencies of the behaviorally inhibited child, marked by greater awareness of, and sensitivity to, uncertainty and novelty may set the stage for a cognitive, behavioral, and social profile that tends to favor exploitation versus exploration. This initial tendency may be reinforced by feedback from the environment, parental signals, and the negative feedback loop that emerges with the first signs of anxiety and social withdrawal. For the child, processing and interpreting ambiguous cues, and the negative emotions that then arise, may take time away from interacting with and learning from the environment (Aktar et al., 2016), which could potentially ameliorate these initial anxiety-inducing response patterns.

The pattern that emerges for any one behaviorally inhibited child is therefore shaped by the specific contours of his or her environment. Children must create a resource allocation system that deploys limited mechanisms and processes, such as attention, based on competing forces, goals, and choices, each of which is likely to shift over time (Fox, Hane, & Pine, 2007). As such, it is unlikely that we can predict with certainty that a child will necessarily show patterns of bias or avoidance in every context. However, understanding past experience in light of the child's interpretation and subjective experience of events can help better understand emerging socioemotional patterns.

For example, Hane and Fox (2006) noted that the early environment can change the phenotypic expression of stress reactivity. The environment can also prime the child's responses to stress and uncertainty, increasing the likelihood that they will respond with a similar behavioral repertoire in the future. Importantly, the later experience of threat and novelty in adolescence into adulthood may reactivate the earlier programmed stress response. Thus understanding early experience may help us better understand behavioral and psychological responses that do not seem to "match" the circumstances facing the individual in the here and now.

For children exposed to high levels of early stress, it may be advantageous—in the short term—to specialize their coping skills repertoire to focus narrowly on the problem at hand and increase their ability to adapt. This specialized repertoire, which can include withdrawal, repression, and aggression, is geared toward idiosyncratic goals and here and now survival (Suor, Sturge-Apple, Davies, & Cicchetti, 2017). Belsky, Schlomer, and Ellis (2012) suggest that this is a "fast" life-history approach to the environment and development, in which the individual's response mechanisms are engaged and calcified earlier in life, at the expense of the flexibility needed to engage with later evolving challenges and environments. Behaviorally inhibited children, particularly when confronted with harsh environments, may be particularly likely to engage in this "fast" approach. The rigid behavioral repertoire, in turn, may fuel a tendency to exploit, rather than explore, the environment in the face of stress and ambiguity.

Focusing the attentional spotlight on a specific aspect of the environment could thus be an early, reactive, compensatory mechanism for behaviorally inhibited children (Rossi & Pourtois, 2017). However, over time, as challenges broaden and become more complex, this initially (if only partially) adaptive response can lead to its own difficulties, particularly when coupled with elevated anxiety and/or an unpredictable environment. This pattern of focused attention, coupled with a lack of engagement with the environment, may emerge early in life.

Behavioral inhibition, particularly when coupled with stressful like events, may sensitize the stress response, shifting the child's typical response from exploration to exploitation, from flexibility to habit. This fast transition (Belsky et al., 2012) may be analogous to the data emerging from studies of early adversity and pediatric anxiety. Work from Tottenham (Tottenham, 2013), Gee (Gee et al., 2013), and Hajcak (Meyer, Weinberg, Klein, & Hajcak, 2012) suggest that early stress and anxiety is associated with earlier transitions from immature neural profiles to more mature profiles. For example, children who experienced early maternal deprivation exhibit mature frontolimbic connectivity patterns (negative amygdala–mPFC coupling), which is more similar to adult patterns, relative to the immature pattern (positive amygdala-mPFC coupling) seen in comparison children. Accelerated amygdala-prefrontal development may be the child's adaptive response to early adversity. In typical development, the transition to adult profiles is associated with greater adaptation, flexibility, and goal-directed control. However, premature shifts are linked to maladaptation, psychopathology, and poor attainment of developmental markers (Meyer, 2017).

In the case of behavioral inhibition, we then have to interpret observed behavioral strategies as a function of context and current goals. For example, one phenotypic marker of behavioral inhibition is an immediate but inflexible regulatory mechanism. Inflexibility, in and of itself, is not an unusual trait among young children, nor is the stubborn use of a single problem-solving mode. However, with age, it may be that behaviorally inhibited children are more likely than their non-inhibited peers to cling to early processes and strategies that seemed to work for them—even in the face of shifting environmental demands and repeated evidence that previous responses are no longer effective or efficient. In the context of the current chapter, behaviorally inhibited children may continue to exploit resources and strategies even when the diminishing "rate of return" would suggest that they should explore and test new cognitive and behavioral repertoires.

In toddlerhood, newly emerging skills evident across domains (e.g., motor, language, memory) allow for more varied individual differences to emerge (Kiel & Hummel, 2017). One central component of visibly evident individual differences is the child's ability to balance mechanisms of reactivity and self-regulation across specific challenges and environments. For these individual differences to emerge, we, as researchers, must either seek out or provide opportunities for choice and alternative pathways to emerge. For example, if we place children in a situation that is extremely frightening, imagine a theme park haunted house, we may expect the vast majority to show signs of fear and withdrawal—we have wiped out individual differences. By the same token, an environment without any discernable challenges would also homogenize a group of children. Thus, the challenge is to find the "sweet spot" in which behaviorally inhibited and reticent children will emerge from the backdrop of normative patterns of behavior.

Buss (Buss, 2011; Buss et al., 2013; Morales, Beekman, Blandon, Stifter, & Buss, 2015; Morales, Pérez-Edgar, & Buss, 2015) has carried out a series of studies examining just such a spot, identifying children who show dysregulated fear. These children show signs of fear and distress across both challenging and benign circumstances. Non-dysregulated children, in contrast, will show fear in highly charged situations and then typical patterns of behavior when the challenge is removed. That is, they show flexible responses to the environment, modulating patterns of withdrawal and exploration to match the demands of the moment.

To illustrate, Kiel and Buss (2011) had toddlers engage with a series of risky stimuli in the laboratory, including a gorilla mask. Based on video, they noted how long the children visually attended to the mask as well as their proximity to the mask. They found that attention to threat most strongly predicted social inhibition in kindergarten when toddlers stayed furthest away from the mask. This pattern suggests that social inhibition may be linked to attentional vigilance without exploration, which allows for only a shallow learning opportunity. The threat response is triggered, but then the child does not engage in the interactions needed to show that the cue is not truly threatening. Importantly, the toddler's vigilance to the threatening mask was evident in the context of having other enjoyable activities available to them in the room. Thus, this salient pattern of vigilance and avoidance also curtails alternate opportunities for exploration and learning.

When in specific environments, such as confronting a gorilla mask, the behaviorally inhibited child may display reactive vigilance that is triggered by environmental changes and provides the individual with the time to decide to flee, fight, or engage. However, the canalization of affect-biased attention and accompanying behavioral patterns may lead to preemptive vigilance, which is divorced from the specific contours of the current environment. Preemptive vigilance may underlie the rigid behavior patterns seen in behavioral inhibition. Rigidity across contexts may also lead to cognitive and affective fatigue. Indeed, a hallmark of preemptive vigilance is that it is costly to performance (Lima & Dill, 1990), echoing arguments in ACT (Eysenck et al., 2007). In addition, it removes the individual from goal-oriented behavior and rest when threat is low.

Children may also engage processing resources in a way that is neither effective nor efficient. Wolfe and Bell (2014) assessed electroencephalogram (EEG) power in shy children at rest and during a cognitive task. They found that shy children exhibited increases in EEG power from baseline to task regardless on their eventual level of performance. In contrast, non-shy peers only exhibited the same neural increase in activation when they also showed high levels of task performance. That is, processing resources were harnessed in the service of reaching the specific goal in front of them. Wolfe and Bell suggest that the EEG increase in the shy children is a marker of a diffuse, and trait-level, "cognitive busyness." Patterns of cognitive busyness also help better situate a pattern in the literature in which we find little to no behavioral differences when comparing behaviorally inhibited and non-inhibited children in laboratory tasks. Associated biological measures (both central and peripheral) suggest that typically developing behaviorally inhibited children can match their peers, but the effort comes at a greater cost. We also see patterns of resting-state functional connectivity in behaviorally inhibited children that blur the lines between task-specific processes and default mode processes (Taber-Thomas, Morales, Hillary, & Pérez-Edgar, 2016). From this formulation, children at temperamental risk for anxiety appear to have goal-directed salience and executive networks that are less goal-focused and a resting-state default network that is less restful.

Preemptive vigilance (Lima & Dill, 1990), porous functional connectivity (Taber-Thomas et al., 2016), and cognitive busyness (Wolfe & Bell, 2014), each reflect underlying processes that are altered in both behavioral inhibition and anxiety (Clauss et al., 2014). Uninhibited individuals show increased prefrontal cortex activity and decreased amygdala activity in anticipation of threat. This pattern suggests that the individual is adaptively preparing for the threat to come. One can imagine this response would also be adaptive when preparing to explore an unknown location, social group, or task. Behaviorally inhibited individuals do not show this adaptive response and instead show distinct patterns of prefrontal cortex and limbic activity, which are often weighted toward habitual stimulus-driven behavior, as opposed to flexible goal-directed patterns of behavior.

The emergence of clinical anxiety in behaviorally inhibited children may further harden the tendency for exploitation (habit) versus exploration (flexibility). Anxiety is associated with low-risk, low-reward decision-making under threat (Humphreys

et al., 2015). It is also marked by withdrawal in the face of mild threat. Overcoming these initial responses is dependent on the ability to process external cues that disconfirm negative beliefs concerning threat in the environment (Heeren & McNally, 2016). This process builds on core learning and extinction processes (see the chapter "Behavioral Inhibition and the Associative Learning of Fear" by Reynolds et al. and the chapter "The Biological Bridge Between Behavioral Inhibition and Psychopathology" by Sylvester and Pine). Indeed, extinction is a cornerstone of treating anxiety through exposure therapy. *By definition*, this process requires exploration and immersion in novel settings—which can be heavily social in nature. Often targeted treatments to young children emphasize the need to be "brave" and confront sources of fear and anxiety (see the chapter "Behavioural Inhibition and the Prevention of Internalising Distress in Early Childhood" by Rapee and Bayer).

Anxiety in behaviorally inhibited children may build on the prior benefits accrued through exploitation under conditions of threat, creating context-linked adaptation (Humphreys et al., 2015). Thus, exploitation is often used in the service of maintaining the status quo (Scholer, Zou, Fujita, Stroessner, & Higgins, 2010), creating the boundary for safe and acceptable functioning. This is a conservative approach that works to support gains and prevent losses in an environment deemed to be threatening, unstable, and adverse (Humphreys et al., 2015). Overcoming this tendency may rely on the child's willingness to open themselves up to uncertainty and risk.

Shaping Patterns of Exploration and Exploitation

Up to this point, the current chapter has argued that behaviorally inhibited children are at increased risk for anxiety partially due to a shared sensitivity to attend to threat in the environment and withdraw from perceived threat. This pattern is evident in profiles that favor exploiting past environments and behaviors rather than explore for uncertain rewards. The cascade of experiences shaped by the exploration-exploitation trade-off is then evident at the neural, cognitive, and behavioral level.

We should then ask which aspects of the child's life may be most influential in supporting and shaping these patterns. As with most discussions focusing on young children, our first inclination is to examine the role of parenting. Central to temperament research is the notion of "goodness of fit," which refers to the extent to which a child's temperament is compatible with the context of development, often in the form of parental characteristics (Chess & Thomas, 2013). The term "fit" implies a synchrony or transaction between temperament and context, and fit is considered "good" when the environment can meet the demands of a child's temperament and provides opportunities for growth and sets expectations for regulation that are in accordance with that temperament. Dissonance between temperament and contextual demands would be considered a poor fit and could potentially lead to maladaptive outcomes. The dynamic interaction between temperament and context may buffer or exacerbate the evolution of temperament traits into personality traits and psychopathology (Shiner & Caspi, 2003).

In parallel, the animal literature illustrates how parental care can "adaptively program" exploratory strategies (Diorio & Meaney, 2007; Reader, 2015). Multiple studies have shown that care can vary in levels of consistency (McEwen & Morrison, 2013), licking and grooming (Francis, Diorio, Liu, & Meaney, 1999), and neglect (Cohen et al., 2013). These variations not only shift how individuals interact with the environment (Hane & Fox, 2006, 2016) but may also open and close the developmental windows for sensitivity to environmental input (Cameron, Eagleson, Fox, Hensch, & Levitt, 2017).

Thus, the animal literature suggests that young children, in particular, may be sensitive to parental input with respect to (1) judging the environment and (2) shaping how they engage with the world. Simply observing parental behavior influences socioemotional patterns. Vicarious or observational learning is an adaptive strategy to increase the odds of survival since the child need not directly experience an environmental stimulus in order to derive goal-relevant information (Aktar et al., 2016; Field, 2006). Parental display of negative affect or fear when interacting with the environment could transmit to the child that the environment is threatening, unpredictable, or stressful. Emerging data suggest that the impact of vicarious learning may be most acute in infancy (Aktar et al., 2016; Aktar, Majdandžić, De Vente, & Bögels, 2017), perhaps as part of the imprinting process suggested by Hane and Fox (Hane & Fox, 2006, 2016). For example, we see that toddlers high in behavioral inhibition show increased avoidance as preschoolers when parents display anxious behaviors (Aktar et al., 2017). The combination of behavioral inhibition and parental anxiety is also associated with a fraught combination of insecure attachment (Shamir-Essakow, Ungerer, & Rapee, 2005) and high levels of separation anxiety (Kiel, Premo, & Buss, 2016).

One core function of attachment is to provide the infant with a secure and safe base, providing the motivation and reassurance needed to venture out and explore the environment. It may be that an insecure attachment limits the child's comfort with exploring his environment, initially literally and then metaphorically. The lack of exploration, coupled with a subjective view of the world as unsupportive, unpredictable, and threatening, could serve as the foundation for other anxiogenic mechanisms to take root. Separation anxiety may be a failure to reach the developmental task of gaining independent mastery over the environment (Kiel et al., 2016). In this framework, anxiety, especially as manifested in separation and social anxiety, may mark the extreme marker of the clinical and developmental manifestation of privileging exploitation over exploration. Indeed, recent work suggests that neural markers of attention bias impact levels of separation anxiety in behaviorally inhibited 9- to 12-year-old children (Liu, Taber-Thomas, Fu, & Pérez-Edgar, 2018).

Parental behaviors also shape how the child comes to translate initial biases and experiences into long-term patterns of behavior. Maternal protection in low-threat environments may lead to increased fear (Kiel & Buss, 2012). Overprotection may block the child's ability to engage in exploratory behavior in relatively safe contexts. As such, low-threat environments play an important role in providing a "testing ground" for the child to deploy and refine exploratory skills and compile a rich and broad behavioral repertoire (Buss, 2011; Kiel & Buss, 2014). Indeed, patterns

of parental protection mediate the developmental progression from temperament to shyness (Kiel & Buss, 2010).

Behaviorally inhibited children may be particularly sensitive to variations in the environment. Mild challenges can promote the development of independent regulation (Chorpita & Barlow, 1998) and refine the neural systems that shape reactivity to stress (Fox et al., 2007). For young children, parents and parenting behavior serve as a primary conduit by which the environment impacts the child. Recent work (Kiel et al., 2016) has specifically focused on maternal behaviors marked by encouragement to approach novelty (ETAN). ETAN helps grant autonomy and models both interaction and approach. From this support and example, children may have the confidence and skills necessary for exploring the environment. Parents who engage in a quick fix may diminish the child's distress, but do so at the expense of long-term skill building. Degnan and colleagues (Degnan et al., 2015) suggest that the parent must gently challenge the infant to confront novelty and task-focused, rather than distress-focused, parenting styles are associated with decreases in internalizing concerns.

Conclusion

The current chapter examined the impact attention mechanisms may have on the developmental trajectories of behaviorally inhibited children. In particular, early automatic biases may trigger responses that color how children engage with the environment, take in new information, update prior expectations, and create their own environmental niches. This process begins in infancy and continues throughout the life span. The literature reviewed here suggests that the interrelated forces are exceedingly complex and require holistic approaches. Thus, we examine the impact of any one mechanism in the context of larger characteristics that shape its form, function, and outcome.

For example, Brooker (Brooker et al., 2011) examined levels of anxiety risk in a sample of adopted infants as a function of individual differences in attention control. They found that higher levels of attention control were associated with increased risk if both the adoptive mother and the biological mother had elevated levels of anxiety. However, increased attention control in the context of low anxiety in the adoptive mother was associated with decreased levels of risk, even if the biological mother had high levels of anxiety. Thus, this study suggests that the gene by environment interaction does not generate differences in the child's level of attention control, but rather shapes the *consequences* of attention control.

In the same way, early temperament traits are not deterministic in that they do not stamp the child with an imprinted trait that simply unfolds over time. Rather, it is a probabilistic process that is shaped by subsequent experience. Focusing on mechanism in context, and expanding the definition of context to include neural, cognitive, and socioemotional processes, may help better understand both typical developmental trajectories and idiosyncratic arcs that reflect the child's unique life experiences.

The data suggest that detrimental outcomes are associated, in general, with a lack of flexibility in the way individuals approach the social world.

If an individual only engages in exploration, they never reap the gains of bringing new knowledge to their already honed behavioral repertoire, potentially increasing the efficiency and efficacy of past strategies (Laureiro-Martínez, Brusoni, & Zollo, 2010). If the individual only engages in exploitation, the behavioral repertoire stagnates and is very likely to become maladaptive as the environment shifts around them. Thus, it appears that a central goal of development is to scaffold flexible socioemotional, cognitive, and behavioral skills that can be deployed as needed to reflect current and long-term goals, as well as the shifting dynamics of the environment. Behaviorally inhibited children may be particularly vulnerable to an overly rigid and habitual response, leading to increased risk for maladaptation and anxiety. Thus, intervention efforts may need to focus on supporting a more flexible approach to the people, places, and things that inhabit the behaviorally inhibited child's world.

References

Aktar, E., Majdandžić, M., De Vente, W., & Bögels, S. M. (2017). Parental expressions of anxiety and child temperament in toddlerhood jointly predict preschoolers' avoidance of novelty. *Journal of Clinical Child & Adolescent Psychology*, *29,* 1–14.

Aktar, E., Mandell, D. J., de Vente, W., Majdandžić, M., Raijmakers, M. E., & Bögels, S. M. (2016). Infants' temperament and mothers', and fathers' depression predict infants' attention to objects paired with emotional faces. *Journal of Abnormal Child Psychology, 44*, 975–990.

Almas, A. N., Phillips, D. A., Henderson, H. A., Hane, A. A., Degnan, K. A., Moas, O. L., & Fox, N. A. (2011). The relations between infant negative reactivity, non-maternal childcare, and children's interactions with familiar and unfamiliar peers. *Social Development, 20*, 718–740. https://doi.org/10.1111/j.1467-9507.2011.00605.x

Amso, D., & Scerif, G. (2015). The attentive brain: Insights from developmental cognitive neuroscience. *Nature Reviews Neuroscience, 16*, 606–619.

Anaya, B., & Pérez-Edgar, K. (in press). Personality development in the context of temperament and parenting dynamics. *New Ideas in Psychology*. https://doi.org/10.1016/j.newideapsych.2018.03.002

Auday, E., Taber-Thomas, B. C., & Pérez-Edgar, K. E. (2018). Neural correlates of attention bias to masked facial threat cues: Examining children at-risk for social anxiety disorder. *NeuroImage: Clinical, 19*, 202–212.

Belsky, J., Schlomer, G. L., & Ellis, B. J. (2012). Beyond cumulative risk: Distinguishing harshness and unpredictability as determinants of parenting and early life history strategy. *Developmental Psychology, 48*, 662–673.

Biederman, J., Faraone, S. V., Hirshfeld-Becker, D. R., Friedman, D., Robin, J. A., & Rosenbaum, J. F. (2001). Patterns of psychopathology and dysfunction in high-risk children of parents with panic disorder and major depression. *American Journal of Psychiatry, 158*, 49–57. https://doi.org/10.1176/appi.ajp.158.1.49

Brooker, R. J., Neiderhiser, J. M., Ganiban, J. M., Leve, L. D., Shaw, D. S., & Reiss, D. (2014). Birth and adoptive parent anxiety symptoms moderate the link between infant attention control and internalizing problems in toddlerhood. *Development and Psychopathology, 26*(2), 347–359.

Brooker, R. J., Neiderhiser, J. M., Kiel, E. J., Leve, L. D., Shaw, D. S., & Reiss, D. (2011). The association between infants' attention control and social inhibition is moderated by genetic and environmental risk for anxiety. *Infancy, 16*, 490–507.

Buss, K. A. (2011). Which fearful toddlers should we worry about? Context, fear regulation, and anxiety risk. *Developmental Psychology, 47*, 804–819.

Buss, K. A., Davis, E. L., Kiel, E. J., Brooker, R. J., Beekman, C., & Early, M. C. (2013). Dysregulated fear predicts social wariness and social anxiety symptoms during kindergarten. *Journal of Clinical Child & Adolescent Psychology, 42*(5), 603–616. https://doi.org/10.1080/15374416.2013.769170

Cameron, J. L., Eagleson, K. L., Fox, N. A., Hensch, T. K., & Levitt, P. (2017). Social origins of developmental risk for mental and physical illness. *Journal of Neuroscience, 37*, 10783–10791.

Capitanio, J. P. (2017). Naturally occurring nonhuman primate models of psychosocial processes. *ILAR Journal, 58*, 226–234.

Cavigelli, S. A., & McClintock, M. K. (2003). Fear of novelty in infant rats predicts adult corticosterone dynamics and an early death. *Proceedings of the National Academy of Sciences, 100*, 16131–16136.

Cavigelli, S. A., Stine, M. M., Kovacsics, C., Jefferson, A., Diep, M. N., & Barrett, C. E. (2007). Behavioral inhibition and glucocorticoid dynamics in a rodent model. *Physiology & Behavior, 92*, 897–905.

Chess, S., & Thomas, A. (2013). *Goodness of fit: Clinical applications, from infancy through adult life*. New York, NY: Routledge.

Chorpita, B. F., & Barlow, D. H. (1998). The development of anxiety: The role of control in the early environment. *Psychological Bulletin, 124*(1), 3–21.

Chronis-Tuscano, A., Degnan, K. A., Pine, D. S., Perez-Edgar, K., Henderson, H. A., Diaz, Y., … Fox, N. A. (2009). Stable behavioral inhibition during infancy and early childhood predicts the development of anxiety disorders in adolescence. *Journal of the American Academy of Child & Adolescent Psychiatry, 48*, 928–935. https://doi.org/10.1097/CHI.ob013e3181ae09df

Clauss, J. A., Avery, S. N., VanDerKlok, R. M., Rogers, B. P., Cowan, R. L., Benningfield, M. M., & Blackford, J. U. (2014). Neurocircuitry underlying risk and resilience to social anxiety disorder. *Depression and Anxiety, 31*, 822–833.

Clauss, J. A., & Blackford, J. U. (2012). Behavioral inhibition and risk for developing social anxiety disorder: A meta-analytic study. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*, 1066–1075. https://doi.org/10.1016/j.jaac.2012.08.002

Cohen, M. M., Jing, D., Yang, R. R., Tottenham, N., Lee, F. S., & Casey, B. J. (2013). Early-life stress has persistent effects on amygdala function and development in mice and humans. *Proceedings of the National Academy of Sciences, 110*, 18274–18278.

Colombo, J. (2001). The development of visual attention in infancy. *Annual Review of Psychology, 52*, 337–367.

Colombo, J., & Salley, B. (2015). Biopsychosocial perspectives on the development of attention in infancy. In S. B. Calkins (Ed.), *Handbook of infant biopsychosocial development* (pp. 71–96). New York, NY: Guilford Publications.

Coplan, R. J., Rubin, K. H., Fox, N. A., Calkins, S. D., & Stewart, S. L. (1994). Being alone, playing alone, and acting alone: Distinguishing among reticence and passive and active solitude in young children. *Child Development, 65*, 129–137. https://doi.org/10.1111/j.1467-8624.1994.tb00739.x

Cremone, A., Kurdziel, L. B., Fraticelli-Torres, A., McDermott, J. M., & Spencer, R. (2017). Napping reduces emotional attention bias during early childhood. *Developmental Science, 20*(4). https://doi.org/10.1111/desc.12411

Degnan, K. A., & Fox, N. A. (2007). Behavioral inhibition and anxiety disorders: Multiple levels of a resilience process. *Development and Psychopathology, 19*, 729–746. https://doi.org/10.1017/S0954579407000363

Degnan, K. A., Hane, A. A., Henderson, H. A., Walker, O. L., Ghera, M. M., & Fox, N. A. (2015). Emergent patterns of risk for psychopathology: The influence of infant avoidance and maternal caregiving on trajectories of social reticence. *Development and Psychopathology, 27*, 1163–1178.

Diorio, J., & Meaney, M. J. (2007). Maternal programming of defensive responses through sustained effects on gene expression. *Journal of Psychiatry & Neuroscience, 32*, 275–284.

Dodd, H. F., Vogt, J., Turkileri, N., & Notebaert, L. (2017). Task relevance of emotional information affects anxiety-linked attention bias in visual search. *Biological Psychology, 122*, 13–20.

Dudeney, J., Sharpe, L., & Hunt, C. (2015). Attentional bias towards threatening stimuli in children with anxiety: A meta-analysis. *Clinical Psychology Review, 40*, 66–75.

Ehlers, M. R., & Todd, R. M. (2017). Genesis and maintenance of attentional biases: The role of the locus coeruleus-noradrenaline system. *Neural Plasticity, 2017*, 1–15.

Eisenberg, N., & Spinrad, T. L. (2004). Emotion-related regulation: Sharpening the definition. *Child Development, 75*, 334–339. https://doi.org/10.1111/j.1467-8624.2004.00674.x

Ellis, L. K., Rothbart, M. K., & Posner, M. I. (2004). Individual differences in executive attention predict self-regulation and adolescent psychosocial behaviors. *Annals of the New York Academy of Sciences, 1021*, 337–340. https://doi.org/10.1196/annals.1308.041

Eysenck, M. W., Derakshan, N., Santos, R., & Calvo, M. G. (2007). Anxiety and cognitive performance: Attentional control theory. *Emotion, 7*, 336–353.

Field, A. (2006). Watch out for the beast: Fear information and attentional biases in children. *Journal of Clinical Child & Adolescent Psychology, 35*, 431–439.

Fox, N. A., Hane, A. A., & Pine, D. S. (2007). Plasticity for affective neurocircuitry: How the environment affects gene expression. *Current Directions in Psychological Science, 16*, 1–5.

Fox, N. A., Henderson, H. A., Marshall, P. J., Nichols, K. E., & Ghera, M. M. (2005). Behavioral inhibition: Linking biology and behavior within a developmental framework. *Annual Review of Psychology, 56*, 235–262.

Fox, N. A., Rubin, K. H., Calkins, S. D., Marshall, T. R., Coplan, R. J., Porges, S. W., … Stewart, S. (1995). Frontal activation asymmetry and social competence at four years of age. *Child Development, 66*, 1771–1784. https://doi.org/10.1111/j.1467-8624.1995.tb00964.x

Francis, D., Diorio, J., Liu, D., & Meaney, M. J. (1999). Nongenomic transmission across generations of maternal behavior and stress responses in the rat. *Science, 286*, 1155–1158.

Gao, W., Zhu, H., Giovanello, K. S., Smith, J. K., Shen, D., Gilmore, J. H., & Lin, W. (2009). Evidence on the emergence of the brain's default network from 2-week-old to 2-year-old healthy pediatric subjects. *Proceedings of the National Academy of Sciences, 106*, 6790–6795.

García Coll, C., Kagan, J., & Reznick, J. S. (1984). Behavioral inhibition in young children. *Child Development, 55*, 1005–1019. https://doi.org/10.2307/1130152

Gee, D. G., Humphreys, K. L., Flannery, J., Goff, B., Telzer, E. H., Shapiro, M., … Tottenham, N. (2013). A developmental shift from positive to negative connectivity in human amygdala–prefrontal circuitry. *The Journal of Neuroscience, 33*, 4584–4593.

Grupe, D. W., & Nitschke, J. B. (2013). Uncertainty and anticipation in anxiety: An integrated neurobiological and psychological perspective. *Nature Reviews Neuroscience, 14*, 488–501.

Hane, A. A., & Fox, N. A. (2006). Ordinary variations in maternal caregiving influence human infants' stress reactivity. *Psychological Science, 17*, 550–556.

Hane, A. A., & Fox, N. A. (2016). Early caregiving and human biobehavioral development: A comparative physiology approach. *Current Opinion in Behavioral Sciences, 7*, 82–90.

Heeren, A., & McNally, R. J. (2016). An integrative network approach to social anxiety disorder: The complex dynamic interplay among attentional bias for threat, attentional control, and symptoms. *Journal of Anxiety Disorders, 42*, 95–104.

Henderson, H. A. (2010). Electrophysiological correlates of cognitive control and the regulation of shyness in children. *Developmental Neuropsychology, 35*, 177–193. https://doi.org/10.1080/87565640903526538

Henderson, H. A., Pine, D. S., & Fox, N. A. (2015). Behavioral inhibition and developmental risk: A dual-processing perspective. *Neuropsychopharmacology, 40*, 207–224.

Henderson, H. A., & Wilson, M. J. (2017). Attention processes underlying risk and resilience in behaviorally inhibited children. *Current Behavioral Neuroscience Reports, 4*, 99–106.

Hoehl, S., & Striano, T. (2010). The development of emotional face and eye gaze processing. *Developmental Science, 13*(6), 813–825.

Hummel, A. C., Premo, J. E., & Kiel, E. J. (2017). Attention to threat as a predictor of shyness in the context of internalizing and externalizing behavior. *Infancy, 22*, 240–255.

Humphreys, K. L., Lee, S. S., Telzer, E. H., Gabard-Durnam, L. J., Goff, B., Flannery, J., & Tottenham, N. (2015). Exploration—Exploitation strategy is dependent on early experience. *Developmental Psychobiology, 57*, 313–321.

Kagan, J. (1997). Temperament and the reactions to unfamiliarity. *Child Development, 68*, 139–143.

Kagan, J. (2012). The biography of behavioral inhibition. In M. Zentner & R. L. Shiner (Eds.), *Handbook of temperament* (pp. 69–82). New York, NY: Guilford Press.

Kagan, J., Reznick, J. S., & Snidman, N. (1987). The physiology and psychology of behavioral inhibition in children. *Child Development, 58*, 1459–1473. https://doi.org/10.2307/1130685

Kagan, J., Snidman, N., McManis, M., & Woodward, S. (2001). Temperamental contributions to the affect family of anxiety. *The Psychiatric Clinics of North America, 24*(4), 677–688. https://doi.org/10.1016/S0193-953X(05)70257-4

Kayser, A. S., Mitchell, J. M., Weinstein, D., & Frank, M. J. (2015). Dopamine, locus of control, and the exploration-exploitation tradeoff. *Neuropsychopharmacology, 40*, 454–462.

Kiel, E. J., & Buss, K. A. (2010). Maternal expectations for toddlers' reactions to novelty: Relations of maternal internalizing symptoms and parenting dimensions to expectations and accuracy of expectations. *Parenting: Science and Practice, 10*, 202–218.

Kiel, E. J., & Buss, K. A. (2011). Toddlers' duration of attention toward putative threat. *Infancy, 16*, 198–210.

Kiel, E. J., & Buss, K. A. (2012). Associations among context-specific maternal protective behavior, toddlers' fearful temperament, and maternal accuracy and goals. *Social Development, 21*, 742–760.

Kiel, E. J., & Buss, K. A. (2014). Dysregulated fear in toddlerhood predicts kindergarten social withdrawal through protective parenting. *Infant and Child Development, 23*, 304–313.

Kiel, E. J., & Hummel, A. C. (2017). Contextual influences on concordance between maternal report and laboratory observation of toddler fear. *Emotion, 17*, 240–250.

Kiel, E. J., Premo, J. E., & Buss, K. A. (2016). Maternal encouragement to approach novelty: A curvilinear relation to change in anxiety for inhibited toddlers. *Journal of Abnormal Child Psychology, 44*, 433–444.

Lau, J. Y., & Waters, A. M. (2017). Annual Research Review: An expanded account of information-processing mechanisms in risk for child and adolescent anxiety and depression. *Journal of Child Psychology and Psychiatry, 58*, 387–407.

Laureiro-Martínez, D., Brusoni, S., & Zollo, M. (2010). The neuroscientific foundations of the exploration−exploitation dilemma. *Journal of Neuroscience, Psychology, and Economics, 3*, 95.

Leppänen, J. M., & Nelson, C. A. (2009). Tuning the developing brain to social signals of emotions. *Nature Reviews Neuroscience, 10*(1), 37–47.

Lima, S. L., & Dill, L. M. (1990). Behavioral decisions made under the risk of predation: A review and prospectus. *Canadian Journal of Zoology, 68*, 619–640.

Liu, P., Taber-Thomas, B. C., Fu, X., & Pérez-Edgar, K. (2018). Biobehavioral markers of attention bias modification in temperamental risk for anxiety: A randomized control trial. *Journal of the American Academy of Child and Adolescent Psychiatry, 57*, 103–110.

LoBue, V., Rakison, D., & DeLoache, J. S. (2010). Threat perception across the lifespan: Evidence for multiple converging pathways. *Current Directions in Psychological Science, 19*, 375–379.

McEwen, B. S., & Morrison, J. H. (2013). The brain on stress: Vulnerability and plasticity of the prefrontal cortex over the life course. *Neuron, 79*, 16–29.

Meyer, A. (2017). A biomarker of anxiety in children and adolescents: A review focusing on the error-related negativity (ERN) and anxiety across development. *Developmental Cognitive Neuroscience, 27*, 58–68.

Meyer, A., Weinberg, A., Klein, D. N., & Hajcak, G. (2012). The development of the error-related negativity (ERN) and its relationship with anxiety: Evidence from 8 to 13 year-olds. *Developmental Cognitive Neuroscience, 2*, 152–161.

Morales, S., Beekman, C., Blandon, A. Y., Stifter, C. A., & Buss, K. A. (2015). Longitudinal associations between temperament and socioemotional outcomes in young children: The moderating role of RSA and gender. *Developmental Psychobiology, 57*, 105–119.

Morales, S., Brown, K. M., Taber-Thomas, B. C., LoBue, V., Buss, K. A., & Pérez-Edgar, K. (2017). Maternal anxiety predicts attentional bias towards threat in infancy. *Emotion, 17*, 874–883.

Morales, S., Fu, X., & Pérez-Edgar, K. (2016). A developmental neuroscience perspective on affect biased attention. *Developmental Cognitive Neuroscience, 21*, 26–41.

Morales, S., Pérez-Edgar, K., & Buss, K. A. (2015). Attention biases towards and away from threat mark the relation between early dysregulated fear and the later emergence of social withdrawal. *Journal of Abnormal Child Psychology, 43*, 1067–1078.

Morales, S., Taber-Thomas, B. C., & Pérez-Edgar, K. (2017). Patterns of attention to threat across tasks in behaviorally inhibited children at risk for anxiety. *Developmental Science, 20*, e12391.

Munakata, Y., Snyder, H. R., & Chatham, C. H. (2012). Developing cognitive control: Three key transitions. *Current Directions in Psychological Science, 21*(2), 71–77.

Nozadi, S. S., Troller-Renfree, S., White, L. K., Frenkel, T., Degnan, K. A., Bar-Haim, Y., … Fox, N. A. (2016). The moderating role of attention biases in understanding the link between behavioral inhibition and anxiety. *Journal of Experimental Psychopathology, 7*, 451–465.

Pacheco-Unguetti, A. P., Acosta, A., Callejas, A., & Lupiáñez, J. (2010). Attention and anxiety different attentional functioning under state and trait anxiety. *Psychological Science, 21*, 298–304.

Peltola, M. J., Hietanen, J. K., Forssman, L., & Leppänen, J. M. (2013). The emergence and stability of the attentional bias to fearful faces in infancy. *Infancy, 18*(6), 905–926.

Peltola, M. J., Leppanen, J. M., Maki, S., & Hietanen, J. K. (2009). Emergence of enhanced attention to fearful faces between 5 and 7 months of age. *Social Cognitive and Affective Neuroscience, 4*, 134–142.

Peltola, M. J., Leppanen, J. M., Palokangas, T., & Hietanen, J. K. (2008). Fearful faces modulate looking duration and attention disengagement in 7-month-old infants. *Developmental Science, 11*, 60–68.

Peltola, M. J., Yrttiaho, S., & Leppänen, J. M. (2018). Infants' attention bias to faces as an early marker of social development. *Developmental Science*, e12687. https://doi.org/10.1111/desc.12687

Pérez-Edgar, K. (2015). Effortful control in adolescence: Individual differences within a unique developmental window. In G. Oettingen & P. M. Gollwitzer (Eds.), *Self-regulation in adolescence* (pp. 78–102). Cambridge, England: Cambridge University Press.

Pérez-Edgar, K., Bar-Haim, Y., McDermott, J. M., Chronis-Tuscano, A., Pine, D. S., & Fox, N. A. (2010). Attention biases to threat and behavioral inhibition in early childhood shape adolescent social withdrawal. *Emotion, 10*, 349–357. https://doi.org/10.1037/a0018486

Pérez-Edgar, K., & Fox, N. A. (2005). Temperament and anxiety disorders. *Child and Adolescent Psychiatric Clinics of North America, 14*, 681–706. https://doi.org/10.1016/j.chc.2005.05.008

Pérez-Edgar, K., & Guyer, A. E. (2014). Behavioral inhibition: Temperament or prodrome? *Current Behavioral Neuroscience Reports, 1*(3), 182–190.

Pérez-Edgar, K., McDermott, J. M., Korelitz, K., Degnan, K. A., Curby, T. W., Pine, D. S., & Fox, N. A. (2010). Patterns of sustained attention in infancy shape the developmental trajectory of social behavior from toddlerhood through adolescence. *Developmental Psychology, 46*, 1723–1730. https://doi.org/10.1037/a0021064

Pérez-Edgar, K., Morales, S., LoBue, V., Taber-Thomas, B. C., Allen, E. K., Brown, K. M., & Buss, K. A. (2017). The impact of negative affect on attention patterns to threat across the first two years of life. *Developmental Psychology, 53*, 2219–2232.

Pérez-Edgar, K., Reeb-Sutherland, B. C., McDermott, J. M., White, L. K., Henderson, H. A., Degnan, K. A., … Fox, N. A. (2011). Attention biases to threat link behavioral inhibition to social withdrawal over time in very young children. *Journal of Abnormal Child Psychology, 39*, 885–895. https://doi.org/10.1007/s10802-011-9495-5

Pérez-Edgar, K., Taber-Thomas, B., Auday, E., & Morales, S. (2014). Temperament and attention as core mechanisms in the early emergence of anxiety. In K. Lagattuta (Ed.), *Children and emotion: New insights into developmental affective science* (Vol. 26, pp. 42–56). Basel, Switzerland: Karger Publishing.

Posner, M. I., Rothbart, M. K., Sheese, B. E., & Voelker, P. (2012). Control networks and neuromodulators of early development. *Developmental Psychology, 48*, 827–835. https://doi.org/10.1037/a0025530

Reader, S. M. (2015). Causes of individual differences in animal exploration and search. *Topics in Cognitive Science, 7*, 451–468.

Reeb-Sutherland, B. C., Vanderwert, R. E., Degnan, K. A., Marshall, P. J., Pérez-Edgar, K., Chronis-Tuscano, A., … Fox, N. A. (2009). Attention to novelty in behaviorally inhibited adolescents moderates risk for anxiety. *Journal of Child Psychology and Psychiatry, 50*, 1365–1372.

Rossi, V., & Pourtois, G. (2017). Someone's lurking in the dark: The role of state anxiety on attention deployment to threat-related stimuli. *Biological Psychology, 122*, 21–32.

Rothbart, M. K., Ellis, L. K., Rueda, M. R., & Posner, M. I. (2003). Developing mechanisms of temperamental effortful control. *Journal of Personality, 71*(6), 1113–1143.

Rothbart, M. K., Sheese, B. E., Rueda, M. R., & Posner, M. I. (2011). Developing mechanisms of self-regulation in early life. *Emotion Review, 3*, 207–213. https://doi.org/10.1177/1754073910387943

Roy, A. K., Dennis, T. A., & Warner, C. M. (2015). A critical review of attentional threat bias and its role in the treatment of pediatric anxiety disorders. *Journal of Cognitive Psychotherapy, 29*(3), 171–184.

Rubin, K., Chen, X., & Hymel, S. (1993). Socioemotional characteristics of withdrawn and aggressive children. *Merrill-Palmer Quarterly, 39*, 518–534.

Schmidt, L. A., Fox, N. A., Rubin, K. H., Sternberg, E. M., Gold, P. W., Smith, C. C., & Schulkin, J. (1997). Behavioral and neuroendocrine responses in shy children. *Developmental Psychobiology, 30*, 127–140.

Schmidt, L. A., Fox, N. A., Schulkin, J., & Gold, P. W. (1999). Behavioral and psychophysiological correlates of self-presentation in temperamentally shy children. *Developmental Psychobiology, 35*, 119–135. https://doi.org/10.1002/(SICI)1098-2302(199909)35:2<119::AID-DEV5>3.0.CO;2-G

Scholer, A. A., Zou, X., Fujita, K., Stroessner, S. J., & Higgins, E. T. (2010). When risk seeking becomes a motivational necessity. *Journal of Personality and Social Psychology, 99*, 215–231.

Shamir-Essakow, G., Ungerer, J. A., & Rapee, R. M. (2005). Attachment, behavioral inhibition, and anxiety in preschool children. *Journal of Abnormal Child Psychology, 33*, 131–143.

Shiner, R., & Caspi, A. (2003). Personality differences in childhood and adolescence: Measurement, development, and consequences. *Journal of Child Psychology and Psychiatry, 44*(1), 2–32.

Shulman, G. L., Astafiev, S. V., Franke, D., Pope, D. L. W., Snyder, A. Z., McAvoy, M. P., & Corbetta, M. (2009). Interaction of stimulus-driven reorienting and expectation in ventral and dorsal frontoparietal and basal ganglia-cortical networks. *Journal of Neuroscience, 29*, 4392–4407. https://doi.org/10.1523/JNEUROSCI.5609-08.2009

Suor, J. H., Sturge-Apple, M. L., Davies, P. T., & Cicchetti, D. (2017). A life history approach to delineating how harsh environments and hawk temperament traits differentially shape children's problem-solving skills. *Journal of Child Psychology and Psychiatry, 58*, 902–909.

Susa, G., Pitică, I., Benga, O., & Miclea, M. (2012). The self regulatory effect of attentional control in modulating the relationship between attentional biases toward threat and anxiety symptoms in children. *Cognition & Emotion, 26*, 1069–1083. https://doi.org/10.1080/02699931.2011.638910

Sylvester, C. M., Hudziak, J. J., Gaffrey, M. S., Barch, D. M., & Luby, J. L. (2016). Stimulus-driven attention, threat bias, and sad bias in youth with a history of an anxiety disorder or depression. *Journal of Abnormal Child Psychology, 44*, 219–231.

Taber-Thomas, B., Morales, S., Hillary, F., & Pérez-Edgar, K. (2016). Altered topography of intrinsic functional connectivity in childhood risk for social anxiety. *Depression and Anxiety, 33*, 995–1004.

Todd, R. M., Cunningham, W. A., Anderson, A. K., & Thompson, E. (2012). Affect-biased attention as emotion regulation. *Trends in Cognitive Sciences, 16*, 365–372. https://doi.org/10.1016/j.tics.2012.06.003

Toelch, U., Bruce, M. J., Meeus, M. T., & Reader, S. M. (2011). Social performance cues induce behavioral flexibility in humans. *Frontiers in Psychology, 2*, 160.

Tottenham, N. (2013). The importance of early experiences for neuro-affective development. In *The neurobiology of childhood* (pp. 109–129). Berlin, Germany: Springer.

Verbeek, M. E., Drent, P. J., & Wiepkema, P. R. (1994). Consistent individual differences in early exploratory behaviour of male great tits. *Animal Behaviour, 48*, 1113–1121.

Vogt, J., De Houwer, J., Crombez, G., & Van Damme, S. (2013). Competing for attentional priority: Temporary goals versus threats. *Emotion, 13*(3), 587.

Wass, S. V., Scerif, G., & Johnson, M. H. (2012). Training attentional control and working memory—Is younger, better? *Developmental Review, 32*, 360–387.

Wells, A., & Matthews, G. (1996). Modeling cognition in emotional disorder: The S-REF model. *Behaviour Research and Therapy, 34*, 881–888. https://doi.org/10.1016/S0005-7967(96)00050-2

White, L. K., Degnan, K. A., Henderson, H. A., Pérez-Edgar, K., Walker, O. L., Schechner, T., … Fox, N. A. (2017). Developmental relations between behavioral inhibition, anxiety, and attention biases to threat and positive information. *Child Development, 88*, 141–155.

Williams, L. R., Degnan, K. A., Pérez-Edgar, K., Henderson, H. A., Rubin, K. H., Pine, D. S., … Fox, N. A. (2009). Impact of behavioral inhibition and parenting style on internalizing and externalizing problems from early childhood through adolescence. *Journal of Abnormal Child Psychology, 37*, 1063–1075. https://doi.org/10.1007/s10802-009-9331-3

Wolfe, C. D., & Bell, M. A. (2014). Brain electrical activity of shy and non-shy preschool-aged children during executive function tasks. *Infant and Child Development, 23*, 259–272.

Behavioral Inhibition and the Associative Learning of Fear

Gemma Reynolds, Chris Askew, and Andy P. Field

Abstract Fear and anxiety symptoms can be acquired through (1) a direct traumatic experience, (2) the transmission of verbal information, and (3) vicarious (observational) learning. All three pathways have gained empirical support, and all appear to conform to predictions made by theories of Pavlovian associative learning. Consequently, a number of integrated models of fear learning based on associative learning principles have been proposed. Field and Purkis' (Anxiety disorders in children and adolescents: Research, assessment and intervention, 2011) model suggests that learning experiences evoke links between a neutral stimulus (CS) and threat-related US. Therefore, a single mechanism underlies all three fear learning pathways, and thus the pathways can have additive and multiplicative effects on the strength of the CS-US link. Crucially, the model acknowledges the role of individual differences in learning. This chapter will discuss the evidence demonstrating the influence of two temperamental constructs, behavioral inhibition (the tendency to react to a novel or unfamiliar situation with excessive apprehension and avoidance) and the behavioral inhibition system (a neurological system, which is linked to behavioral inhibition, that controls the experience of anxiety in response to anxiety-relevant cues). In particular, the chapter will explore the effect of behavioral inhibition and the behavioral inhibition system on both the strength of the CS-US link formed during a learning episode, as well as post-learning processes. Taken together, it is clear that behavioral inhibition interacts with the associative learning of fear to facilitate fear learning.

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Behavioral Inhibition and the Associative Learning of Fear

Childhood fears and anxieties are highly prevalent developmental problems (Gullone, 2000). Typical childhood fears include fears of animals (e.g., spiders), medical issues (e.g., injections), and situational and environmental factors (e.g., heights) (Muris & Field, 2010). For most children, fears are considered mild and a normative part of development with adaptive value (King, Hamilton, & Ollendick, 1988), often being short-lived and spontaneously receding as quickly as they first appeared (e.g., Ferrari, 1986). However, for a sizable minority of children (approximately 22%), childhood fears can persist, becoming severe and taking on pathological properties reflecting more severe phobias and anxiety disorders (Muris, 2007; Muris, Merckelbach, Mayer, & Prins, 2000). Subsequently, fears and anxieties significantly interfere with daily functioning and often continue into adulthood (Muris et al., 2000). In such cases, a diagnosis of a specific phobia or an anxiety disorder may be warranted (see Diagnostic and Statistical Manual of Mental Disorders, fifth edition; American Psychiatric Association, 2013).

The fear and anxiety response are made up of subjective (cognition), behavioral (avoidance), and physiological (e.g., heart rate increases) components (Lang, 1968). With respect to cognition, distinctive patterns of processing threat information have been causally implicated in creating anxiety (Mathews & MacLeod, 2002). Anxious people tend both to attend selectively to threat in their environment (attentional bias) and overinterpret ambiguity as threat (interpretation bias). Any model of fear learning has to explain how these processing styles develop as well as behavioral and physiological responses.

Theories of Fear Learning

Developmental Trajectories of Anxiety

Developmental models of anxiety symptoms (i.e., attention, interpretation) distinguish between *integral bias*, *moderation*, and *acquisition* trajectories for anxiety-related cognition (Field & Lester, 2010a). "Integral bias" equates to the mechanisms underpinning anxiety-related symptoms being unaffected by the environment. In other words, the growth trajectory for anxiety-related symptoms is flat: your early (presumably inherited) propensity for anxiety-related symptoms is unwavering in the face of environmental influence. Acquisition and moderation models both represent growth trajectories for anxiety-related symptoms that change over time and, therefore, imply some environmental influence. The difference between them lies in whether it is assumed that the propensity for anxiety-related symptoms is low in very early life and acquired over time (acquisition) or whether it is high early in life but gets toned down through environmental influences (moderation). In both the acquisition and moderation models, it is assumed that the change in anxiety

symptoms over time will not just be a function of learning from environmental experiences but that these experiences will interact with inherited characteristics of the child (e.g., temperament).

Although, at present, there is not sufficient evidence to determine which trajectory is most likely, a review of what evidence there is suggests that the integral bias model can be ruled out because of the considerable evidence that anxiety-related cognitions in children change over time (Field & Lester, 2010a). The same review concludes that because attentional biases to threat stimuli have been found very early in life (see LoBue & Rakison, 2013, for a review), a moderation model is most likely for attentional components of the anxiety response. Conversely, because there are currently no evidence that interpretational components of threat processing are present early in life and good reasons to assume that such relatively high-level processing would depend upon developmental foundations, such as understanding ambiguity, and multiple outcomes from an event, it is assumed that the development of anxiety-related symptoms is best characterized by an acquisition model.

Mechanisms of Fear Learning

Irrespective of whether anxiety symptoms follow a moderation or acquisition model of growth, some learning is involved, and, therefore, it is important to identify the mechanisms underlying that learning. Models of fear and anxiety learning implicate several contributing mechanisms including biological (e.g., genes, temperament) and behavioral processes (e.g., classical and operant conditioning, observational learning), as well as interpersonal (e.g., attachment, parent/child interaction) and cognitive factors (e.g., information processing biases) (see Silverman & Field, 2011, for a review). Even after accounting for genetic transmission, a strong relation between parental and offspring anxiety still exists, thus leaving a large proportion of variance explained by shared environmental factors (Eley et al., 2015; Gregory & Eley, 2011)

An obvious cause of anxiety symptoms is direct traumatic experience. Nearly a century ago, Watson and Rayner's (1920) "Little Albert" study implicated direct negative experiences (aversive classical conditioning) in fear development. Put simply, fear of a neutral stimulus (a conditioned stimulus, CS; e.g., a dog) can be learned through that stimulus becoming associated with an aversive event (an unconditioned stimulus, US; e.g., a bite). Through this association, the formerly neutral stimulus comes to elicit a conditioned fear response (CR). This is a highly conserved learning mechanism, providing opportunities for comparative studies across human and nonhuman models of fear-learning and behavioral inhibition (see the chapter "Behavioral Inhibition in Rodents: A Model to Study Causes and Health Consequences of Temperament" by Cavigelli).

A century of clinical practice and laboratory research has established that direct traumatic experiences (e.g., road traffic accidents) are commonly associated with anxiety symptoms such as re-experiencing the event, intrusive images, nightmares, hyperarousal, and avoidance. For example, 37.1% of people exposed to

"intentional" traumas (e.g., war, assault) develop post-traumatic stress symptoms (Santiago et al., 2013). However, within that group 34.8% remit within 1 month, whereas symptoms in 39.1% are chronic. These figures suggest that the impact of direct traumatic experiences is moderated by other factors. For example, in a meta-analysis on child post-traumatic stress symptoms, predictors of trauma response were categorized as pre- (e.g., demographic characteristics), peri- (e.g., perceived threat during the trauma), and post-trauma (e.g., social support, strategies for dealing with trauma). Broadly speaking, the severity of symptoms after trauma increased as a function of these categories, with the severest symptoms associated with post-trauma variables (Trickey, Siddaway, Meiser-Stedman, Serpell, & Field, 2012). Interestingly, these post-traumatic predictors of trauma severity included characteristics of the individual such as comorbid psychological problems, social withdrawal, and thought suppression.

Direct trauma is not the only pathway through which fears are acquired. It has long been acknowledged that verbal information and observational learning are powerful pathways through which anxiety symptoms evolve (Rachman, 1977). These pathways have been substantiated both through retrospective studies in which anxious people reflect back on earlier experiences related to their anxiety and laboratory studies in which subjective, behavioral, and physiological responses to novel stimuli (typically animals) are measured after different types of verbal information or vicarious experiences.

For example, in numerous studies with children aged 6–13, threat information (compared to positive or no information) about a novel animal has been shown to increase directly and indirectly measured subjective feelings of fear (Field, 2006a, 2006c; Field & Lawson, 2003; Field & Lawson, 2008; Field & Price-Evans, 2009; Field & Schorah, 2007; Field & Storksen-Coulson, 2007; Price-Evans & Field, 2008), latency to approach (Field, 2006a; Field & Lawson, 2003; Field & Lawson, 2008; Field, Lawson, & Banerjee, 2008), and heart rate (Field & Schorah, 2007) when approaching a box that the child believes contains the animal. Similar effects have been found using a "nature reserve task" in which children are given a board decorated as a nature reserve with animals positioned within it and are asked to place a toy figure in the park to represent where they would like to be. The distance from the threat information animal relative to other animals is taken as a measure of avoidance (Field & Storksen-Coulson, 2007). These effects persist at least up to 6 months (Field et al., 2008).

Similar experiments have been conducted in youths in which pictures of novel animals are presented alongside facial expressions of fear or videos of others acting afraid (or neutral or happy). As with the verbal information studies, it has been shown repeatedly that an association with another person's fear response is sufficient to increase directly and indirectly measured subjective feelings of fear (Askew, Dunne, Özdil, Reynolds, & Field, 2013; Askew & Field, 2007; Askew, Reynolds, Fielding-Smith, & Field, 2016; Broeren, Lester, Muris, & Field, 2011; Dunne & Askew, 2013; Reynolds, Field, & Askew, 2014, 2015), latency to approach (Askew & Field, 2007; Reynolds et al., 2014), and heart rate (Reynolds et al., 2014) when approaching a box that the child believes contains the animal. The same pattern is

evident when examining distance from the animal using the nature research task described above (Askew et al., 2013; Askew et al., 2016). These effects persist for weeks after the initial learning (Askew & Field, 2007; Reynolds et al., 2014).

To cut a very long story short, fear learning through direct experience, verbal information, and observational learning all appear to conform fairly consistently to predictions that emerge from theories of Pavlovian associative learning. Given this, several authors have proposed integrated models of fear learning based on associative learning principles (Davey, 1997; Field, 2006b; Field & Purkis, 2011; Mineka & Zinbarg, 2006). These models all have at their heart a stimulus-stimulus (S-S) association formed between a CS and US (i.e., between a previously neutral stimulus and an aversive stimulus). Traditionally, this "association" was seen as a mental connection between the relevant events and stimuli encountered during a learning episode (Hall, 2002; Pearce & Bouton, 2001).

However, decades of research has shown that these associations are not simple, automatic connections between two discrete stimuli but are highly detailed representations of the environment that contain information about past experience, learning context, features of the stimuli (and their existing associations to other things), and individual characteristics of the organism and can be influenced by nonautomatic processing. To reflect this complexity, Field and Purkis (2011) refer to a CS-US "link' because, unlike "association," this term does not imply automatic processing.

Figure 1 shows Field and Purkis' (2011) model, which integrates and updates ideas from earlier models (Davey, 1997; Field, 2006b; Mineka & Zinbarg, 2006). Direct traumatic experiences are at the center of Davey's and Mineka and Zinbarg's models. Verbal information and vicarious learning are conceptualized as vulnerability

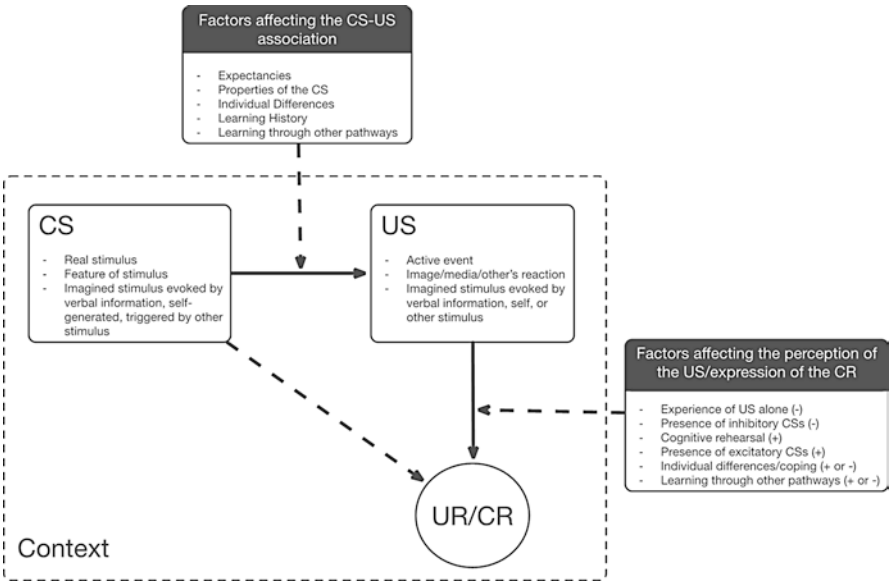

Fig. 1 Field and Purkis's (2011) associative learning model of fear

factors before learning (they create expectations that influence the strength of the link formed between the CS and US during a learning episode) or modifying factors after learning (e.g., information after the event that strengthens or weakens the CS-US link). In contrast, Field and Purkis suggest all three pathways can create a mental link between a stimulus and a threat-relevant outcome.

For example, in an informational learning event, a novel stimulus (CS) becomes linked with the threat information (US) and the related representations of threat (and its related qualia) that it evokes (Field, 2006b). Similarly, in vicarious learning the CS becomes linked with another person's observed response to threat (Mineka & Cook, 1993) and the related representations evoked by observing that response. Field and Purkis' model (2011; and Field, 2006c before it) also acknowledges work demonstrating that mental representations can act as CSs and USs (Dwyer, 1999, 2001, 2003; Dwyer, Mackintosh, & Boakes, 1998). For example, a US does not need to be a direct aversive experience; it can be an aversive thought, idea, or image.

To summarize the model, learning experiences forge links between a real or imagined neutral stimulus (CS) and real or imagined threat-related US (be it a direct experience, a distressing mental image, verbal information, or observing a fearful response to something). The link may be formed between the whole CS or specific salient features of it. Once the link is formed, it drives a fear response to the CS that was formerly evoked by the US. The strength of this response is determined by the strength of the link which itself is influenced by prior learning/experience (e.g., protective positive experiences), properties of the CS (e.g., the so-called "fear-relevant" stimuli such as spiders are primed to rapidly form a link to threat), and individual characteristics (such as behavioral inhibition). The strength of the conditioned fear response can also be influenced post-learning by habituation to the US, subsequent learning (e.g., verbal information that revalues the US as more threatening), the presence of other stimuli that reduce or enhance fear, and individual differences in how the learning event and US are processed (which, again, could be influenced by characteristics such as behavioral inhibition). Finally, the learning event itself occurs within a context that influences what is learnt. For example, CS-US links formed in specific contexts may only elicit fear responses in those same contexts.

Field and Lester (2010b) have further argued that associative learning can explain the emergence of attentional and interpretational aspects of anxious cognition. In the case of attentional bias to threat, if we assume that we are primed to attend to threat from an early age, then this system must learn what is and is not threatening (see the chapter "Attention Mechanisms in Behavioral Inhibition: Exploring, and Exploiting, the Environment" by Pérez-Edgar). When attending to the environment, an infant might pick up on the stimuli to which a caregiver is attending (through social referencing). In other words, caregivers direct attention to particular facets of the environment that then become a CS. The caregiver's own responses (vicarious learning) and responses involving the infant (e.g., removing them from the situation) act as a US that is linked to the facet of the environment to which attention was drawn.

Similarly, with interpretational biases, ambiguity (CS) in the environment will typically be resolved by a caregiver through verbal information or their reaction to the situation (vicarious learning). If the caregiver tends to resolve these situations in

a threatening way, then their child will form a strong link between ambiguity (CS) and threat outcomes (US). Essentially, over many trials, a caregiver prone to threat interpretations will "train" their child to have similar responses by forging an association between ambiguity and threat representations (see the chapter "The Social World of Behaviorally Inhibited Children: A Transactional Account" by Henderson et al.). Children's tendencies to interpret ambiguity in a threatening way have been linked to their mother's tendency to react cautiously to ambiguous situations (Lester, Seal, Nightingale, & Field, 2010).

Field and Purkis' (2011) model is a parsimonious account of how the three pathways to fear contribute to fear learning because it assumes that a single mechanism underlies all three pathways and that the pathways can, therefore, have additive and multiplicative effects on the strength of the CS-US link. It also allows for a coherent set of variables that impact on the CS-US link and the expression of fear regardless of which pathway, or combination of pathways, contributed to the formation of the CS-US link.

Theories of Behavioral Inhibition and the Behavioral Inhibition System

The models of anxiety just discussed acknowledge the role of individual differences in learning. For example, temperamental characteristics are believed to affect the strength of the link formed during a learning episode, as well as how the event is processed after learning (Fig. 1). Similarly, the trajectories of attentional and interpretational aspects of anxiety are assumed to interact with temperamental characteristics of the person. Many temperamental constructs predict fear and anxiety, including negative emotionality (Tellegen, 1985), negative affect (Clark & Watson, 1991), neuroticism-negative affect (Lonigan, Vasey, Phillips, & Hazen, 2004), fear (Rothbart, Ahadi, & Evans, 2000), and behavioral inhibition (Kagan, Reznick, & Snidman, 1987), suggesting that such constructs may be best viewed as different conceptualizations of trait anxiety (e.g., Field, 2006c; Lonigan et al., 2004). We discuss two of these—behavioral inhibition and behavioral inhibition system—in detail.

Behavioral Inhibition

Behavioral inhibition is a biologically driven trait defined by Kagan (Kagan, Reznick, Clarke, Snidman, & García-Coll, 1984) to describe a tendency to react to novel or unfamiliar situations with excessive apprehension, avoidance, and reticence (e.g., Fox, Henderson, Marshall, Nichols, & Ghera, 2005; Kagan, 1994; Kagan et al., 1987; Kagan, Reznick, & Gibbons, 1989; Kagan & Snidman, 1999). It is typically associated with a disposition to display extreme shyness, fearfulness,

and withdrawal (e.g., Hirshfeld-Becker, Biederman, & Rosenbaum, 2004) and is believed to have its basis in amygdala reactivity. Approximately 15% of infants show high levels of behavioral inhibition (Fox et al., 2005), and around 50% of children demonstrate stability in their behavioral inhibition from infancy through childhood (Kagan, 1994; Kagan, Reznick, Snidman, Gibbons, & Johnson, 1988) and adolescence (Kagan, Snidman, Kahn, & Towsley, 2007).

The persistence of behavioral inhibition may be influenced by other temperament or personality traits such as positive emotionality. Johnson et al. (2016) demonstrated that behavioral inhibition at age 3 was predictive of behavioral inhibition at age 6 only when children also presented with low to moderate levels of positive emotionality. This makes intuitive sense because children who have high levels of both behavioral inhibition and positive emotionality in early childhood may gradually become less inhibited as they develop due to positive emotionality encouraging approach behaviors and increasing exposure to novelty.

Early behavioral inhibition can be predictive of later psychopathology. Research on temperament has found that 21-month-old children categorized as having high levels of behavioral inhibition have a greater likelihood of presenting with specific fears and phobias at age 7–8 years compared to uninhibited children (Biederman et al., 1990). Behaviorally inhibited children are at greater risk of a number of other anxiety disorders (for a review, see Biederman, Rosenbaum, Chaloff, & Kagan, 1995; Rosenbaum et al., 1993), particularly social anxiety disorder (Chronis-Tuscano et al., 2009; Clauss & Blackford, 2012). Hudson and Dodd (2012) demonstrated that children categorized as high in behavioral inhibition at age 4 were at increased risk for social phobia, separation anxiety disorder, and generalized anxiety disorder at age 9. Highly behaviorally inhibited children were already at risk for specific phobia at age 4. In addition, Hudson and Dodd found that even after controlling for early anxiety at age 4, behavioral inhibition remained a significant predictor of anxiety at age 9 suggesting that while behavioral inhibition and early anxiety both contribute to later anxiety risk, they are relatively independent constructs (see the chapter "Behavioral Inhibition as a Precursor to Psychopathology" by Klein and Mumper).

The fact that behavioral inhibition in infancy predicts later anxiety symptoms suggests that (1) behavioral inhibition is an early manifestation of anxiety, (2) measures of behavioral inhibition act as proxy measures for trait anxiety, or (3) behavioral inhibition facilitates learning about threat. The first two possibilities both imply that behavioral inhibition and trait anxiety are the same or at least overlap conceptually. For example, the increased risk for fear and anxiety in behaviorally inhibited children may be part of a larger defensive response, or neurological system, which is triggered more easily in children with reactive temperaments. Such a system is described in Gray's (1970, 1987) reinforcement sensitivity theory of temperament. Gray suggested that a subcortical circuit known as the behavioral inhibition system, with its anatomical substrate in the septohippocampal system, controls the experience of anxiety in response to anxiety-relevant cues.

The Behavioral Inhibition System (BIS)

The BIS is thought to be sensitive to novelty, punishment, and lack of reward (or frustrative non-reward when, e.g., positive reinforcement is expected but not received). As such, the BIS activates when an individual is confronted with an unpredictable, aversive, or novel stimuli, leading to a fear response. Thus, from this perspective, sensitivity in arousal of particular brain areas leads to both behavioral consequences (such as avoidance behavior) as well as influencing fear conditioning itself (Gray, 1981). The behavioral outputs of the BIS include increases in attention and arousal and inhibition of ongoing behavior. In addition, higher sensitivity in the BIS leads to higher trait anxiety (Gray & McNaughton, 2003). Anxiety proneness may therefore be attributed to a lowered threshold for behavioral inhibition system activation (Gray, 1987). It is likely that there are temperamental differences between individuals in BIS functioning (Muris, Merckelbach, de Jong, & Ollendick, 2002). Gray (1987; Gray & McNaughton, 2003) argued that *activity* in the BIS/septo-hippocampal system corresponds to state anxiety and that individual differences in the *sensitivity* of the BIS to unpredictability and novelty corresponds to trait anxiety.

The BIS is, therefore, seen as a neurological system that underpins trait anxious responses to environmental stimuli. It can also be linked to the temperamental construct of behavioral inhibition. According to Lonigan et al. (2004), affect and temperament can be described by two high-order factors they call negative affectivity/neuroticism (NA/N) and positive affectivity/surgency (PA/S), with BIS aligned in particular with the NA/N factor. Lonigan and colleagues draw attention to the conceptual overlap between NA/N and behavioral inhibition, with children classified as high in behavioral inhibition also showing high NA/N characteristics such as verbal distress and inhibited approach. As a neurological construct, inhibited behavior is theorized to be one of the outputs of the BIS (Gray & McNaughton, 2003). Together this suggests that the BIS may be the neurological system underpinning at least one of the dimensions of behavioral inhibition. Given this link, high BIS sensitivity is often interpreted as indicative of high behavioral inhibition (though see Morgan, 2006).

Behavioral Inhibition and Associative Learning Models of Anxiety

As discussed, models of fear acquisition (e.g., Davey, 1997; Field, 2006c; Field & Purkis, 2011; Mineka & Zinbarg, 2006) emphasize the importance of the strength of the link between a CS and US. Field and Purkis argue that both direct and indirect experiences (i.e., contact with a direct aversive event, vicarious learning, and verbal information) reflect associative learning episodes that can lead to a mental representation in which a CS is linked with a US. In their model, temperament (e.g., trait anxiety, BIS sensitivity, behavioral inhibition) moderates the effects of these learning experiences. We will now look at the evidence supporting this model.

With respect to direct aversive learning experiences, Zinbarg and Mohlman (1998) used an approach-avoidance task in which participants discriminated cues (numbers on a computer screen such as 22 or 29) that signaled financial punishment (loss of 25 cents) and reward (gaining 25 cents) when a key was pressed. Essentially, participants had to decide for which cues they should press the key. Participants received blocks of 72 trials, and researchers measured the number of key presses to cues within each block and expectancies (a rating on a 9-point scale how likely they felt it was that they would lose/gain money) at the end of each block. Individuals high on self-reported BIS sensitivity acquired punishment expectancies faster than participants low in BIS sensitivity. As such, BIS sensitivity affected the speed of acquisition of punishment contingencies. This study shows how behavioral inhibition (as marked by BIS sensitivity) might contribute to fear learning by speeding up the rate of acquisition of threat contingencies.

There is also work showing that behavioral inhibition facilitates fear learning through the so-called indirect pathways. For example, a wealth of research has demonstrated that non-clinically anxious children show increased fear responses and attentional bias toward novel animals following threatening information about them, compared to other animals they have received positive or no information about (see above). Attentional bias effects found by Field (2006b) were relatively weak. This lead to further research exploring whether external factors, such as temperament, may have moderated the effects. Field (2006a) measured children's (age 6–9 years) behavioral avoidance (via a touch box task) and attentional bias (via a dot-probe task) toward novel animals paired with either threatening, positive, or no information. BIS sensitivity, measured via an age-downward version of Carver and White's (1994) BIS scale, was found to facilitate avoidance behavior for animals paired with threatening information, as well as attentional bias toward the threatening animal.

Field and Price-Evans (2009) extended these findings, demonstrating that children with greater BIS sensitivity also showed greater physiological responding (increases in heart rate) when they believed they were touching the threat information animal during an approach task. Therefore, findings suggest that children who were inherently vulnerable to acquire fears were more sensitive to the effects of threatening verbal information with the elicitation of fear responses in all three of Lang's (1968) fear response systems: cognition, behavioral avoidance, and physiological responding.

With regard to vicarious learning, Askew, Hagel, and Morgan (2015) explored the relation between levels of behavioral inhibition and the strength of vicarious learning of social anxiety in children. They measured social anxiety-related fear beliefs and emotional Stroop interference for social anxiety-related words after children watched animated films with either socially negative or socially neutral outcomes. They found that socially negative vicarious learning led to increases in children's social fear beliefs and an emotional Stroop bias for socially anxious words. Higher behavioral inhibition was associated with higher levels of social fear beliefs before and after vicarious learning.

These findings are all consistent with Field and Purkis' notion that temperamental characteristics such as behavioral inhibition/BIS sensitivity interact with associative fear learning processes to facilitate fear learning. As mentioned earlier,

attention to threat and the tendency to interpret ambiguity in a threatening way may be "trained," through associative learning, by parents and other key caregivers directing a child's attention toward threatening outcomes/situations (Field & Lester, 2010b) via social referencing. Social referencing, or social information gathering, is a crucial skill that infants develop around 10 months of age. This is the ability of infants to use emotional signals from adults to determine and modify behavioral and emotional responses when confronted with a novel or ambiguous situation or stimulus (Feinman, 1982; Feinman, Roberts, Hsieh, Sawyer, & Swanson, 1992). Feinman et al. (1992) suggested that children's responses in social referencing situations correspond to parental reactions, suggesting that parental appraisals in a novel or ambiguous situation directly influence the infant's response. Thus, social referencing may arguably be a mechanism involved in, and contributing to, vicarious fear learning (Aktar, Majdandzic, de Vente, & Bögels, 2013).

Behavioral inhibition can influence social referencing (e.g., Murray et al., 2008). Maternal anxiety may interact with behavioral inhibition to increase vulnerability to anxiety by encouraging avoidance behaviors, rather than facilitating positive engagement with novelty. Avoidance may also be coupled with a lack of positive reinforcement when approaching novel or potentially threatening situations (Fisak & Grills-Taquechel, 2007; Murray, Creswell, & Cooper, 2009). Using a range of situations (home and lab visits) and standardized tasks, Aktar et al. (2013) demonstrated that 12-month-old infants' avoidance of novel strangers or toys was predicted by the interaction between infant behavioral inhibition and expressed parental anxiety. Infants who were categorized as highly behaviorally inhibited showed greater fear and avoidance during social referencing, and this temperamental predisposition was more influential in determining fear responses than parental anxiety expressions.

De Rosnay, Cooper, Tsigaras, and Murray (2006) also demonstrated that 12- to 14-month-old infants categorized as highly inhibited were more vulnerable to the negative impact of anxious maternal expressions in response to strangers. In an experimental design, mothers' expressions were manipulated to be either socially anxious or nonanxious. They demonstrated that behavioral inhibition and maternal expressions of social anxiety predicted increased stranger avoidance in the anxious condition only, in that highly behaviorally inhibited infants were significantly more avoidant than low behaviorally inhibited infants. This finding indicates a causal role for expressed maternal anxiety on infant avoidance, moderated by infant behavioral inhibition.

Similarly, Murray et al. (2008) used a social referencing paradigm in which a female stranger conversed with mothers for 2 min with their child present; then the stranger approached the infant and picked them up. Findings indicated that behavioral inhibition moderates the effects of parental social anxiety disorder on children's avoidance. That is, infants high in behavioral inhibition who had clinically socially anxious mothers demonstrated more avoidant behaviors from 10 to 14 months. The relationship between parental anxiety and infant behavioral inhibition was attributed to lower levels of maternal encouragement to infants high in behavioral inhibition

As children develop and gain experience and confidence in novel situations, the effect of social referencing becomes indirect (Feinman et al., 1992). Inconsistent with previous findings with infants, Aktar, Majdandzic, de Vente, and Bögels (2014)

demonstrated that for toddlers (30 months old) categorized as high in behavioral inhibition, fear/avoidance responses were not predicted by parental trait or state anxiety. However, they did find that infants who were highly inhibited at 12 months were more likely to show fearful and avoidant responses in a maternal social referencing task at 30 months. This effect was not found for fathers. Thus, paternal social referencing appears to be independent of early behavioral inhibition, despite research implicating the important role of fathers in the development of child anxiety (e.g., Bögels & Perotti, 2011; Bögels & Phares, 2008).

The Influence of Behavioral Inhibition on the Strength of the CS-US Link

Differences in sensitivity to conditioning may mediate the effects of behavioral inhibition on fear and anxiety acquisition. There is some support (e.g., Kendler, Neale, Kessler, Heath, & Eaves, 1992) for a genetically based vulnerability to phobias that is mediated by fear conditioning (e.g., Hettema, Annas, Neale, Kendler, & Fredrikson, 2003) and personality variables such as trait anxiety. Studies have found that trait anxiety influences the speed and strength of conditioning, with more rapid and stronger aversive conditioning shown by individuals high in trait anxiety (e.g., Zinbarg & Mohlman, 1998). This may explain the role of high trait anxiety, and therefore also BIS sensitivity, as a vulnerability factor in phobia and anxiety acquisition.

The BIS may also interact with indirect pathways to fear by, for example, increasing US salience or threat expectancies, which serve to strengthen the CS-US link (Field & Purkis, 2011). Indeed, children who are categorized as high in behavioral inhibition have been found to show enhanced reactivity to stressors (Smoller et al., 2005). Compared to children categorized as low on behavioral inhibition, highly behaviorally inhibited children may experience an aversive US as more salient because of greater sensitivity to aversive events, leading to a stronger CS-US link and a larger learned fear response. Researchers have argued that the greater incidence of aversive life events or adverse family environments, such as parental divorce, found among clinically anxious children is not directly responsible for fear or anxiety acquisition. Rather, the impact of such negative events is worsened by vulnerability factors like behavioral inhibition (see the chapter "Behavioural Inhibition and the Prevention of Internalising Distress in Early Childhood" by Rapee and Bayer) (Spence & Dadds, 1996).

One mechanism via which the BIS may enhance reactivity to stressors is by increasing attentional bias toward threat-related stimuli given that high BIS sensitivity/trait anxiety is related to greater devotion of attentional resources to anxiogenic cues (see Gray & McNaughton, 2003). Research shows that BIS overactivity is associated with earlier and more frequent detection of aversive stimuli (Poy, Eixarch, & Avila, 2004) and BIS sensitivity is related to negative emotional processing (Gomez & Gomez, 2002). Theoretically, high BIS sensitivity is likely to

increase attention to negative USs, which in turn increase either the number of CS-US pairings or the salience of the US during learning.

Properties of the CS may also interact with behavioral inhibition to strengthen the CS-US link. In one study, Dubi, Rapee, Emerton, and Schniering (2008) explored whether fear relevance influenced the magnitude of the learning effect. They presented toddlers with one fear-relevant stimulus (e.g., a toy snake) and one fear-irrelevant stimulus (e.g., a flower) in the presence of either positive or negative expressions from the toddler's mother. They replicated De Rosnay et al.'s (2006) finding that children were more likely to react to the stimuli with fear after observing their mothers reacting negatively, regardless of fear relevance. However, highly behaviorally inhibited children showed no differences in learning compared to non-vulnerable children. It is possible that the differences in findings may have been due to the lack of highly behaviorally inhibited children in the sample or the fact that animal fear learning was studied rather than social anxiety.

Field and Purkis' model also emphasizes the importance of the child's prior learning experiences in strengthening the CS-US link. Specific parental rearing styles are likely to influence a child's learning history, expectancies, and coping strategies and may place a child at greater risk of clinically significant fear or anxiety. Parenting styles, defined as attitudes expressed toward the child across different situations, and parenting behaviors, which are expressed toward the child in specific situations, are thought to provide an emotional climate for the parent-child relationship (Baumrind, 1967). Critically, children who have high levels of behavioral inhibition are more likely to experience negative or hostile parenting (Hane, Cheah, Rubin, & Fox, 2008; Hirshfeld, Biederman, Brody, Faraone, & Rosenbaum, 1997), overinvolved or intrusive parenting (Degnan, Henderson, Fox, & Rubin, 2008; Hudson, Dodd, & Bovopoulos, 2011; Rapee, 2002; Rubin, Burgess, & Hastings, 2002), critical parenting characterized by dissatisfaction (e.g., Hirshfeld et al., 1997), overprotective parenting (Johnson et al., 2016), low levels of encouragement, positive reinforcement or autonomy promotion (Murray et al., 2008), and greater levels of control and derision (Rubin et al., 2002) that may contribute toward child anxiety (Murray et al., 2009).

The relation between these parenting styles/behaviors and the stability of behavioral inhibition over time is likely to have an effect on fear and anxiety acquisition through shaping the child's learning histories, expectancies, and coping (see Fig. 1). For instance, parents who allow their child autonomy and appropriate levels of independence are likely to provide their child with more opportunities to be exposed to novelty, which may present children with greater opportunities for positive or neutral learning with stimuli. Prior positive or neutral learning can inhibit subsequent negative fear-related learning (Askew et al., 2016; Golkar & Olsson, 2016) by creating neutral or positive expectancies about the outcome of a learning event with the stimulus. Moreover, autonomy and exposure to novel experiences may enhance children's coping and adaptive skills when faced with ambiguous or anxiety-eliciting situations, promoting a sense of competence and mastery and therefore leading to a gradual decrease in behavioral inhibition (e.g., Muris, van Brakel, Arntz, & Schouten, 2011).

The Influence of Post-Learning Processes on the Strength of the Learned Response

As identified above, a number of post-learning processes may also contribute to the strength of the response. One such factor is individual coping styles in that operant conditioning processes may contribute to the strengthening of the response by reinforcing avoidance strategies. One of the outputs of the BIS is the inhibition of ongoing behavior (Gray & McNaughton, 2003), and avoidance behavior may be viewed as an extreme form of inhibition (Field, 2006a). During development, children categorized as highly behaviorally inhibited are more likely to experience social rejection and are more likely to avoid social stressors and respond to rejection with avoidant coping (e.g., Fox et al., 2005). Therefore, higher levels of BIS sensitivity (or trait anxiety) in children would be associated with greater motivation to avoid novel stimuli associated with threat and consequently would lead to inhibition of approach behavior and greater avoidance behavior. The avoidance is likely to be negatively reinforced by reducing levels of anxiety as a result of less exposure (see Weems & Stickle, 2005) and also by caregivers through inadvertent approval of avoidance behaviors.

If behavioral avoidance limits the variability of children's learning histories, they will have fewer opportunities for positive encounters with stimuli. Learning theory predicts that subsequent aversive experiences with a stimulus would therefore have greater negative impact because learning for stimulus-threat outcome contingencies is uninhibited (Field, 2006c). Taken together, based on Field and Purkis' model (Fig. 1), poor coping skills, such as avoidance behaviors, are likely to inflate the aversiveness of the US and subsequently enhance the CR.

Research has also shown that infant development is improved if highly behaviorally inhibited children are provided with opportunities to socialize with others, for example, by being placed in nonparental caregiving environments (e.g., Almas et al., 2011; Furman, Rahe, & Hartup, 1979). In support, Laird, Pettit, and Mize (1994) found that interacting with other children, combined with mother-child conversations about the child's peers, was associated with enhanced child competence.

Conclusion

Behavioral inhibition interacts with associative fear learning processes to facilitate fear learning. Temperament is thought to moderate the effects of both direct (contact with a direct aversive event) and indirect (via transmission of information or vicarious learning) associative learning episodes. This chapter has outlined the influence of behavioral inhibition and the behavioral inhibition system on relevant associative learning models of anxiety, with an emphasis on the influence of behavioral inhibition on the strength of the CS-US link and the influence of post-learning processes

on the strength of the learned response. This is an important addition to our understanding of how temperament factors such as behavioral inhibition and BIS sensitivity moderate the effects of negative learning experiences and contribute to fear learning in children. Increasing understanding of the interaction between temperament and environmental factors during fear learning has the potential to improve early identification of children who are particularly vulnerable to developing fears and phobias. Preventative interventions could be specifically targeted at these children, as well as more effective treatments should develop fear and anxiety.

References

Aktar, E., Majdandzic, M., de Vente, W., & Bögels, S. M. (2013). The interplay between expressed parental anxiety and infant behavioural inhibition predicts infant avoidance in a social referencing paradigm. *The Journal of Child Psychology and Psychiatry, 54*, 144–156.

Aktar, E., Majdandzic, M., de Vente, W., & Bögels, S. M. (2014). Parental social anxiety disorder prospectively predicts toddlers' fear/avoidance in a social referencing paradigm. *Journal of Child Psychology and Psychiatry, 55*, 77–87.

Almas, A. N., Degnan, K. A., Fox, N. A., Phillips, D. A., Henderson, H. A., Moas, O. L., & Hane, A. A. (2011). The relations between infant negative reactivity, non-maternal childcare, and children's interactions with familiar and unfamiliar peers. *Social Development, 20*, 718–740.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Askew, C., Dunne, G., Özdil, Z., Reynolds, G., & Field, A. P. (2013). Stimulus fear-relevance and the vicarious learning pathway to fear. *Emotion, 13*, 915–925.

Askew, C., & Field, A. P. (2007). Vicarious learning and the development of fears during childhood. *Behaviour Research and Therapy, 45*, 2616–2627.

Askew, C., Hagel, A., & Morgan, J. (2015). Vicarious learning of children's social-anxiety-related fear beliefs and emotional Stroop bias. *Emotion, 15*(4), 501–510.

Askew, C., Reynolds, G., Fielding-Smith, S., & Field, A. P. (2016). Inhibition of vicariously learned fear in children using positive modeling and prior exposure. *Journal of Abnormal Psychology, 125*(2), 279–291.

Baumrind, D. (1967). Child care practices anteceding three patterns of preschool behavior. *Genetic Psychology Monographs, 75*, 43–88.

Biederman, J., Rosenbaum, J. F., Chaloff, J., & Kagan, J. (1995). Behavioral inhibition as a risk factor for anxiety disorders. In J. S. March (Ed.), *Anxiety disorders in children and adolescents*. New York, NY: Guilford Press.

Biederman, J., Rosenbaum, J. F., Hirshfeld, D. R., Farone, S. V., Bolduc, E. A., Gersten, M., et al. (1990). Psychiatric correlates of behavioral inhibition in young children of parents with and without psychiatric disorders. *Archives of General Psychiatry, 47*, 21–26.

Bögels, S. M., & Perotti, E. C. (2011). Does father know best? A formal model of the paternal influence on childhood social anxiety. *Journal of Child and Family Studies, 20*, 171–181.

Bögels, S. M., & Phares, V. (2008). Fathers' role in the etiology, prevention and treatment of child anxiety: A review and a new model. *Clinical Psychology Review, 28*, 539–558.

Broeren, S., Lester, K. J., Muris, P., & Field, A. P. (2011). They are afraid of the animal, so therefore I am too: Influence of peer modeling on fear beliefs and approach-avoidance behaviors towards animals in typically developing children. *Behaviour Research and Therapy, 49*(1), 50–57. https://doi.org/10.1016/j.brat.2010.11.001

Carver, C. S., & White, T. L. (1994). Behavioral inhibition, behavioural activation, and affective responses to impending reward and punishment: The BIS/BAS scales. *Journal of Personality and Social Psychology, 67*, 319–333.

Chronis-Tuscano, A., Degnan, K. A., Pine, D. S., Pérez-Edgar, K., Henderson, H. A., & Diaz, Y. (2009). Stable early maternal report of behavioral inhibition predicts lifetime social anxiety disorder in adolescence. *Journal of the American Academy of Child and Adolescent Psychiatry, 48*, 928–935.

Clark, L. A., & Watson, D. (1991). Tripartite model of anxiety and depression: Psychometric evidence and taxonomic implications. *Journal of Abnormal Psychology, 100*, 316–336.

Clauss, J. A., & Blackford, J. U. (2012). Behavioral inhibition and risk for developing social anxiety disorder: A meta-analytic study. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*, 1066–1075.

Davey, G. C. L. (1997). A conditioning model of phobias. In G. C. L. Davey (Ed.), *Phobias: A handbook of theory, research and treatment* (pp. 301–322). Chichester, England: Wiley.

De Rosnay, M., Cooper, P. J., Tsigaras, N., & Murray, L. (2006). Transmission of social anxiety from mother to infant: An experimental study using a social referencing paradigm. *Behaviour Research and Therapy, 44*, 1165–1175.

Degnan, K. A., Henderson, H. A., Fox, N. A., & Rubin, K. H. (2008). Predicting social wariness in middle childhood: The moderating roles of childcare history, maternal personality and maternal behavior. *Social Development, 17*, 471–487.

Dubi, K., Rapee, R. M., Emerton, J. L., & Schniering, C. A. (2008). Maternal modeling and the acquisition of fear and avoidance in toddlers: Influence of stimulus preparedness and child temperament. *Journal of Abnormal Child Psychology, 36*, 499–512.

Dunne, G., & Askew, C. (2013). Vicarious learning and un-learning of fear in children via mother and stranger models. *Emotion, 13*, 974–980.

Dwyer, D. M. (1999). Retrospective revaluation or mediated conditioning? The effect of different reinforcers. *The Quarterly Journal of Experimental Psychology Section B, 52*(4), 289–306.

Dwyer, D. M. (2001). Mediated conditioning and retrospective revaluation with LiCl then flavour pairings. *The Quarterly Journal of Experimental Psychology Section B, 54*(2), 145–165.

Dwyer, D. M. (2003). Learning about cues in their absence: Evidence from flavour preferences and aversions. *The Quarterly Journal of Experimental Psychology Section B, 56*(1), 56–67.

Dwyer, D. M., Mackintosh, N. J., & Boakes, R. A. (1998). Simultaneous activation of the representations of absent cues results in the formation of an excitatory association between them. *Journal of Experimental Psychology: Animal Behavior Processes, 24*(2), 163–171.

Eley, T. C., McAdams, T. A., Rijsdijk, F. V., Lichtenstein, P., Narusyte, J., Reiss, D., … Neiderhiser, J. M. (2015). The intergenerational transmission of anxiety: A children-of-twins study. *American Journal of Psychiatry, 172*, 630–637.

Feinman, B. (1982). Social referencing in infancy. *Merrill-Palmer Quarterly, 28*, 445–470.

Feinman, S., Roberts, D., Hsieh, K., Sawyer, D., & Swanson, D. (1992). A critical review of social referencing in infancy. In S. Feinman (Ed.), *Social referencing and the social construction of reality in infancy* (pp. 4–15). New York, NY: Plenum Press.

Ferrari, M. (1986). Fears and phobias in childhood: Some clinical and developmental considerations. *Child Psychiatry and Human Development, 17*, 75–87.

Field, A. P. (2006a). The behavioral inhibition system and the verbal information pathway to children's fears. *Journal of Abnormal Psychology, 115*(4), 742–752.

Field, A. P. (2006b). Watch out for the beast: Fear information and attentional bias in children. *Journal of Clinical Child and Adolescent Psychology, 35*, 431–439.

Field, A. P. (2006c). Is conditioning a useful framework for understanding the development and treatment of phobias? *Clinical Psychology Review, 26*, 857–875.

Field, A. P., & Lawson, J. (2003). Fear information and the development of fears during childhood: Effects on implicit fear responses and behavioral avoidance. *Behavior Research and Therapy, 41*, 1277–1293.

Field, A. P., & Lawson, J. (2008). The verbal information pathway to fear and subsequent causal learning in children. *Cognition & Emotion, 22*(3), 459–479. https://doi.org/10.1080/02699930801886532

Field, A. P., Lawson, J., & Banerjee, R. (2008). The verbal threat information pathway to fear in children: The longitudinal effects of fear cognitions and the immediate effects on avoidance behavior. *Journal of Abnormal Psychology, 117*, 214–224.

Field, A. P., & Lester, K. J. (2010a). Is there room for 'development' in developmental models of information processing biases to threat in children and adolescents? *Clinical Child and Family Psychology Review, 13*(4), 315–332. https://doi.org/10.1007/s10567-010-0078-8

Field, A. P., & Lester, K. J. (2010b). Learning of information processing biases in anxious children and adolescents. In J. A. Hadwin & A. P. Field (Eds.), *Information processing biases and anxiety: A developmental perspective* (pp. 253–278). Chichester, England: Wiley-Blackwell.

Field, A. P., & Price-Evans, K. (2009). The behavioral inhibition system moderates the effect of the verbal threat information pathway on children's heart rate responses to novel animals. *Behaviour Research and Therapy, 47*, 431–436.

Field, A. P., & Purkis, H. M. (2011). The role of learning in the aetiology of child and adolescent fear and anxiety. In W. K. Silverman & A. P. Field (Eds.), *Anxiety disorders in children and adolescents: Research, assessment and intervention* (2nd ed., pp. 227–256). Cambridge, England: Cambridge University Press.

Field, A. P., & Schorah, H. (2007). The verbal information pathway to fear and heart rate changes in children. *Journal of Child Psychology and Psychiatry, 48*(11), 1088–1093. https://doi.org/10.1111/j.1469-7610.2007.01772.x

Field, A. P., & Storksen-Coulson, H. (2007). The interaction of pathways to fear in childhood anxiety: A preliminary study. *Behaviour Research and Therapy, 45*(12), 3051–3059. https://doi.org/10.1016/j.brat.2007.09.001

Fisak, B., Jr., & Grills-Taquechel, E. A. (2007). Parental modelling, reinforcement, and information transfer: Risk factors in the development of child anxiety? *Clinical Child and Family Psychology Review, 10*, 213–231.

Fox, N. A., Henderson, H. A., Marshall, P. J., Nichols, K. E., & Ghera, M. M. (2005). Behavioural inhibition: Linking biology and behaviour within a developmental framework. *Annual Review of Psychology, 56*, 235–262.

Furman, W., Rahe, D. F., & Hartup, W. W. (1979). Rehabilitation of socially withdrawn preschool children through mixed-age and same-age socialization. *Child Development, 50*, 915–922.

Golkar, A., & Olsson, A. (2016). Immunization against social fear learning. *Journal of Experimental Psychology: General, 145*, 665–671.

Gomez, A., & Gomez, R. (2002). Personality traits of the behavioral approach and inhibition systems: Associations with processing of emotional stimuli. *Personality and Individual Differences, 32*, 1299–1316.

Gray, J. A. (1970). The psychophysiological basis of introversion-extraversion. *Behavior Research and Therapy, 8*, 249–266.

Gray, J. A. (1981). A critique of Eysenck's theory of personality. In H. J. Eysenck (Ed.), *A model for personality* (pp. 246–276). Berlin, Germany: Springer.

Gray, J. A. (1987). Perspectives on anxiety and impulsivity: A commentary. *Journal of Research in Personality, 21*, 493–509.

Gray, J. A., & McNaughton, N. (2003). *The neuropsychology of anxiety: An enquiry into the functions of the septo-hippocampal system*. Oxford, England: Oxford University Press.

Gregory, A. M., & Eley, T. C. (2011). The genetic basis of child and adolescent anxiety. In W. K. Silverman & A. P. Field (Eds.), *Anxiety disorders in children and adolescents* (2nd ed., pp. 161–178). Cambridge, England: Cambridge University Press.

Gullone, E. (2000). The development of normal fear: A century of research. *Clinical Psychology Review, 20*, 429–451.

Hall, G. (2002). Associative structures in Pavlovian and instrumental conditioning. In C. R. Gallistel (Ed.), *Stevens' handbook of experimental psychology* (Vol. 3, 3rd ed., pp. 1–45). New York, NY: Wiley.

Hane, A. A., Cheah, C., Rubin, K. H., & Fox, N. A. (2008). The role of maternal behaviour in the relation between shyness and social reticence in early childhood and social withdrawal in middle childhood. *Social Development, 17*(4), 795–811.

Hettema, J. M., Annas, P., Neale, M. C., Kendler, K. S., & Fredrikson, M. (2003). A twin study of the genetics of fear conditioning. *Archives of General Psychiatry, 60*, 702–707.

Hirshfeld, D. R., Biederman, J., Brody, L., Faraone, S. V., & Rosenbaum, J. F. (1997). Expressed emotion toward children with behavioral inhibition: Associations with maternal anxiety disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*, 910–917.

Hirshfeld-Becker, D. R., Biederman, J., & Rosenbaum, J. F. (2004). Behavioral Inhibition. In T. L. Morris & J. S. March (Eds.), *Anxiety disorders in children and adolescents* (pp. 27–58). New York, NY: Guildford Press.

Hudson, J. L., & Dodd, H. F. (2012). Informing early intervention: Preschool predictors of anxiety disorders in middle childhood. *PLos One, 7*, e42359.

Hudson, J. L., Dodd, H. F., & Bovopoulos, N. (2011). Temperament, family environment and anxiety in preschool children. *Journal of Abnormal Child Psychology, 39*, 939–951.

Johnson, V. C., Olino, T. M., Klein, D. N., Dyson, M. W., Bufferd, S. J., Durbin, C. E., … Hayden, E. P. (2016). A longitudinal investigation of predictors of the association between age 3 and age 6 behavioural inhibition. *Journal of Research in Personality, 63*, 51–61.

Kagan, J. (1994). Inhibited and uninhibited temperaments. In W. B. Carey & S. C. McDevitt (Eds.), *Prevention and early intervention: Individual differences as risk factors for the mental health of children* (pp. 35–41). New York, NY: Brunner/Mazel.

Kagan, J., Reznick, J. S., Clarke, C., Snidman, N., & García-Coll, C. (1984). Behavioral inhibition to the unfamiliar. *Child Development, 55*, 2212–2225.

Kagan, J., Reznick, J. S., & Gibbons, J. (1989). Inhibited and uninhibited types of children. *Child Development, 58*, 1459–1473.

Kagan, J., Reznick, J. S., & Snidman, N. (1987). The physiology and psychology of behavioral inhibition in children. *Child Development, 58*, 1459–1473.

Kagan, J., Reznick, J. S., Snidman, N., Gibbons, J., & Johnson, M. O. (1988). Childhood derivatives of inhibition lack of inhibition to the unfamiliar. *Child Development, 59*, 1580–1589.

Kagan, J., & Snidman, N. (1999). Early childhood predictors of adult anxiety disorders. *Society of Biological Psychiatry, 46*, 1536–1541.

Kagan, J., Snidman, N., Kahn, V., & Towsley, S. (2007). The preservation of two infant temperaments into adolescence. In *Monographs of the Society for Research in Child Development, No. 287*. Boston, MA: Blackwell.

Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1992). The genetic epidemiology of phobias in women: The interrelationship of agoraphobia, social phobia, situational phobia, and simple phobia. *Archives of General Psychiatry, 49*, 273–281.

King, N. J., Hamilton, D. I., & Ollendick, T. H. (1988). *Children's phobias: A behavioural perspective*. Chichester, England: Wiley.

Laird, R. D., Pettit, G. S., & Mize, J. (1994). Motherchild conversations about peers: Contributions to competence. *Family Relations, 43*, 425–432.

Lang, P. J. (1968). Fear reduction and fear behavior: Problems in treating a construct. In J. M. Schlien (Ed.), *Research in psychotherapy* (Vol. 3, pp. 90–102). Washington, DC: American Psychological Association.

Lester, K. J., Seal, K., Nightingale, Z. C., & Field, A. P. (2010). Are children's own interpretations of ambiguous situations based on how they perceive their mothers have interpreted ambiguous situations for them in the past? *Journal of Anxiety Disorders, 24*(1), 102–108.

LoBue, V., & Rakison, D. H. (2013). What we fear most: A developmental advantage for threat-relevant stimuli. *Developmental Review, 33*(4), 285–303.

Lonigan, C. J., Vasey, M. W., Phillips, B. M., & Hazen, R. A. (2004). Temperament, anxiety, and the processing of threat-relevant stimuli. *Journal of Clinical Child and Adolescent Psychology, 33*, 8–20.

Mathews, A., & MacLeod, C. (2002). Induced processing biases have causal effects on anxiety. *Cognition & Emotion, 16*(3), 331–354.

Mineka, S., & Cook, M. (1993). Mechanisms involved in the observational conditioning of fear. *Journal of Experimental Psychology: General, 122*(1), 23–38.

Mineka, S., & Zinbarg, R. (2006). A contemporary learning theory perspective on the etiology of anxiety disorders. It's not what you thought it was. *American Psychologist, 61*, 10–26.

Morgan, B. E. (2006). Behavioral inhibition: A neurobiological perspective. *Current Psychiatry Reports, 8*, 270–278. https://doi.org/10.1007/s11920-006-0062-7

Muris, P. (2007). *Normal and abnormal fear and anxiety in children and adolescents*. Oxford, England: Elsevier.

Muris, P., & Field, A. P. (2010). The role of verbal threat information in the development of childhood fear. "Beware the Jabberwock!". *Clinical Child and Family Psychology Review, 13*, 129–150.

Muris, P., Merckelbach, H., de Jong, P. J., & Ollendick, T. H. (2002). The etiology of specific fears and phobias in children: A critique of the non-associative account. *Behaviour Research and Therapy, 40*, 185–195.

Muris, P., Merckelbach, H., Mayer, B., & Prins, E. (2000). How serious are common childhood fears? *Behaviour Research and Therapy, 38*, 217–228.

Muris, P., van Brakel, A. M. L., Arntz, A., & Schouten, E. (2011). Behavioral inhibition as a risk factor for the development of childhood anxiety disorders: A longitudinal study. *Journal of Child and Family Studies, 20*(2), 157–170.

Murray, L., Creswell, C., & Cooper, P. J. (2009). The development of anxiety disorders in childhood: An integrative review. *Psychological Medicine, 39*, 1413–1423.

Murray, L., De Rosnay, M., Pearson, J., Bergeron, C., Schofield, E., Royal-Lawson, M., & Cooper, P. J. (2008). Intergenerational transmission of social anxiety: The role of social referencing processes in infancy. *Child Development, 79*, 1049–1064.

Pearce, J. M., & Bouton, M. E. (2001). Theories of associative learning in animals. *Annual Review of Psychology, 52*, 111–139.

Poy, R., Eixarch, M. D., & Avila, C. S. (2004). On the relationship between attention and personality: Covert visual orienting of attention in anxiety and impulsivity. *Personality and Individual Differences, 36*, 1471–1481.

Price-Evans, K., & Field, A. P. (2008). A neglectful parenting style moderates the effect of the verbal threat information pathway on children's heart rate responses to novel animals. *Behavioural and Cognitive Psychotherapy, 36*(4), 473–482. https://doi.org/10.1017/s1352465808004396

Rachman, S. J. (1977). The conditioning theory of fear acquisition: A critical examination. *Behaviour Research and Therapy, 15*, 372–387.

Rapee, R. (2002). The development and modification of temperamental risk for anxiety disorders: Prevention of a lifetime of anxiety? *Biological Psychiatry, 52*, 941–957.

Reynolds, G., Field, A., & Askew, C. (2014). Effect of vicarious fear learning on children's heart rate responses and attentional bias for novel animals. *Emotion, 14*, 995–1006.

Reynolds, G., Field, A. P., & Askew, C. (2015). Preventing the development of observationally learnt fears in children by devaluing the model's negative response. *Journal of Abnormal Child Psychology, 43*(7), 1355–1367.

Rosenbaum, J. F., Biederman, J., Bolduc-Murphy, E. A., Faraone, S. V., Chaloff, J., Hirshfeld, D. R., & Kagan, J. (1993). Behavioural inhibition in childhood: A risk factor for anxiety disorders. *Harvard Review of Psychiatry, 1*, 2–16.

Rothbart, M. K., Ahadi, S. A., & Evans, D. E. (2000). Temperament and personality: Origins and outcomes. *Journal of Personality and Social Psychology, 78*, 122–135.

Rubin, K. H., Burgess, K. B., & Hastings, P. D. (2002). Stability and social-behavioral consequences of toddlers' inhibited temperament and parenting behaviors. *Child Development, 73*, 483–495.

Santiago, P. N., Ursano, R. J., Gray, C. L., Pynoos, R. S., Spiegel, D., Lewis-Fernandez, R., … Fullerton, C. S. (2013). A systematic review of PTSD prevalence and trajectories in DSM-5 defined trauma exposed populations: Intentional and non-intentional traumatic events. *PLoS One, 8*(4), e59236.

Silverman, W. K., & Field, A. P. (Eds.). (2011). *Anxiety disorders in children and adolescents: Research, assessment and intervention* (2nd ed.). Cambridge, England: Cambridge University Press.

Smoller, J. W., Yamaki, L. H., Fagerness, J. A., Biederman, J., Racette, S., Laird, N. M., … Sklar, P. B. (2005). The corticotropin-releasing hormone gene and behavioral inhibition in children at risk for panic disorder. *Biological Psychiatry, 57*, 1485–1492.

Spence, S. H., & Dadds, M. R. (1996). Preventing childhood anxiety disorders. *Behaviour Change, 13*, 241–249.

Tellegen, A. (1985). Structure of mood and personality and their relevance to assessing anxiety, with an emphasis on self-report. In A. H. Tuma & J. D. Maser (Eds.), *Anxiety and the anxiety disorders* (pp. 681–706). Hillsdale, NJ: Erlbaum.

Trickey, D., Siddaway, A. P., Meiser-Stedman, R., Serpell, L., & Field, A. P. (2012). A meta-analysis of risk factors for post-traumatic stress disorder in children and adolescents. *Clinical Psychology Review, 32*(2), 122–138.

Watson, J. B., & Rayner, R. (1920). Conditioned emotional reaction. *Journal of Experimental Psychology, 3*, 1–14.

Weems, C. F., & Stickle, T. R. (2005). Anxiety disorders in childhood: Casting a nomological net. *Clinical Child and Family Psychology Review, 8*, 107–134.

Zinbarg, R. E., & Mohlman, J. (1998). Individual differences in the acquisition of affectively valenced associations. *Journal of Personality and Social Psychology, 74*, 1024–1040.

Behavioral Inhibition as a Precursor to Psychopathology

Daniel N. Klein and Emma E. Mumper

Abstract Understanding the association between temperamental behavioral inhibition (BI) and psychopathology has implications for elucidating etiological factors, identifying early indicators of risk, and informing prevention. We begin by discussing the relations between behavioral inhibition and other widely used temperament/personality constructs and go on to outline a number of conceptual models of the temperament-psychopathology relationship. We then review data from cross-sectional, follow-up, and family studies that are relevant to these models. The data indicate that behavioral inhibition is associated with the anxiety disorders, particularly social anxiety disorder, and possibly with depressive disorders as well. Of the various conceptual models of temperament and psychopathology, the literature provides the greatest support for behavioral inhibition as being at least partially distinct from anxiety, but predisposing to the development of anxiety disorders in the presence of neurocognitive and environmental moderators. Moreover, behavioral inhibition appears to influence and be influenced by other factors, suggesting that levels of temperamental vulnerability may change over time, consistent with a dynamic vulnerability model. In contrast, behavioral inhibition does not simply appear to be a milder form of, or precursor to, anxiety disorders. We conclude by considering the heterogeneity of behavioral inhibition and its role within broader frameworks for psychopathology.

The construct of temperamental behavioral inhibition (BI) was introduced by Kagan (e.g., Kagan, Reznick, Clarke, Snidman, & Garcia-Coll, 1984) to refer to young children who exhibit fear, wariness, and reticence in unfamiliar situations and with unfamiliar people. The implications of behavioral inhibition for psychopathology were recognized fairly early, with links posited initially with panic disorder and later with social anxiety disorder (i.e., social phobia) (Rosenbaum, Biederman, Hirshfeld, Bolduc, & Chaloff, 1991). Notably, the construct of behavioral inhibition and subsequent research on its links with psychopathology has focused almost

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exclusively on young children. In contrast, the larger literature on the associations of temperament and personality with psychopathology has focused primarily on adolescents and adults. Hence, these two literatures have evolved separately, with less contact than might be expected given their overlapping concerns (for an exception, see Pérez-Edgar & Guyer, 2014). In this chapter, we will examine the link between behavioral inhibition and psychopathology within the broader framework of conceptualizing the relationship between temperament/personality and psychopathology. We should note that, consistent with others (e.g., Caspi & Shiner, 2006), we do not believe that there is a fundamental distinction between temperament and personality traits but generally follow the convention of applying the former term to younger children and the latter term to older youth and adults.

Behavioral Inhibition and Models of Temperament/ Personality Traits

Behavioral inhibition represents a unique and distinct stream within developmental and personality psychology. First, as noted above, the behavioral inhibition literature has been largely limited to infants and young children, although there has been some interest in presentations of behavioral inhibition in older youth and adults, and measures of behavioral inhibition in adults (or adults' retrospective reports of behavioral inhibition in childhood) have been developed (e.g., Gladstone & Parker, 2005). In contrast, research on other dispositional traits has often been conducted with a variety of age groups, ranging from early childhood to old age, with increasing evidence of continuity across the lifespan (Caspi & Shiner, 2006). Second, behavioral inhibition was developed inductively based on observations rather than derived from theory (e.g., Big Three models) or lexical analysis (e.g., the Big Five) (John, Naumann, & Soto, 2008). Third, it focuses on a single trait rather than aiming to create a model or taxonomy of the broad domain of temperament. Fourth, Kagan (e.g., Kagan, 2003) conceptualized behavioral inhibition as a categorical construct, although many current behavioral inhibition researchers treat it as continuous. In contrast, most other temperament/personality models treat traits as continuous dimensions. A categorical conceptualization of behavioral inhibition aligns well with traditional psychiatric classification systems, which conceptualize disorders as present or absent. However, psychopathology is increasingly being viewed as continuous (e.g., Widiger & Samuel, 2005), and the preference for dimensional models may influence views of behavioral inhibition. Finally, behavioral inhibition has traditionally been assessed with observations of infants' and children's responses to situations and stimuli arranged by the experimenter, although parent-report questionnaires for behavioral inhibition are also used. In contrast, research on most other temperament and personality traits typically rely on self- and parent-report questionnaires.

It is useful to locate behavioral inhibition in the conceptual space created by comprehensive trait models, particularly the Big Three: neuroticism (N), extraversion (E), and constraint (C). N refers to the disposition to experience negative emotions,

such as fear, sadness, and irritability. E refers to a tendency toward positive affect, sociability, reward sensitivity, and engagement with the environment. C refers to having a high level of inhibitory control (often referred to as effortful control in children), as opposed to impulsivity and risk-taking. Behavioral inhibition intersects with all three higher-order dimensions, overlapping with N, particularly the facet of fearfulness; low E, especially low levels of the facet of sociability; and C, particularly as reflected by constrained, inhibited behavior. However, behavioral inhibition is an inherently contextual construct, differing from temperament/personality traits which are presumed to be evident across situations. Thus, behavior associated with N/fearfulness, low E/sociability, and C/inhibition is much more likely to be evident in unfamiliar situations and with unfamiliar people than in familiar contexts (Laptook, Klein, Olino, Dyson, & Carlson, 2010).

The rich connections between the personality and psychopathology literatures provide clues regarding the trait-psychopathology relations expected for behavioral inhibition. Thus, N is associated with all forms of psychopathology, but particularly with internalizing disorders such as depressive and anxiety disorders. Low E is associated with depression and to a lesser degree with social anxiety disorder (SAD). Within E the link with depression is primarily due to positive affectivity, while the relationship with social anxiety disorder is primarily due to low sociability (Watson, Stasik, Ellickson-Larew, & Stanton, 2015). In contrast, high E may be associated with externalizing disorders such as substance use disorders and antisocial personality and conduct disorder, particularly when the measure of E emphasizes content related to impulsivity and venturesomeness. Finally, externalizing disorders are characterized by low C (Clark, 2005). From this perspective, behavioral inhibition should exhibit the strongest associations with anxiety disorders and especially social anxiety disorder. In addition, one might expect some degree of association with depressive disorders and a null or inverse association with externalizing disorders.

Models of Temperament and Psychopathology

A variety of conceptual models of the relation between temperament and psychopathology have been proposed (e.g., Clark, 2005; Klein, Dyson, Kujawa, & Kotov, 2012; Krueger & Tackett, 2003). As outlined in Table 1, they include the following: (1) Temperament and psychopathology have common causes. (2) Temperament traits and mental disorders are part of a continuous spectrum. (3) Temperament traits are precursors of mental disorders. (4) Temperament predisposes individuals to developing psychopathology. (5) Temperament has pathoplastic effects on psychopathology (i.e., it affects the expression or course of symptoms, without influencing the likelihood of onset). (6) Temperament traits are state-dependent concomitants of psychiatric symptoms. (7) Temperament traits are consequences (or scars) of psychopathology. The distinctions between some of these accounts are subtle, and the models are not mutually exclusive. However, they provide a useful framework for thinking about temperament-psychopathology relationships.

Table 1 Key predictions of models of temperament/personality-psychopathology relationships

Model	Predictions about behavioral inhibition and its relation to psychopathology
Common cause	Shared etiology accounts for much of the observed association of trait and disorder
Continuum/ spectrum	Similar etiology; trait-disorder association is specific to that disorder and nonlinear (i.e., at one point on trait dimension, risk for disorder sharply increases)
Precursor	Similar etiology; trait predicts subsequent onset of disorder
Predisposition	Trait predicts disorder onset, but other variables mediate or moderate this link
Pathoplasticity	Trait predicts variation in the presentation or course of the disorder
Concomitants	Trait is altered during an episode of the disorder but returns to premorbid level after recovery
Consequences/ scars	Trait is altered during an episode of the disorder and the change persists even after recovery

The seven models can be divided into three groups (Klein, Kotov, & Bufferd, 2011). The first three models (common cause, continuum/spectrum, and precursor) view temperament and psychopathology as having similar causal influences but do not see one domain as having a causal influence on the other. The fourth and fifth models (predisposition and pathoplasticity) hold that temperament has causal effects on the onset or maintenance of psychopathology. The sixth and seventh models (concomitants and consequences) view psychopathology as having a causal influence on temperament.

The *common cause model* views temperament and mental disorders as distinct entities that arise from the same, or at least an overlapping, set of etiological processes. From this perspective, temperament and psychopathology are not directly related. Rather, the association is due to shared third variables, for example, overlapping sets of genes or common biological or environmental processes.

The *spectrum model* emphasizes the conceptual and phenotypic overlap between temperament and psychopathology and argues for a fundamental continuity between them. A mental disorder is thought to characterize individuals who have the most extreme scores on a relevant trait. Like the common cause model, the spectrum model assumes that temperament and psychopathology arise from similar, if not identical, causal factors. However, it goes further in positing that the association between the trait and disorder should be fairly specific (i.e., there should be a high degree of homotypic continuity), as they are on the same continuum. Moreover, this association is expected to approximate a nonlinear step function, so that almost nobody below a particular point, or threshold, on the trait dimension has the diagnosis but nearly everyone above that point meets criteria for the disorder.

The *precursor model* views temperament as an early manifestation of the disorder. Like the common cause and spectrum accounts, the precursor model posits that temperament and psychopathology are caused by similar etiologic factors. Also like the spectrum account, it implies that there is at least some phenotypic similarity between the trait and the disorder. However, the precursor model differs from both

of these other models in that it assumes a developmental sequence, with the temperament trait being evident prior to the onset of the disorder. As such, unlike the common cause and spectrum models, the precursor model implies escalation from trait to disorder within individuals over time.

The common cause, spectrum, and precursor models do not posit causal relations between temperament and mental disorders. In contrast, the *predisposition model* holds that temperament plays a causal role in the onset of psychopathology. However, the predisposition model is similar to the precursor model in that both propose that the relevant traits are evident prior to the onset of the disorder. The major difference between these two accounts is that the precursor model assumes that temperament and psychopathology derive from the same set of etiological processes. In contrast, the predisposition model posits that the processes underlying temperament differ from those that lead to psychopathology and that other factors are necessary for the trait to lead to a disorder. Thus, the predisposition account implies interplay among risk factors involving moderation and/or mediation, and this is what distinguishes it from the precursor model. The most common example—the diathesis-stress model—conceptualizes temperament as the diathesis and stress as a moderator that precipitates the onset of psychopathology. Alternatively, stress may be a mediator, so that temperamental vulnerability leads to negative experiences (e.g., peer or academic difficulties), which in turn increase the probability of developing psychopathology. A second difference between these models is that the predisposition model does not assume that there must be phenotypic similarities between temperament traits and psychopathology. Finally, as the trait and disorder are not manifestations of the same etiological processes, they are likely to differ on some biological, cognitive, and affective correlates.

The *pathoplasticity model* is similar to the predisposition model in that it also views temperament as having a causal influence on psychopathology. However, rather than contributing to the onset of mental disorders, the pathoplasticity model posits that temperament influences the expression of the disorder after onset. This influence can include the severity or patterning of symptomatology, course, and response to interventions.

The last two models also assume that there is a causal relation between temperament and psychopathology. However, these models reverse the direction of causality. In the *concomitants (or state-dependent) model*, assessments of temperament are colored, or distorted, by psychiatric symptoms. However, this model implies that temperament returns to baseline after recovery from the disorder. In contrast, the *consequences (or scar) model* holds that the disorder has an enduring effect on temperament, such that the changes in temperament persist after recovery.

These models consider traits to be perfectly stable, which is demonstrably false for all major temperament/personality traits (e.g., Roberts & DelVecchio, 2000), including BI, which exhibits only moderate stability (Fox, Henderson, Rubin, Calkins, & Schmidt, 2001; Johnson et al., 2016; Pfeifer, Goldsmith, Davidson, & Rickman, 2002). Models of temperament-psychopathology relationships can be expanded to create *dynamic vulnerability models* that recognize the malleability of traits (e.g., Klein et al., 2011; Ormel, Oldehinkel, & Brilman, 2001). For example,

one can posit a *dynamic precursor model* in which early temperament defines the baseline level of risk but subsequent experiences modify temperamental liability to psychopathology.

The disorder emerges when the temperamental liability reaches a latent threshold necessary for the onset of psychopathology. Individuals who are born with an elevated temperamental liability or those with a rapidly increasing trait trajectory due to other factors would have an earlier onset of the disorder, while those with a lower initial, or more slowly increasing, trait trajectory would not cross the threshold until much later, if ever. Moreover, a pathological trait trajectory may be checked or reversed by positive experiences (Ormel & de Jong, 1999). In fact, temperament/personality generally tends to change in a more adaptive direction with age (Roberts, Walton, & Viechtbauer, 2006), although this pattern is not universal (Johnson, Hicks, McGue, & Iacono, 2007) (see the chapter "Behavioural Inhibition and the Prevention of Internalising Distress in Early Childhood" by Rapee and Bayer). This may help to explain why the probability of many forms of psychopathology peak in adolescence, as many traits reach their maximum level of maladaptiveness at that age (Durbin & Hicks, 2014; Klein et al., 2011).

Similarly, the predisposition model can also be expanded to accommodate change in the temperament trait (Klein et al., 2011). This *dynamic predisposition model* (Ormel et al., 2001) acknowledges transactions between temperament and the environment and integrates them with the environmental moderation and mediation mechanisms of the classic predisposition model. In the environmental moderation version of this account, other factors such as negative life experiences influence levels of trait vulnerability, which may, in turn, lead to additional life stress. If this vicious cycle is perpetuated, trait liability continues to increase, and at some point, a negative life event can overwhelm coping capabilities and trigger a psychiatric disorder. Importantly, and in contrast to the dynamic precursor model, in this account maladaptive traits alone are not sufficient to cause psychopathology, and additional etiological factors, such as stress, are necessary.

Research on the Relation of Behavioral Inhibition to Psychopathology

In the following sections, we selectively review research on behavioral inhibition that is relevant to these conceptual models of temperament-psychopathology relations, organized by research question and design. Most of this work has focused on the anxiety disorders owing to the phenotypic similarities between behavioral inhibition and anxiety symptoms. However, there is also some evidence for a link between behavioral inhibition and depressive disorders.

First, we consider the issue of overlap in phenotypic presentation and cross-sectional associations between behavioral inhibition and anxiety disorders, which is most relevant to the spectrum and precursor models. Second, we discuss follow-up

studies of psychopathology in behaviorally inhibited children, which provide critical tests for the precursor and predisposition models. Third, we review studies examining the familial associations between behavioral inhibition and psychiatric disorders, which are relevant to the common cause, spectrum, precursor, and predisposition models. Fourth, we briefly consider twin studies, which are critical for evaluating the common cause model. Fifth, we discuss the little available research on the effects of behavioral inhibition on the presentation and course of anxiety disorders, which bears on the pathoplasticity model. Sixth, although relevant data are lacking, we briefly consider whether psychopathology influences behavioral inhibition, as posited by the concomitants and consequences models. Finally, we examine moderators and mediators of BI-psychopathology relationships, which are relevant to the predisposition model as well as dynamic vulnerability models.

Overlap and Associations Between Behavioral Inhibition and Anxiety Disorders

Behavioral inhibition and anxiety disorders show considerable overlap in phenotypic characteristics and course and often co-occur. Fear and avoidance are core characteristics of both behavioral inhibition and anxiety disorders. In addition, both behavioral inhibition and anxiety disorders often have an early and gradual onset and are relatively stable over time (Rapee & Coplan, 2010). These similarities are particularly striking for SAD and generalized anxiety disorder (GAD), which tend to be evident across multiple situations (with the exception of the performance-only subtype of SAD) and have a persistent course. This overlap is consistent with the spectrum and precursor models. Further support for the spectrum model comes from evidence that anxiety disorders are associated with greater impairment than behavioral inhibition (Goldsmith & Lemery, 2000; Rapee & Coplan, 2010), which is consistent with the idea that the former is a more severe form of the latter.

However, there are also important differences between behavioral inhibition and most of the anxiety disorders. While behavioral inhibition, by definition, is evident by early childhood, social anxiety disorder often has an onset in adolescence, and the onsets of GAD, agoraphobia, and panic disorder are typically in adolescence and young adulthood. An exception is separation anxiety disorder, which generally (although not always) has an early childhood onset. Behavioral inhibition also differs from panic disorder in that the onset of the latter is acute, rather than gradual (Rapee & Coplan, 2010).

Finally, behavioral inhibition and anxiety disorders frequently co-occur. However, the magnitude of this association in cross-sectional studies is typically in the moderate range using categorical (e.g., Hudson, Dodd, & Bovopoulos, 2011) and continuous (e.g., Lemery, Essex, & Smider, 2002) measures of both constructs. The phenotypic differences between behavioral inhibition and most anxiety disorders and the only moderate degree of co-occurrence argue against the view that behavioral

inhibition and anxiety disorders (especially SAD) are identical phenomena (Rapee & Coplan, 2010)—an extreme version of the spectrum model. The fact that the majority of individuals with anxiety disorders do not have histories of behavioral inhibition (Clauss & Blackford, 2012) is even stronger evidence against the spectrum model, which cannot explain why someone with the more severe expression of the trait (i.e., the disorder) does not also have the milder form (i.e., the trait alone).

Follow-Up Studies of Behaviorally Inhibited Children

Following children with varying levels of behavioral inhibition over time and examining the emergence of psychopathology is one of the most informative approaches to understanding the relation between behavioral inhibition and psychiatric disorders. This line of research is critical for evaluating the precursor and predisposition models, both of which assume that behavioral inhibition precedes the onset of psychopathology.

A number of studies have examined the association between behavioral inhibition in early childhood and later psychiatric disorders or symptoms in middle childhood, adolescence, or young adulthood. There is consistent evidence for a link between early behavioral inhibition and later SAD (e.g., Chronis-Tuscano et al., 2009; Essex, Klein, Slattery, Goldsmith, & Kalin, 2009; Hirshfeld-Becker et al., 2007; Muris, van Brakel, Arntz, & Schouten, 2011; Schwartz, Snidman, & Kagan, 1999). These findings are particularly strong when behavioral inhibition is stable over at least several years (Chronis-Tuscano et al., 2009; Essex et al., 2009). In a meta-analysis, Clauss and Blackford (2012) reported that a significantly greater proportion of children with (43%), than without (12%), behavioral inhibition subsequently developed SAD. This finding was robust to study differences in methods of assessing behavioral inhibition and SAD and age at which behavioral inhibition and SAD were assessed. Importantly, however, the magnitude of the effect diminished as a function of the length of the interval between assessing behavioral inhibition and SAD. Thus, the risk of SAD appears to diminish as children with high behavioral inhibition age, although it is unknown if the risk for other conditions with later onsets, such as GAD and depression, increases.

A number of longitudinal studies have reported that behavioral inhibition also predicts anxiety disorders in the aggregate as well as other specific anxiety disorders. Significant effects have been reported for any anxiety disorder (Hudson & Dodd, 2012; Paulus, Backes, Sander, Weber, & von Gontard, 2015), multiple anxiety disorders (Biederman et al., 1993; Hudson & Dodd, 2012), specific phobia (Paulus et al., 2015), GAD (Hudson & Dodd, 2012), separation anxiety disorder (Biederman et al., 1993; Hudson & Dodd, 2012; Paulus et al., 2015), and panic disorder and agoraphobia (Biederman et al., 1993).

There is also some evidence that behavioral inhibition predicts later depressive disorders. Caspi, Moffitt, Newman, and Silva (1996) found that behaviorally observed inhibition at age 3 predicted depression diagnoses in young adulthood.

However, Caspi and colleagues did not use a standard behavioral inhibition measure, and other studies have not found associations between behavioral inhibition and subsequent depression (e.g., Biederman et al., 2001; Muris et al., 2011).

Finally, behavioral inhibition is unrelated to, or may even predict lower levels of, externalizing symptoms and disorders (Biederman et al., 2001; Frenkel et al., 2015; Muris et al., 2011; Thorell, Bohlin, & Rydell, 2004). In a rare exception, Lahat et al. (2012) reported that children with high levels of behavioral inhibition who also exhibited striatal hypersensitivity to rewards had an increased risk for substance use in adolescence, suggesting that other biobehavioral systems can alter the trajectory of behavioral inhibition over the course of development (see the chapter "The Biological Bridge Between Behavioral Inhibition and Psychopathology" by Sylvester and Pine).

These data are consistent with behavioral inhibition being a precursor or predisposition to psychopathology, as these models posit a developmental sequence in which the trait precedes the onset of the disorder. Although the precise range of mental disorders predicted by behavioral inhibition remains to be elucidated, prospective relations between behavioral inhibition and psychopathology are evident for anxiety disorders and especially for SAD.

There are several important caveats, however. A number of the longitudinal studies did not assess psychopathology at the time of the behavioral inhibition assessment; hence they cannot rule out the possibility that the disorder was already present at the beginning of the study. The failure to assess baseline psychopathology may stem from the assumption that diagnosable psychopathology is very rare in early childhood (Egger & Emde, 2011)—a position that is no longer justified given recent studies of the substantial prevalence of anxiety disorders in preschoolers (Dougherty et al., 2013; Franz et al., 2013). For example, rates of any anxiety disorder in community samples of preschoolers have ranged from 9.4% to 19.6% (Bufferd, Dougherty, Carlson, & Klein, 2011; Egger & Angold, 2006). In addition, few of these studies have considered the presence of comorbid psychopathology in the outcome assessment. Thus, it is conceivable that what appears to be an association between early behavioral inhibition and the target disorder may actually be accounted for by a coexisting condition.

In conclusion, the fact that many children with SAD (or any anxiety disorder) do not have histories of behavioral inhibition raises serious questions about the validity of the spectrum model. The uncertain specificity of the BI-psychopathology relationship is also problematic for both the spectrum and precursor models, which posit a high degree of homotypic continuity in trait-disorder associations.

Family Studies

Studies of the intergenerational association between behavioral inhibition and psychopathology are relevant to the common cause, spectrum, precursor, and predisposition models. Such studies have compared rates of behavioral inhibition in the

offspring of parents with and without psychiatric disorders (top-down designs) and compared rates of psychopathology in relatives of children with and without behavioral inhibition (bottom-up designs). Top-down studies have reported that the young children of parents with panic disorder and agoraphobia have higher rates of behavioral inhibition than offspring of healthy controls (Battaglia et al., 1997; Rosenbaum et al., 1988), although one study found this was limited to parents who also had major depression (Rosenbaum et al., 2000).

Conversely, in bottom-up studies, Rosenbaum et al. (1991) reported that parents of young children with behavioral inhibition had significantly higher rates of multiple anxiety disorders and SAD. Hudson et al. (2011) also found that mothers of young children with behavioral inhibition had higher rates of any anxiety disorder and a greater number of maternal anxiety disorders than non-BI children. However, Olino, Klein, Dyson, Rose, and Durbin (2010) failed to find an association between behavioral inhibition in young children and anxiety disorders in their parents.

Data on familial relationships between behavioral inhibition and depression are mixed. Kochanska (1991) found higher rates of behavioral inhibition in young children of mothers with depressive disorders. Consistent with this, Olino et al. (2010) reported that elevated behavioral inhibition in preschoolers was associated with an increased rate of depressive disorders in their parents. However, others have not found familial associations between behavioral inhibition and parental depression (Durbin, Klein, Hayden, Buckley, & Moerk, 2005; Rosenbaum et al., 1988), particularly in the absence of comorbid anxiety disorders (Rosenbaum et al., 2000). Finally, Hill, Lowers, Locke, Snidman, and Kagan (1999) reported that behavioral inhibition was elevated in children with a first- or second-degree relative with alcoholism compared to children without family histories of alcoholism.

Overall, this literature reveals fairly consistent evidence that behavioral inhibition and anxiety disorders aggregate in families, although the temperament-disorder association appears to be evident for multiple forms of anxiety and possibly for depression and alcoholism as well. The cross-generational link between behavioral inhibition and anxiety disorders is consistent with the common cause, spectrum, precursor, and predisposition models, although, as in the follow-up studies, the questionable diagnostic specificity of these associations raises problems for the spectrum and precursor perspectives.

Twin Studies

Twin studies can determine if there are overlapping genetic and environmental influences on two phenotypes, such as behavioral inhibition and a mental disorder. This design is particularly useful in testing the common cause model and is also relevant to the spectrum and precursor models. A number of studies have used this design to examine personality and psychopathology in adults. For example, the majority of genetic variance in N overlaps with that of most anxiety disorders

(Hettema, Neale, Myers, Prescott, & Kendler, 2006). To our knowledge, the only relevant twin data examining overlapping genetic and environmental influences on behavioral inhibition and psychopathology were described in preliminary form in review papers by Goldsmith and colleagues (Goldsmith & Lemery, 2000; Goldsmith, Lemery-Chalfant, Schmidt, Arneson, & Schmidt, 2007). They reported that the relation between early temperamental fearfulness and later overanxious symptoms (similar to generalized anxiety) was attributable to the same additive genetic influences, whereas the association between fearfulness and later separation anxiety symptoms was due to the same environmental influences. Clearly further data are needed. However, these findings suggest that there may be common causes shared by behavioral inhibition and some anxiety disorders, although the nature of these overlapping influences may differ for different forms of anxiety.

Behavioral Inhibition and the Course of Psychopathology

In order to test the pathoplasticity model, it is important to examine the effect of behavioral inhibition on the presentation and subsequent course of psychopathology. There are a large number of studies documenting the effects of N and E on the course of psychopathology in adolescents and adults (Klein et al., 2011), but to our knowledge, only one study has examined this issue with respect to behavioral inhibition. Bufferd et al. (2016) obtained laboratory assessments and parent reports of behavioral inhibition in preschoolers and conducted diagnostic interviews with a parent about the child. They found that among the preschoolers with an anxiety disorder, higher laboratory and parent-reported behavioral inhibition significantly predicted whether the child met criteria for an anxiety disorder again 3 years later. These findings are consistent with behavioral inhibition having a pathoplastic effect on the course of anxiety. However, additional research is necessary to elucidate the processes underlying this relation. For example, behavioral inhibition could be associated with greater avoidance behavior or lead to parenting practices (e.g., overprotectiveness) that maintain anxiety disorders (see the chapter "The Social World of Behaviorally Inhibited Children: A Transactional Account" by Henderson et al. and the chapter "Behavioural Inhibition and the Prevention of Internalising Distress in Early Childhood" by Rapee and Bayer). In addition, it is necessary to rule out the alternative explanation that behavioral inhibition is a marker for an etiologically distinct subtype of anxiety disorder with a more persistent or recurrent course.

Psychopathology Influencing Behavioral Inhibition

The concomitants and consequences models propose that psychopathology influences temperament; the former holds that this occurs over a relatively short time frame of active symptomatology, while the latter posits more enduring effects, even

after remission. The concomitants model has typically been concerned with the effects of clinical states on self-reports of personality, which is not relevant in young children, although it is plausible that a child's clinical state influences parents' reports of the child's temperament and children's behavior in observational paradigms. The consequences model has probably not been considered for the same reason that baseline anxiety is often not assessed in follow-up studies of young children with behavioral inhibition—psychopathology has traditionally been assumed to be rare in early childhood (Egger & Emde, 2011). However, it is conceivable that an early-onset anxiety disorder might lead a child to become increasingly apprehensive, wary, and avoidant in unfamiliar contexts. Indeed, this highlights the difficulty of disentangling markers of behavioral inhibition from symptoms of anxiety, given the relatively narrower behavioral, verbal, and cognitive repertoire of young children.

There is strong evidence for the concomitants model with respect to self-reports of other temperament/personality traits, but much less support for the consequences model (see Klein et al., 2011, 2012). However, to our knowledge, data addressing the concomitants and consequences models do not exist for behavioral inhibition.

Moderators of the BI-Psychopathology Relation

The major distinction between the precursor and predisposition models is that the former posits a direct relation between the trait and the disorder, whereas the latter requires an intervening factor to operate as a moderator or mediator. A number of studies have examined whether the relation between behavioral inhibition and subsequent psychopathology (generally anxiety disorders) is moderated by other factors. These have included neurocognitive variables, such as error monitoring, executive function, and attention biases (see the chapter "Relations Between Behavioral Inhibition, Cognitive Control and Anxiety: Novel Insights Provided by Parsing Subdomains of Cognitive Control" by Buzzell et al. and the chapter "Attention Mechanisms in Behavioral Inhibition: Exploring, and Exploiting, the Environment" Pérez-Edgar and the chapter "Behavioral Inhibition and the Associative Learning of Fear" by Reynolds et al.), parenting styles and practices (see the chapter "The Social World of Behaviorally Inhibited Children: A Transactional Account" by Henderson et al.), peer relationships (see the chapter "Peer Relations and the Behaviorally Inhibited Child" by Rubin et al.), and life stress (see the chapter "The Temperamentally Shy Child as the Social Adult: An Exemplar of Multifinality" by Poole et al.). In contrast, few studies have examined mediation (however, see the chapter "Relations Between Behavioral Inhibition, Cognitive Control and Anxiety: Novel Insights Provided by Parsing Subdomains of Cognitive Control" by Buzzell et al.).

Neurocognitive Factors

A number of studies have examined whether individual differences in neurocognitive processes moderate the association between behavioral inhibition and anxiety symptoms or disorders. The error-related negativity (ERN) is a component of the event-related potential (ERP) that is elicited by errors on speeded decision tasks. Several studies have reported that early childhood behavioral inhibition interacts with middle childhood or adolescent ERN, such that youth with elevated levels of both factors exhibit the highest rates of anxiety disorders (McDermott et al., 2009) and the greatest increase in SAD symptoms (Lahat et al., 2014). In addition, Meyer et al. (2017) found a three-way interaction between behavioral inhibition at age 3, ERN at age 6, and stress associated with a nature disaster at age 10 on increases in anxiety symptoms. The greatest increase in anxiety was observed in children with the combination of high behavioral inhibition, high ERN, and high stress exposure.

Several studies have also reported that in behaviorally inhibited children, greater inhibitory control and poorer attentional shifting in laboratory tasks were associated with higher levels of anxiety symptoms (Thorell et al., 2004; White, McDermott, Degnan, Henderson, & Fox, 2011). In addition, several studies have reported that attention bias toward threat and novelty moderated the effects of behavioral inhibition on anxiety. White et al. (2017) found that early behavioral inhibition predicted subsequent anxiety symptoms among children who exhibited attentional biases toward threat or away from positive stimuli. Reeb-Sutherland et al. (2009) reported related results in an ERP study, finding that children with a history of behavioral inhibition were more likely to develop anxiety disorders as adolescents if they displayed an increased P3 amplitude to novel stimuli, suggesting an attentional bias to novelty.

Parenting

Rubin, Burgess, and Hastings (2002) hypothesized that parental overprotection and control may amplify the effects of childhood behavioral inhibition by enabling the child's avoidance behavior, limiting opportunities to attenuate anxiety via exposure, and discouraging independence, which reduces opportunities to develop adaptive coping skills. Several studies have examined the role of parenting styles and behaviors as moderators of the association between behavioral inhibition and psychopathology. Williams et al. (2009) assessed behavioral inhibition at 14 and 24 months of age, self-report of maternal parenting style at 7 years of age, and maternal report of child internalizing and externalizing symptoms at 4, 7, and 15 years. They reported that initial levels of internalizing problems were greatest among behaviorally inhibited children who were also exposed to permissive parenting. However, this effect was not evident in the two subsequent waves of symptom assessments.

Lewis-Morrarty et al. (2012) found that maternal overcontrol at age 7 moderated the association between behavioral inhibition across childhood and parent reports of adolescent SAD symptoms in adolescence, such that higher behavioral inhibition predicted later symptoms in the presence of greater maternal control.

Peer Relationships

There is considerable evidence indicating that behavioral inhibition in early childhood predicts later social reticence and withdrawal (Rubin et al., 2002; Rubin, Coplan, & Bowker, 2009). This may be a significant source of stress, particularly in adolescence, when peer relationships assume a particularly important role (Brown & Larson, 2009). Frenkel et al. (2015) reported that low levels of peer involvement and smaller social networks in adolescence moderated the effects of early behavioral inhibition on anxiety disorders in young adulthood, such that behavioral inhibition predicted increased risk for anxiety when adolescent social involvement was low, but not when it was high.

Life Events

A number of studies in the larger temperament/personality-psychopathology literature have tested the predisposition model by examining stressful life events as moderators (Klein et al., 2011; Kushner, 2015). However, only a small handful of studies of behavioral inhibition have explored this issue, and most reported that life events had an independent effect on anxiety but did not interact with behavioral inhibition (e.g., Broeren, Newall, Dodd, Locker, & Hudson, 2014; Muris et al., 2011). More recently, however, Kopala-Sibley et al. (2016) reported that the association between laboratory assessed temperamental fearfulness at age 3 and increases in parent-reported anxiety symptoms from age 9 to age 10 was moderated by exposure to a natural disaster occurring approximately 2 months before the last assessment. As noted above, Meyer et al. (2017) subsequently found that these results were further qualified by an interaction with error monitoring, such that fearful preschoolers who exhibited greater ERNs at age 6 and also had high disaster-related exposure experienced the largest increase in internalizing symptoms.

Dynamic Effects

Dynamic models augment classical trait-psychopathology models by recognizing that traits are not fixed, and therefore levels of trait vulnerability may change over time. Behavioral inhibition is, at most, moderately stable (Johnson et al., 2016;

Kagan & Snidman, 2004), suggesting that it may be influenced by other factors. We focus here on parenting, as parents are one of the most salient aspects of children's environments and their effects on the stability of behavioral inhibition are relatively well-studied, although other factors such as maternal personality (Degnan, Henderson, Fox, & Rubin, 2008) and other dimensions of child temperament, such as low positive emotionality (Johnson et al., 2016), have also been shown to influence behavioral inhibition stability.

Rubin et al. (2002) posited a reciprocal relation between behavioral inhibition and parenting, such that parents perceive behaviorally inhibited children to be vulnerable and therefore treat them in an overprotective, controlling, and/or oversolicitous manner. This leads high behavioral inhibition children to become overly reliant on adults and internalize the belief that they are unable to independently cope with anxiety-provoking situations, maintaining their behavioral inhibition and social reticence and impeding the normative development of social and coping skills (Bohlin, Hagekull, & Andersson, 2005).

A number of studies have reported evidence supporting this general model. Child behavioral inhibition predicts later parental overprotective, controlling, and overly solicitous behavior (Kiel & Buss, 2011; Lengua & Kovacs, 2005; Rubin, Nelson, Hastings, & Asendorpf, 1999). In turn, parental overprotection, control, and oversolicitousness predict children's subsequent behavioral inhibition and social reticence with peers (Degnan et al., 2008; Hane, Cheah, Rubin, & Fox, 2008; Kiel & Buss, 2011; Rubin et al., 2002). For example, Johnson et al. (2016) obtained self-reports and interviewer assessments of parental overprotective behavior and laboratory observations of behavioral inhibition for a large sample of 3-year-olds and repeated the lab assessment of behavioral inhibition 3 years later. They found that parental overprotection moderated the stability of behavioral inhibition, such that the association between behavioral inhibition at ages 3 and 6 was strongest in children with higher levels of parental overprotection.

We are unaware of studies that have combined an examination of parenting or other influences on the stability of behavioral inhibition with tests of moderators of the relationship between behavioral inhibition and subsequent psychopathology, which is required for a full test of the dynamic predisposition model. However, the existing data support the plausibility of dynamic vulnerability models of trait-psychopathology relationships and suggest the value of more comprehensive tests.

Discussion

We examined the relation between behavioral inhibition and psychopathology in the context of the larger literature on temperament/personality-psychopathology associations. Evidence of familial aggregation of behavioral inhibition with many anxiety disorders, and possibly depression, is consistent with the common cause model. However, more direct evidence from twin designs is sparse, although preliminary data suggest that there are some shared genetic and environmental influences

between behavioral inhibition and multiple forms of anxiety (Goldsmith et al., 2007). Phenotypic similarities of behavioral inhibition and some anxiety disorders are consistent with the spectrum model. However, differences in age of onset and the questionable specificity of the BI-SAD association argue against a spectrum account. In addition, many, if not the majority, of youth with anxiety disorders in general, and SAD in particular, do not have a history of behavioral inhibition (Clauss & Blackford, 2012; Hudson & Dodd, 2012; Rapee & Coplan, 2010). This is inconsistent with the spectrum model's implication that when behavioral inhibition reaches a sufficient level of severity, it manifests as a full-blown anxiety disorder and that below that severity threshold, clinically significant anxiety disorders are not evident.

The precursor and predisposition models are both supported by family and follow-up studies showing that behavioral inhibition aggregates in families with anxiety disorders and predicts the later onset of anxiety disorders, particularly SAD. However, familial and longitudinal associations with a variety of anxiety disorders and perhaps also depression are somewhat problematic for the precursor model, which posits phenotypic similarity between the trait and disorder. In addition, evidence that a variety of other factors moderate the relationship between behavioral inhibition and anxiety disorders suggests that other factors are required for behaviorally inhibited children to develop clinically significant anxiety. This favors the predisposition model over the precursor model. In addition, studies indicating that factors such as overprotective and controlling parenting can maintain or increase behavioral inhibition indicate that there are dynamic influences on trait development, consistent with a dynamic predisposition model. Thus, the evidence to date appears to be most consistent with a predisposition account, particularly one incorporating dynamic elements.

The pathoplasticity model is supported by evidence that behavioral inhibition influences the course of anxiety disorders following onset. This is not necessarily inconsistent with a dynamic predisposition model, which may explain the onset of anxiety disorders, while pathoplastic effects influence the subsequent course of the disorder. However, as there is only one study that has attempted to address pathoplasticity (Bufferd et al., 2016), further research is indicated. Finally, we are unaware of data directly testing the concomitants and consequences models for behavioral inhibition and anxiety disorders, suggesting that this warrants investigation.

Similar to the spectrum model, it has been argued that there is no fundamental distinction between behavioral inhibition and the anxiety disorders (see Rapee & Coplan, 2010 for a discussion of this issue). However, the literature suggests that there are sufficient differences between these two constructs to consider them as at least partially distinct, although it is plausible that they share some etiological and pathophysiological processes. Instead, behavioral inhibition appears to be better conceptualized as a predisposition that, in the presence of other factors, increases the likelihood of developing clinically significant internalizing psychopathology. However, the precise phenotype or range of phenotypes that behavioral inhibition predisposes to is still uncertain.

Family and follow-up studies suggest that behavioral inhibition may be characterized by multifinality (Clauss & Blackford, 2012). Although behavioral inhibition has the closest relation with SAD, children with behavioral inhibition also appear to be at risk for other internalizing conditions, and many do not appear to develop any psychopathology, although no studies have followed children through the full risk period for internalizing disorders. Unfortunately, many studies of the outcomes of behaviorally inhibited children have focused exclusively on SAD, rather than examining a broader range of psychiatric phenotypes.

The association between behavioral inhibition and depression is particularly worthy of further exploration (Kagan, 2017). This relation may be indirect and mediated by anxiety disorders. Thus, there is considerable evidence that anxiety disorders often precede the development of depression (Cummings, Caporino, & Kendall, 2014; Jacobson & Newman, 2017; Silk, Davis, McMakin, Dahl, & Forbes, 2012). Indeed, longitudinal twin studies indicate that some of the same genes that are expressed as anxiety in childhood are expressed as depression in adolescence (Waszczuk, Zavos, Gregory, & Eley, 2014). Unfortunately, longitudinal studies of behaviorally inhibited children have rarely extended to late adolescence or adulthood and therefore may not have captured the increase in depression that begins at puberty and continues through young adulthood (Salk, Hyde, & Abramson, 2017). It is plausible that there is a subgroup of children who exhibit behavioral inhibition in early childhood, experience anxiety disorders in later childhood, and develop depression in adolescence. Indeed, Beesdo et al. (2007) reported that among adolescents and young adults with SAD, retrospective reports of childhood behavioral inhibition predicted the subsequent development of depression. Identifying a depression-prone behavioral inhibition phenotype could have important implications for understanding differences in developmental trajectories and pathophysiology in inhibited children and for targeting prevention programs more effectively.

There is now a substantial body of evidence indicating that psychopathology is organized in a hierarchical structure (Kotov et al., 2017; Lahey, Krueger, Rathouz, Waldman, & Zald, 2017). The correlated factors of internalizing and externalizing symptoms/disorders are at the top of the hierarchy, although there is evidence that their covariance may be explained by an even higher-order general factor. At the next level, internalizing and externalizing can be broken down into more specific factors (e.g., internalizing is composed of fear and distress symptoms/disorders). Each of these factors can be further divided, with increasingly finer-grained distinctions emerging at progressively lower levels (Kim & Eaton, 2015). Thus, it is important to examine the association of behavioral inhibition with each level of the hierarchy and determine the level at which it makes the largest unique contribution.

If behavioral inhibition is most closely related to factors such as internalizing or fear that subsume multiple forms of psychopathology, it can be considered a transdiagnostic factor whose influence cuts across traditional diagnostic categories. However, behavioral inhibition could also be transdiagnostic in a way that is not well-captured by a hierarchical classification system that is based on clinical description. That is, behavioral inhibition may have a distinct etiology and pathophysiology

that corresponds to a biobehavioral phenotype (see the chapter "The Neurobiology of Behavioral Inhibition as a Developmental Mechanism" by Blackford et al.) that does not map precisely onto any set of existing psychiatric phenotypes, such as amygdala hyperreactivity, at the circuit level, or intolerance of uncertainty, at the level of self-report (Kagan, 2017). If this is the case, behavioral inhibition may be useful in delineating a new phenotype, similar to what is envisioned in the National Institute of Mental Health Research Domain Criteria (RDoC) initiative (Kozak & Cuthbert, 2016).

From a related perspective, what appears to be multifinality may actually reflect heterogeneity. Thus, if behavioral inhibition is heterogeneous and can be parsed into more homogeneous subtypes or dimensions, it may reveal stronger and more specific associations with psychopathology. This is related to our earlier discussion of moderators, as variables that appear to be moderators may, in fact, be markers of qualitatively distinct subtypes (e.g., children with high versus low error monitoring). Thus, the predisposition model can be difficult to distinguish from a subtype/heterogeneity account. Currently, there are several approaches to subtyping behavioral inhibition that warrant further consideration.

Buss and colleagues (see Buss & McDoniel, 2016 for a review) distinguish between young children who exhibit fearful, inhibited behavior across a range of high to low fear-eliciting contexts and children who exhibit inhibited behavior only in high-fear contexts. Buss has shown that the former group subsequently exhibited greater social withdrawal in kindergarten, heightened reticence with unfamiliar peers, and more mother-reported anxiety symptoms. Thus, displaying fear that is dysregulated and incongruent with the eliciting context appears to be an important source of heterogeneity and may indicate greater risk among behaviorally inhibited children. In addition, it has important implications for assessment, as it suggests that contexts with a weaker, rather than stronger, "press" for eliciting fear may have the greatest utility for identifying behavioral inhibition (see the chapter "Psychobiological Processes in the Development of Behavioral Inhibition" by Buss and Qu).

Another source of heterogeneity may involve the distinction between social and nonsocial fears. Behavioral inhibition has traditionally been assessed by exposing children to a series of unfamiliar stimuli, including both social and nonsocial contents (e.g., Kagan et al., 1984; Pfeifer et al., 2002). Importantly, behavior genetic studies indicate that fears and phobias of social and nonsocial stimuli have somewhat different etiologies (Bienvenu, Hettema, Neale, Prescott, & Kendler, 2007; Kendler, Neale, Kessler, Heath, & Eaves, 1992). Moreover, in laboratory assessments of behavioral inhibition, ratings of inhibition in social and nonsocial contexts are not significantly correlated (Dyson, Olino, Dougherty, Durbin, & Klein, 2011; Kochanska, 1991; Rubin, Hastings, Stewart, Henderson, & Chen, 1997). Indeed, the distinction between social and nonsocial forms of behavioral inhibition may be highly conserved as it is noted in multiple nonhuman behavioral inhibition models (see the chapter "Behavioral Inhibition in Nonhuman Primates: The Elephant in the Room" by Capitanio and the chapter "Behavioral Inhibition in Rodents: A Model to Study Causes and Health Consequences of Temperament" by Cavigelli).

In order to examine differences between social and nonsocial behavioral inhibitions, Dyson et al. (2011) conducted a laboratory assessment of behavioral inhibition with preschoolers that included both social and nonsocial episodes and a diagnostic interview about the child with a parent. Behavioral inhibition in social situations was significantly correlated with SAD symptoms, but not with specific phobia symptoms, whereas nonsocial behavioral inhibition was significantly correlated with specific phobia symptoms but not with SAD symptoms. Notably, in some of the studies cited earlier which found that early behavioral inhibition predicted later SAD, assessments of behavioral inhibition were heavily weighted with social stimuli (e.g., interactions with unfamiliar peers). Dyson et al.'s (2011) findings suggest that the specific psychiatric outcomes observed in follow-up studies may differ depending on the distribution of social and nonsocial content in the behavioral inhibition assessment.

Finally, Kagan (2017) has suggested that there are multiple pathways to behavioral inhibition, including genetic and environmental (or phenocopy) forms (see the chapter "The History and Theory of Behavioral Inhibition" by Kagan). One possible marker of a more genetic form of behavioral inhibition may be parental history of behavioral inhibition. Stumper et al. (2017) recently reported that the association between behavioral inhibition at age 3 and anxiety disorders at age 9 was moderated by parents' retrospective reports of their own childhood history of behavioral inhibition. The findings indicated that behaviorally inhibited children whose parents also had a history of behavioral inhibition were at particularly high risk for developing clinically significant anxiety. Similarly, Muris et al. (2011) found that fathers' trait anxiety moderated the effects of children's early behavioral inhibition on later social anxiety symptoms, such that the combination of higher child behavioral inhibition and higher paternal trait anxiety predicted greater anxiety symptoms. These studies suggest that parental fearfulness may be a marker for a more familial, and possibly more genetic, subtype of behavioral inhibition that is associated with a greater risk for later anxiety.

In conclusion, behavioral inhibition appears to be a significant risk factor for subsequent SAD and probably other forms of internalizing psychopathology. Moreover, it appears to fit the profile of a predisposing or vulnerability factor, rather than a precursor, as other variables may be necessary to transduce behavioral inhibition into a clinically significant disorder. However, further work is needed in a number of areas. First, it is important to elucidate the nature and range of psychiatric phenotypes related to behavioral inhibition, especially taking into account initial and comorbid psychopathology. Second, it would be worthwhile to test a broader range of models of BI-psychopathology relations (e.g., pathoplasticity, consequences). Third, predisposition models involving mediators, rather than moderators, of the link between behavioral inhibition and anxiety disorders should be explored. Finally, more research is needed to determine whether behavioral inhibition is truly characterized by multifinality or whether more specific relationships can be identified by parsing behavioral inhibition's heterogeneity. While interesting in their own right, each of these questions has important implications for investigating the etiology and pathophysiology of anxiety, and possibly depressive, disorders and for developing

more effective and efficient prevention and early intervention programs (see the chapter "Behavioural Inhibition and the Prevention of Internalising Distress in Early Childhood" by Rapee and Bayer).

References

Battaglia, M., Bajo, S., Strambi, L. F., Brambilla, F., Castronovo, C., Vanni, G., & Bellodi, L. (1997). Physiological and behavioral responses to minor stressors in offspring of patients with panic disorder. *Journal of Psychiatric Research, 31*(3), 365–376.

Beesdo, K., Bittner, A., Pine, D. S., Stein, M. B., Höfler, M., Lieb, R., & Wittchen, H. U. (2007). Incidence of social anxiety disorder and the consistent risk for secondary depression in the first three decades of life. *Archives of General Psychiatry, 64*(8), 903–912.

Biederman, J., Hirshfeld-Becker, D. R., Rosenbaum, J. F., Hérot, C., Friedman, D., Snidman, N., … Faraone, S. V. (2001). Further evidence of association between behavioral inhibition and social anxiety in children. *American Journal of Psychiatry, 158*(10), 1673–1679.

Biederman, J., Rosenbaum, J. F., Bolduc-Murphy, E. A., Faraone, S. V., Chaloff, J., Hirshfeld, D. R., & Kagan, J. (1993). A 3-year follow-up of children with and without behavioral inhibition. *Journal of the American Academy of Child and Adolescent Psychiatry, 32*(4), 814–821.

Bienvenu, O. J., Hettema, J. M., Neale, M. C., Prescott, C. A., & Kendler, K. S. (2007). Low extraversion and high neuroticism as indices of genetic and environmental risk for social phobia, agoraphobia, and animal phobia. *American Journal of Psychiatry, 164*, 1714–1721.

Bohlin, G., Hagekull, B., & Andersson, K. (2005). Behavioral inhibition as a precursor of peer social competence in early school age: The interplay with attachment and nonparental care. *Merrill-Palmer Quarterly, 51*(1), 1–19.

Broeren, S., Newall, C., Dodd, H. F., Locker, R., & Hudson, J. L. (2014). Longitudinal investigation of the role of temperament and stressful life events in childhood anxiety. *Development and Psychopathology, 26*(2), 437–449.

Brown, B. B., & Larson, J. (2009). Peer relationships in adolescence. In R. M. Lerner & L. Steinberg (Eds.), *Handbook of adolescent psychology* (3rd ed., pp. 74–103). New York, NY: Wiley.

Bufferd, S. J., Dougherty, L. R., Carlson, G. A., & Klein, D. N. (2011). Parent-reported DSM-IV disorders in a community sample of preschoolers. *Comprehensive Psychiatry, 52*, 359–369.

Bufferd, S.J., Dougherty, L.R., Olino, T.M., Dyson, M.W., Carlson, G.A., & Klein, D.N. (2016). Temperament distinguishes persistent from remitted anxiety disorders across early childhood. *Journal of Clinical Child & Adolescent Psychology*, 1. https://doi.org/10.1080/15374416.2016.1212362

Buss, K. A., & McDoniel, M. E. (2016). Improving the prediction of risk for anxiety development in temperamentally fearful children. *Current Directions in Psychological Science, 25*(1), 14–20.

Caspi, A., Moffitt, T. E., Newman, D. L., & Silva, P. A. (1996). Behavioral observations at age 3 years predict adult psychiatric disorders: Longitudinal evidence from a birth cohort. *Archives of General Psychiatry, 53*(11), 1033–1039.

Caspi, A., & Shiner, R. L. (2006). Personality development. In W. Damon, R. Lerner, & N. Eisenberg (Eds.), *Handbook of child psychology: Vol. 3. Social, emotional, and personality development* (6th ed., pp. 300–364). New York, NY: Wiley.

Chronis-Tuscano, A., Degnan, K. A., Pine, D. S., Pérez-Edgar, K., Henderson, H. A., Diaz, Y., … Fox, N. A. (2009). Stable early maternal report of behavioral inhibition predicts lifetime social anxiety disorder in adolescence. *Journal of the American Academy of Child and Adolescent Psychiatry, 48*(9), 928–935.

Clark, L. A. (2005). Temperament as a unifying basis for personality and psychopathology. *Journal of Abnormal Psychology, 114*(4), 505–521.

Clauss, J. A., & Blackford, J. U. (2012). Behavioral inhibition and risk for developing social anxiety disorder: A meta-analytic study. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*(10), 1066–1075.

Cummings, C. M., Caporino, N. E., & Kendall, P. C. (2014). Comorbidity of anxiety and depression in children and adolescents: 20 years after. *Psychological Bulletin, 140*, 816–845.

Degnan, K. A., Henderson, H. A., Fox, N. A., & Rubin, K. H. (2008). Predicting social wariness in middle childhood: The moderating roles of childcare history, maternal personality and maternal behavior. *Social Development, 17*(3), 471–487.

Dougherty, L. R., Tolep, M. R., Bufferd, S. J., Olino, T. M., Dyson, M. W., Traditi, J., … Klein, D. N. (2013). Preschool anxiety disorders: Comprehensive assessment of clinical, demographic, temperamental, familial, and life stress correlates. *Journal of Clinical Child and Adolescent Psychology, 42*, 577–589.

Durbin, C. E., & Hicks, B. M. (2014). Personality and psychopathology: A stagnant field in need of development. *European Journal of Personality, 28*(4), 362–386.

Durbin, C. E., Klein, D. N., Hayden, E. P., Buckley, M. E., & Moerk, K. C. (2005). Temperamental emotionality in preschoolers and parental mood disorders. *Journal of Abnormal Psychology, 114*, 28–37.

Dyson, M. W., Olino, T. M., Dougherty, L. R., Durbin, C. E., & Klein, D. N. (2011). Social and non-social behavioral inhibition in preschool-age children: Differential associations with parent-reports of temperament and anxiety. *Child Psychiatry and Human Development, 42*, 390–405.

Egger, H. L., & Angold, A. (2006). Common emotional and behavioral disorders in preschool children: Presentation, nosology, and epidemiology. *Journal of Child Psychology and Psychiatry, 47*, 313–337.

Egger, H. L., & Emde, R. N. (2011). Developmentally sensitive diagnostic criteria for mental health disorders in early childhood: The diagnostic and statistical manual of mental disorders—IV, the research diagnostic criteria-preschool age, and the diagnostic classification of mental health and developmental disorders of infancy and early childhood-revised. *American Psychologist, 66*(2), 95–106.

Essex, M. J., Klein, M. H., Slattery, M. J., Goldsmith, H. H., & Kalin, N. H. (2009). Early risk factors and developmental pathways to chronic high inhibition and social anxiety disorder in adolescence. *American Journal of Psychiatry, 167*(1), 40–46.

Fox, N. A., Henderson, H. A., Rubin, K., Calkins, S. D., & Schmidt, L. A. (2001). Continuity and discontinuity of behavioral inhibition and exuberance: Psychophysiological and behavioral influences across the first four years of life. *Child Development, 72*, 1–21.

Franz, L., Angold, A., Copeland, W., Costello, E. J., Towe-Goodman, N., & Egger, H. (2013). Preschool anxiety disorders in pediatric primary care: Prevalence and comorbidity. *Journal of the American Academy of Child and Adolescent Psychiatry, 52*(12), 1294–1303.

Frenkel, T. I., Fox, N. A., Pine, D. S., Walker, O. L., Degnan, K. A., & Chronis-Tuscano, A. (2015). Early childhood behavioral inhibition, adult psychopathology and the buffering effects of adolescent social networks: A twenty-year prospective study. *Journal of Child Psychology and Psychiatry, 56*(10), 1065–1073.

Gladstone, G., & Parker, G. (2005). Measuring a behaviorally inhibited temperament style: Development and initial validation of new self-report measures. *Psychiatry Research, 135*(2), 133–143.

Goldsmith, H. H., & Lemery, K. S. (2000). Linking temperamental fearfulness and anxiety symptoms: A behavior–genetic perspective. *Biological Psychiatry, 48*(12), 1199–1209.

Goldsmith, H. H., Lemery-Chalfant, K., Schmidt, N. L., Arneson, C. L., & Schmidt, C. K. (2007). Longitudinal analyses of affect, temperament, and childhood psychopathology. *Twin Research and Human Genetics, 10*(1), 118–126.

Hane, A. A., Cheah, C., Rubin, K. H., & Fox, N. A. (2008). The role of maternal behavior in the relation between shyness and social reticence in early childhood and social withdrawal in middle childhood. *Social Development, 17*(4), 795–811.

Hettema, J. M., Neale, M. C., Myers, J. M., Prescott, C. A., & Kendler, K. S. (2006). A population-based twin study of the relationship between neuroticism and internalizing disorders. *American Journal of Psychiatry, 163*, 857–864.

Hill, S. Y., Lowers, L., Locke, J., Snidman, N., & Kagan, J. (1999). Behavioral inhibition in children from families at high risk for developing alcoholism. *Journal of the American Academy of Child and Adolescent Psychiatry, 38*(4), 410–417.

Hirshfeld-Becker, D. R., Biederman, J., Henin, A., Faraone, S. V., Davis, S., Harrington, K., & Rosenbaum, J. F. (2007). Behavioral inhibition in preschool children at risk is a specific predictor of middle childhood social anxiety: A five-year follow-up. *Journal of Developmental and Behavioral Pediatrics, 28*(3), 225–233.

Hudson, J. L., & Dodd, H. F. (2012). Informing early intervention: Preschool predictors of anxiety disorders in middle childhood. *PLoS One, 7*(8), e42359.

Hudson, J. L., Dodd, H. F., & Bovopoulos, N. (2011). Temperament, family environment and anxiety in preschool children. *Journal of Abnormal Child Psychology, 39*(7), 939–951.

Jacobson, N. C., & Newman, M. G. (2017). Anxiety and depression as bidirectional risk factors for one another: A meta-analysis of longitudinal studies. *Psychological Bulletin, 143*(11), 1155–1200.

John, O. P., Naumann, L. P., & Soto, C. J. (2008). Paradigm shift to the integrative big-five trait taxonomy: History, measurement, and conceptual issues. In O. P. John, R. W. Robins, & L. A. Pervin (Eds.), *Handbook of personality: Theory and research* (pp. 114–158). New York, NY: Guilford Press.

Johnson, V. C., Olino, T. M., Klein, D. N., Dyson, M. W., Bufferd, S. J., Durbin, C. E., … Hayden, E. P. (2016). A longitudinal investigation of predictors of the stability of behavioural inhibition in early childhood. *Journal of Research in Personality, 63*, 51–61.

Johnson, W., Hicks, B. M., McGue, M., & Iacono, W. G. (2007). Most of the girls are alright, but some aren't: Personality trajectory groups from ages 14 to 24 and some associations with outcomes. *Journal of Personality and Social Psychology, 93*(2), 266.

Kagan, J. (2003). Behavioral inhibition as a temperamental category. In R. J. Davidson, K. R. Scherer, & H. H. Goldsmith (Eds.), *Handbook of affective sciences* (pp. 320–331). New York, NY: Oxford University Press.

Kagan, J. (2017). High-reactive temperament, behavioral inhibition, and vulnerability to psychopathology. In T. P. Beauchaine & S. P. Hinshaw (Eds.), *Child and adolescent psychopathology* (3rd ed., pp. 2133–2236). Hoboken, NJ: Wiley.

Kagan, J., Reznick, J. S., Clarke, C., Snidman, N., & Garcia-Coll, C. (1984). Behavioral inhibition to the unfamiliar. *Child Development, 55*, 2212–2222.

Kagan, J., & Snidman, N. (2004). *The long shadow of temperament*. Cambridge, MA: Harvard University Press.

Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1992). The genetic epidemiology of phobias in women: The interrelationship of agoraphobia, social phobia, situational phobia, and simple phobia. *Archives of General Psychiatry, 49*(4), 273–281.

Kiel, E. J., & Buss, K. A. (2011). Prospective relations among fearful temperament, protective parenting, and social withdrawal: The role of maternal accuracy in a moderated mediation framework. *Journal of Abnormal Child Psychology, 39*(7), 953–966.

Kim, H., & Eaton, N. R. (2015). The hierarchical structure of common mental disorders: Connecting multiple levels of comorbidity, bifactor models, and predictive validity. *Journal of Abnormal Psychology, 124*(4), 1064–1078.

Klein, D. N., Dyson, M. W., Kujawa, A. J., & Kotov, R. (2012). Temperament and internalizing disorders. In M. Zentner & R. Shiner (Eds.), *Handbook of temperament* (pp. 541–561). New York, NY: Guilford Press.

Klein, D. N., Kotov, R., & Bufferd, S. J. (2011). Personality and depression: Explanatory models and review of the evidence. *Annual Review of Clinical Psychology, 7*, 269–295.

Kochanska, G. (1991). Patterns of inhibition to the unfamiliar in children of normal and affectively ill mothers. *Child Development, 62*(2), 250–263.

Kopala-Sibley, D. C., Danzig, A. P., Kotov, R., Bromet, E. J., Carlson, G. A., Olino, T. M., … Klein, D. N. (2016). Negative emotionality and its facets moderate the effects of exposure to Hurricane Sandy on children's post-disaster depression and anxiety symptoms. *Journal of Abnormal Psychology, 125*, 471–481.

Kotov, R., Krueger, R. F., Watson, D., Achenbach, T. M., Althoff, R. R., Bagby, R. M., … Zimmerman, M. (2017). The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. *Journal of Abnormal Psychology, 126*(4), 454–477.

Kozak, M. J., & Cuthbert, B. N. (2016). The NIMH research domain criteria initiative: Background, issues, and pragmatics. *Psychophysiology, 53*(3), 286–297.

Krueger, R. F., & Tackett, J. L. (2003). Personality and psychopathology: Working toward the bigger picture. *Journal of Personality Disorders, 17*, 109–128.

Kushner, S. C. (2015). A review of the direct and interactive effects of life stressors and dispositional traits on youth psychopathology. *Child Psychiatry and Human Development, 46*(5), 810–819.

Lahat, A., Lamm, C., Chronis-Tuscano, A., Pine, D. S., Henderson, H. A., & Fox, N. A. (2014). Early behavioral inhibition and increased error monitoring predict later social phobia symptoms in childhood. *Journal of the American Academy of Child and Adolescent Psychiatry, 53*(4), 447–455.

Lahat, A., Pérez-Edgar, K., Degnan, K. A., Guyer, A. E., Lejuez, C. W., Ernst, M., … Fox, N. A. (2012). Early childhood temperament predicts substance use in young adults. *Translational Psychiatry, 2*(9), e157.

Lahey, B. B., Krueger, R. F., Rathouz, P. J., Waldman, I. D., & Zald, D. H. (2017). A hierarchical causal taxonomy of psychopathology across the life span. *Psychological Bulletin, 143*(2), 142–186.

Laptook, R. S., Klein, D. N., Olino, T. M., Dyson, M. W., & Carlson, G. (2010). Low positive affectivity and behavioral inhibition in preschool-age children: A replication and extension of previous findings. *Personality and Individual Differences, 48*, 547–551.

Lemery, K. S., Essex, M. J., & Smider, N. A. (2002). Revealing the relation between temperament and behavior problem symptoms by eliminating measurement confounding: Expert ratings and factor analyses. *Child Development, 73*, 867–888.

Lengua, L. J., & Kovacs, E. A. (2005). Bidirectional associations between temperament and parenting and the prediction of adjustment problems in middle childhood. *Journal of Applied Developmental Psychology, 26*(1), 21–38.

Lewis-Morrarty, E., Degnan, K. A., Chronis-Tuscano, A., Rubin, K. H., Cheah, C. S., Pine, D. S., … Fox, N. A. (2012). Maternal over-control moderates the association between early childhood behavioral inhibition and adolescent social anxiety symptoms. *Journal of Abnormal Child Psychology, 40*(8), 1363–1373.

McDermott, J. M., Pérez-Edgar, K., Henderson, H. A., Chronis-Tuscano, A., Pine, D. S., & Fox, N. A. (2009). A history of childhood behavioral inhibition and enhanced response monitoring in adolescence are linked to clinical anxiety. *Biological Psychiatry, 65*(5), 445–448.

Meyer, A., Danielson, C., Danzig, A. P., Bhatia, V., Black, S. R., Bromet, E., … Klein, D. N. (2017). Neural reactivity to mistakes and temperamental fearfulness prospectively predict the impact of Hurricane Sandy stressors on internalizing symptoms in children. *Journal of the American Academy of Child and Adolescent Psychiatry, 56*, 410–416.

Muris, P., van Brakel, A. M., Arntz, A., & Schouten, E. (2011). Behavioral inhibition as a risk factor for the development of childhood anxiety disorders: A longitudinal study. *Journal of Child and Family Studies, 20*(2), 157–170.

Olino, T. M., Klein, D. N., Dyson, M. W., Rose, S. A., & Durbin, C. E. (2010). Temperamental emotionality in preschool-aged children and depressive disorders in parents: Associations in a large community sample. *Journal of Abnormal Psychology, 119*, 468–478.

Ormel, J., & De Jong, A. (1999). On vulnerability to common mental disorders: An evidence-based plea for a developmental perspective. In M. Tansella & G. Thornicroft (Eds.), *Common mental disorders in primary care* (pp. 34–351). London, England: Routledge.

Ormel, J., Oldehinkel, A. J., & Brilman, E. I. (2001). The interplay and ecological continuity of neuroticism, difficulties, and life events in the etiology of major and subsyndromal, first and recurrent depressive episodes in later life. *American Journal of Psychiatry, 158*, 885–891.

Paulus, F. W., Backes, A., Sander, C. S., Weber, M., & von Gontard, A. (2015). Anxiety disorders and behavioral inhibition in preschool children: A population-based study. *Child Psychiatry and Human Development, 46*(1), 150–157.

Pérez-Edgar, K. E., & Guyer, A. E. (2014). Behavioral inhibition: Temperament or prodrome? *Current Behavioral Neuroscience Reports, 1*(3), 182–190.

Pfeifer, M., Goldsmith, H. H., Davidson, R. J., & Rickman, M. (2002). Continuity and change in inhibited and uninhibited children. *Child Development, 73*, 1474–1485.

Rapee, R. M., & Coplan, R. J. (2010). Conceptual relations between anxiety disorder and fearful temperament. *New Directions for Child and Adolescent Development, 127*, 17–31.

Reeb-Sutherland, B. C., Vanderwert, R. E., Degnan, K. A., Marshall, P. J., Pérez-Edgar, K., Chronis-Tuscano, A., … Fox, N. A. (2009). Attention to novelty in behaviorally inhibited adolescents moderates risk for anxiety. *Journal of Child Psychology and Psychiatry, 50*(11), 1365–1372.

Roberts, B. W., & DelVecchio, W. F. (2000). The rank-order consistency of personality from childhood to old age: A quantitative review of longitudinal studies. *Psychological Bulletin, 136*, 3–25.

Roberts, B. W., Walton, K. E., & Viechtbauer, W. (2006). Patterns of mean-level change in personality traits across the life course: A meta-analysis of longitudinal studies. *Psychological Bulletin, 132*, 1–25.

Rosenbaum, J. F., Biederman, J., Gersten, M., Hirshfeld, D. R., Meminger, S. R., Herman, J. B., … Snidman, N. (1988). Behavioral inhibition in children of parents with panic disorder and agoraphobia: A controlled study. *Archives of General Psychiatry, 45*(5), 463–470.

Rosenbaum, J. F., Biederman, J., Hirshfeld, D. R., Bolduc, E. A., & Chaloff, J. (1991). Behavioral inhibition in children: A possible precursor to panic disorder or social phobia. *The Journal of Clinical Psychiatry, 52*(Suppl), 5–9.

Rosenbaum, J. F., Biederman, J., Hirshfeld-Becker, D. R., Kagan, J., Snidman, N., Friedman, D., … Faraone, S. V. (2000). A controlled study of behavioral inhibition in children of parents with panic disorder and depression. *American Journal of Psychiatry, 157*(12), 2002–2010.

Rubin, K. H., Burgess, K. B., & Hastings, P. D. (2002). Stability and social-behavioral consequences of toddlers' inhibited temperament and parenting behaviors. *Child Development, 73*(2), 483–495.

Rubin, K. H., Coplan, R. J., & Bowker, J. C. (2009). Social withdrawal in childhood. *Annual Review of Psychology, 60*, 141–171.

Rubin, K. H., Hastings, P. D., Stewart, S. L., Henderson, H. A., & Chen, X. (1997). The consistency and concomitants of inhibition: Some of the children, all of the time. *Child Development, 68*, 467–483.

Rubin, K. H., Nelson, L. J., Hastings, P., & Asendorpf, J. (1999). The transaction between parents' perceptions of their children's shyness and their parenting styles. *International Journal of Behavioral Development, 23*(4), 937–957.

Salk, R. H., Hyde, J. S., & Abramson, L. Y. (2017). Gender differences in depression in representative national samples: Meta-analyses of diagnoses and symptoms. *Psychological Bulletin, 143*, 783–822.

Schwartz, C. E., Snidman, N., & Kagan, J. (1999). Adolescent social anxiety as an outcome of inhibited temperament in childhood. *Journal of the American Academy of Child and Adolescent Psychiatry, 38*(8), 1008–1015.

Silk, J. S., Davis, S., McMakin, D. L., Dahl, R. E., & Forbes, E. E. (2012). Why do anxious children become depressed teenagers? The role of social evaluative threat and reward processing. *Psychological Medicine, 42*, 2095–2107.

Stumper, A., Danzig, A. P., Dyson, M. W., Olino, T. M., Carlson, G. A., & Klein, D. N. (2017). Parents' behavioral inhibition moderates association of preschoolers' BI with risk for age 9 anxiety disorders. *Journal of Affective Disorders, 210*, 35–42.

Thorell, L. B., Bohlin, G., & Rydell, A. M. (2004). Two types of inhibitory control: Predictive relations to social functioning. *International Journal of Behavioral Development, 28*(3), 193–203.

Waszczuk, M. A., Zavos, H. M. S., Gregory, A. M., & Eley, T. C. (2014). The phenotypic and genetic structure of depression and anxiety disorder symptoms in childhood, adolescence, and young adulthood. *JAMA Psychiatry, 71*(8), 905–916.

Watson, D., Stasik, S. M., Ellickson-Larew, S., & Stanton, K. (2015). Extraversion and psychopathology: A facet-level analysis. *Journal of Abnormal Psychology, 124*, 432–446.

White, L. K., Degnan, K. A., Henderson, H. A., Pérez-Edgar, K., Walker, O. L., Shechner, T., … Fox, N. A. (2017). Developmental relations among behavioral inhibition, anxiety, and attention biases to threat and positive information. *Child Development, 88*(1), 141–155.

White, L. K., McDermott, J. M., Degnan, K. A., Henderson, H. A., & Fox, N. A. (2011). Behavioral inhibition and anxiety: The moderating roles of inhibitory control and attention shifting. *Journal of Abnormal Child Psychology, 39*(5), 735–747.

Widiger, T. A., & Samuel, D. B. (2005). Diagnostic categories or dimensions? A question for the diagnostic and statistical manual of mental disorders—Fifth edition. *Journal of Abnormal Psychology, 114*(4), 494–504.

Williams, L. R., Degnan, K. A., Pérez-Edgar, K. E., Henderson, H. A., Rubin, K. H., Pine, D. S., … Fox, N. A. (2009). Impact of behavioral inhibition and parenting style on internalizing and externalizing problems from early childhood through adolescence. *Journal of Abnormal Child Psychology, 37*(8), 1063–1075.

The Biological Bridge Between Behavioral Inhibition and Psychopathology

Chad M. Sylvester and Daniel S. Pine

Abstract In this chapter, we review the biological bridge between early childhood behavioral inhibition (BI) and psychopathology, with an emphasis on anxiety disorders. We contextualize the biology of behavioral inhibition and anxiety disorders within the physiology of the threat system. Behavioral inhibition is conceptualized as reflecting an early-appearing tendency to engage the threat system in the presence of both ambiguous and potentially threatening stimuli. The progression from behavioral inhibition to anxiety disorders is hypothesized to occur when brain-based regulatory systems mature in ways that amplify rather than lessen fear. Specific environmental factors that may influence the progression from behavioral inhibition to anxiety disorders are discussed. We complete this chapter by discussing areas for future work.

Behavioral inhibition (BI) is a stable temperament that appears early in development and is characterized by increased attention and distress to novel stimuli, particularly in social contexts (Kagan, Reznick, Snidman, Gibbons, & Johnson, 1988). Approximately 15–20% of young children demonstrate high behavioral inhibition. Although many of these children do not develop psychopathology later in life, children with high levels of behavioral inhibition, relative to children with low levels, face elevated risk for anxiety, depressive, and substance use problems (Fox, Henderson, Marshall, Nichols, & Ghera, 2005), with a particularly high risk for developing anxiety disorders, especially social anxiety disorder (Clauss & Blackford, 2012).

Anxiety disorders are the most common form of psychiatric illness, with prevalence estimates in the range of 20–30% across the lifespan (Kessler et al., 2005; Merikangas et al., 2010; Sylvester & Pine, 2016). The median age of onset for anxiety disorders is around 6–10 years of age (Merikangas et al., 2010), with many

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children demonstrating subclinical symptoms of anxiety disorders years before full disorder onset. Moreover, specific forms of anxiety disorders typically arise in an age-related fashion, with risk for specific phobias arising early, followed by separation anxiety disorder, social anxiety disorder, and generalized anxiety disorder. Behavioral inhibition can be viewed as a component of this developmental cascade, supporting a broader view of anxiety disorders as disorders of neurodevelopment (Pine, 2007).

The goal of this chapter is to describe the biological bridge between behavioral inhibition and psychopathology. Most work in this area has focused on anxiety disorders, reflecting the particularly strong link between behavioral inhibition and social anxiety disorder (see the chapter "Behavioral Inhibition as a Precursor to Psychopathology" by Klein and Mumper).

The organization of the chapter is as follows: we first describe the neurobiology of the threat system, as a basis for understanding variation in temperament and anxiety symptoms. We next contextualize the biology of behavioral inhibition and anxiety disorders within the physiology of this threat system. The reader is referred to chapters in this volume (the chapter "The Neural Mechanisms of Behavioral Inhibition" by Jarcho and Guyer and the chapter "Psychobiological Processes in the Development of Behavioral Inhibition" by Buss and Qu and the chapter "The Neurobiology of Behavioral Inhibition as a Developmental Mechanism" by Blackford et al.) for a more extensive review of the biology of behavioral inhibition. We follow this discussion by describing studies examining biological links between behavioral inhibition and symptoms of anxiety disorders in the same subjects, as well as the influence of specific individual and environmental factors associated with the progression from behavioral inhibition to symptoms of anxiety disorders. We end with a framework for linking the biology of behavioral inhibition and anxiety disorders before describing limitations of this framework and areas of future work. These considerations are derived, in part, from previous treatments of this topic (Degnan & Fox, 2007; Fox & Kalin, 2014; Henderson, Pine, & Fox, 2015; Pine & Fox, 2015; Sylvester et al., 2012).

Threat System

As a group, mammals display prototypical behavioral and physiologic responses to real or perceived imminent threats, stimuli capable of harming the organism (see the chapter "Behavioral Inhibition in Nonhuman Primates: The Elephant in the Room" by Capitanio). The term "fear" refers to the subjective state reported by people when confronted with a threat. Thus, this term is restricted to humans, whereas the terms "threat response" and "threat reaction" refer to the collection of behavioral and physiologic changes displayed more generally across species following exposure to threats.

A threat reaction refers to rapid, reflexive changes in behavior and physiology, preserved across mammals. Such reactions involve various physiological and behavioral manifestations that are typically adaptive responses to threat. The rapid

nature of these reactions protects organisms from imminent threats. However, another series of behavioral and physiological changes can be deployed more slowly. These second set of changes are termed "threat responses," which exhibit greater cross-species variability. The threat response allows mammals to draw on a species-typical repertoire to modulate initial threat reactions to situations that mobilize competing behavioral goals or to inhibit a threat reaction when a previously threatening stimulus is no longer capable of harming the organism. As such, the human brain has evolved a well-tuned and rapid threat-reactive system shared with other mammals as well as several parallel systems unique to primates or humans to modulate these initial fear reactions (LeDoux & Pine, 2016). As described in more detail below, the biological correlates of behavioral inhibition and anxiety disorders can be contextualized within individual variation of these systems and their dysfunctions.

Much of our understanding of behavior evoked by threats reflects work in rodents as reviewed elsewhere (Calhoon & Tye, 2015; Davis, Walker, Miles, & Grillon, 2010; LeDoux, 2000; Tovote, Fadok, & Luthi, 2015) (see also the chapter "Behavioral Inhibition in Rodents: A Model to Study Causes and Health Consequences of Temperament" by Cavigelli). The rapid detection and automatic categorization of stimuli as threatening is thought to involve several subcortical and cortical brain regions. These brain regions include the superior and inferior colliculi, the primary sensory cortices, the amygdala, bed nucleus of the stria terminalis (BNST), and portions of the hippocampus. The amygdala and BNST are structures that rapidly engage connected brain regions when a stimulus is perceived to be threatening, either based on plasticity that has occurred through prior experiences or through innately threatening aspects of a stimulus. These structures initiate broader changes in the organism through projections to other brain regions, including the motor cortex, to evoke defensive behaviors, the hypothalamus, to regulate hormonal secretions, and various brainstem nuclei, to influence autonomic parameters such as such heart rate and respiration.

In addition to these systems capable of automatic, rapid threat reactions, several other circuits modulate these initial reactions. One set of regulatory systems is involved in implicit, extinction-based regulation of amygdala activity (Etkin, Buchel, & Gross, 2015; LeDoux & Pine, 2016). This first set of regulatory systems has been extensively studied in rodents and possesses homologs in primates. The rodent infralimbic cortex, for example, appears to play an important role in extinction-based threat regulation, by decreasing amygdala response to stimuli that were previously but are no longer threatening. The rodent prelimbic cortex, on the other hand, may increase the threat response by enhancing amygdala activity in response to threatening stimuli. The rodent infralimbic and prelimbic cortices are thought to have homologs in primates within subgenual and pre-genual portions of the cingulate gyrus, respectively. Another set of regulatory systems appear to be involved in explicit regulation of amygdala activity and arose in tandem with primate evolution (Etkin et al., 2015; LeDoux & Pine, 2016). These modulatory regions in the lateral and medial prefrontal cortex allow primates to deploy highly flexible responses to threats, which can dampen or increase the initial reaction to a

threat. These explicit emotion regulation responses include strategic deployment of attention and working memory and may include conscious processes in humans.

Outside the realm of threat-related behaviors, other brain structures involved in motivated behavior have the capacity to modulate circuitry supporting threat reactions. These regions include the ventral tegmental area, the hippocampus, insula cortex, and various nuclei within the hypothalamus. These regions respond to other demands faced by the organism, such as the need to maintain homeostasis and to procreate. These regions interact with other circuitry to modulate activity of the amygdala and associated threat-responsive circuitry to support complex, adaptive behavior in complex environments. Thus, the threat system is beautifully designed to act both very quickly in cases of imminent danger and highly flexibly when competing drives or goals must override the initial threat reaction. Moreover, as mammals evolved to exploit increasingly complex environments, the associated neural machinery became increasingly complex in an adaptive fashion.

Most work on the neuroscience of threat reactions and regulation examines rodents or nonhuman primates. Nevertheless, threats engage physiologic systems in humans that share features with these other species, albeit with substantial modification and expansion of regulatory systems (Blackford & Pine, 2012; Etkin, 2010; Shin & Liberzon, 2010; Sylvester et al., 2012). For the purposes of this chapter, we focus on four different human regulatory systems. Each of these regulatory systems is thought to modify threat-related processes by modulating the activity of regions that are rapidly deployed in the presence of a threat, such as the amygdala and BNST. These four regulatory systems each center on a different brain region: the subgenual anterior cingulate cortex (sgACC), the dorsal anterior cingulate cortex (dACC), the ventrolateral prefrontal cortex (VLPFC), particularly in the right hemisphere, and the dorsolateral prefrontal cortex (DLPFC).

Each of these four brain regions, in turn, is a component of a different "functional brain network." A functional brain network is a group of regions with correlated activity at rest and that work together to perform a set of related functions (Raichle, 2011). As brain imaging data have accrued, individual differences in behavior, as are expressed in anxiety disorders and other forms of psychopathology, are increasingly viewed as reflecting individual in the functions of these networks. Such a network-based perspective differs from earlier views, which attributed individual differences to specific brain regions. In the discussion below, we highlight each of these regulatory systems as well as the associated functional brain network, because the function of the larger brain network informs the biology of the regulatory system. These regions and the associated functional brain networks are illustrated in Fig. 1 (see also the chapter "The Neural Mechanisms of Behavioral Inhibition" by Jarcho and Guyer).

A first regulatory system centers on the subgenual anterior cingulate cortex (sgACC). Among humans, this system is thought to function analogously to systems that allow rodents to regulate response to learned threats through engagement of implicit, extinction-related brain systems (Milad et al., 2007). In addition to other functions, a network centered on the sgACC appears to represent the knowledge that a previously threatening stimulus is no longer threatening, as implicitly learned through repeated safe exposure to the same stimulus.

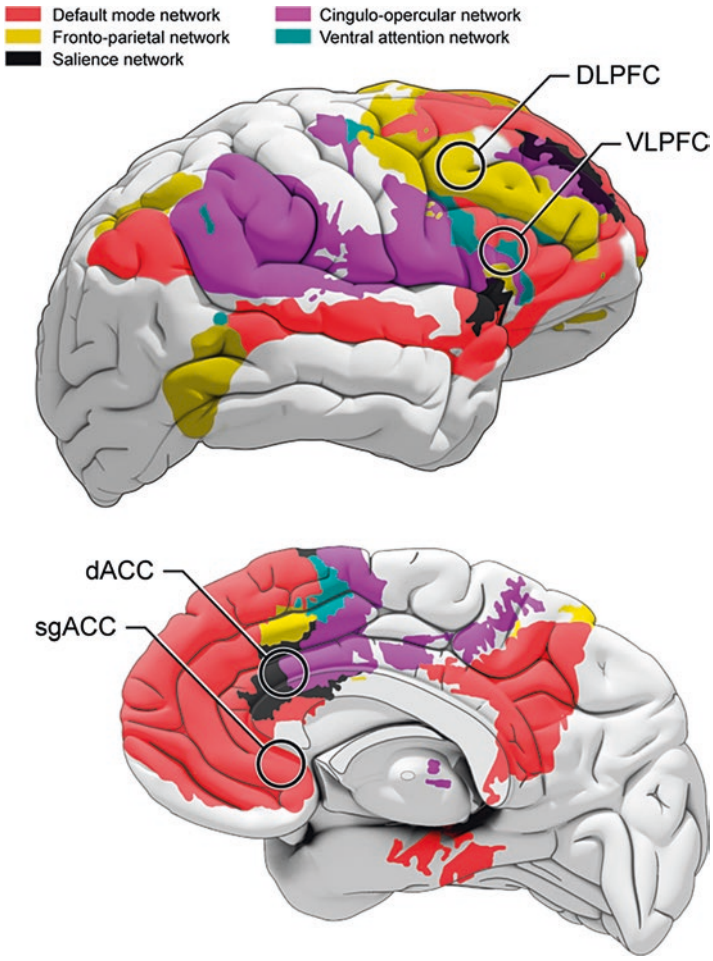

Fig. 1 Brain regions associated with regulation of threat processing and associated functional brain networks. The color of cortex represents the functional brain network assignment, using data from a study of adults (Power et al., 2011). Circles represent approximate locations of regions that are thought to regulate response to threat. Note that the network assignment of some regions is ambiguous. *DLPFC* dorsolateral prefrontal cortex, *VLPFC* ventrolateral prefrontal cortex, *dACC* dorsal anterior cingulate cortex, *sgACC* subgenual anterior cingulate cortex

An experimental paradigm used to examine the role of the sgACC in extinction is depicted in Fig. 2 (see also the chapter "The Neurobiology of Behavioral Inhibition as a Developmental Mechanism" by Blackford et al.). This paradigm has been used to study behavioral inhibition, in the context of an experiment where research participants learn to view previously threatening stimuli as safe (Shechner et al., 2017). The key network encompassing the sgACC and enabling implicit regulation strategies such as extinction has been termed the "default mode network,"

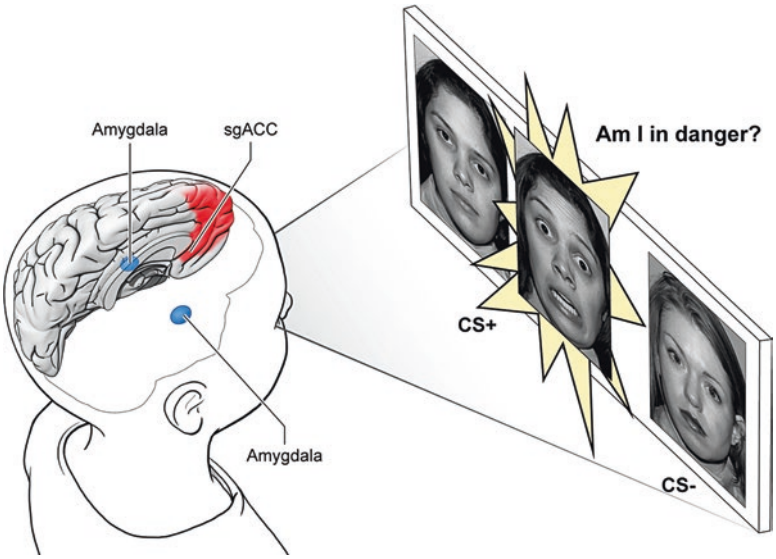

Fig. 2 The subgenual anterior cingulate cortex (sgACC) is hypothesized to regulate threat processing through its role in extinction. The threat response to previously threatening stimuli decreases with repeated presentation of the stimulus in a safe context. This reduction in the threat response with repeated presentation is called extinction and may rely, in part, on the sgACC. In the illustration above, the conditioned stimulus (CS+) is paired with an unconditioned stimulus that evokes a threat response, such as a loud noise. The neutral stimulus (CS-) was previously but is no longer paired with the unconditioned stimulus, and so the sgACC may downregulate the threat response to the CS- in this paradigm

which supports various self-referential processes (Raichle, 2015). Expansion of this system in primates, and interactions with other brain networks involved in attention and working memory, may relate to uniquely flexible behavioral regulation of threats in these species (Barrett, 2017). Brain systems involved in working memory, for example, could modulate activity in the default mode network that corresponds to an internal emotional state, providing an additional layer of regulation not possessed by rodents.

A second set of regulatory systems centers around the dorsal anterior cingulate cortex (dACC) and bilateral anterior insula. This second set of systems appears to amplify, rather than lessen, the initial response to threats. This second set comprises two closely related brain networks, the cingulo-opercular and salience networks, both of which encompass the dACC and insula (Power et al., 2011). The close physical proximity of these two separable networks complicates attempts to dissociate their functions in the context of threat exposure. Outside of threat-related behaviors, considerable neuroscience research delineates the role of these networks in other behaviors. For example, the cingulo-opercular network is more involved in error detection and conflict monitoring than the salience network (Dosenbach et al., 2006),

while the salience network is more involved in altering activity throughout other brain regions, based on the salience of incoming stimuli (Seeley et al., 2007). All of these processes could feasibly amplify initial reactions to threats.

A third regulatory system is centered on the ventrolateral prefrontal cortex (VLPFC), particularly in the right hemisphere, a brain region with significantly increased surface area in humans relative to primates (Hill et al., 2010). The VLPFC is thought to provide primates with flexible responses to threats, through changes in attention, toward or away from potentially threatening stimuli (Blackford & Pine, 2012; Sylvester et al., 2012). A portion of the right VLPFC is situated within the ventral attention network, which supports the capture of attention by novel, salient stimuli (Corbetta, Patel, & Shulman, 2008). Of note, previous studies have not clearly delineated the precise portions of VLPFC that respond to threats. Nevertheless, based on its role in attention, the portion within the ventral attention network is a leading candidate. Although both the ventral attention and salience networks respond to salient external stimuli that reorient attention, the two networks are thought to have distinct anatomical and functional roles. Whereas the ventral attention network is thought to have a specific role in the reorientation of spatial attention to external, behaviorally relevant stimuli (Corbetta et al., 2008), the salience network appears to have a more general role in identifying and labeling salient stimuli in sensory, autonomic, and visceral domains (Uddin, 2015).

A final set of regulatory regions encompass the bilateral dorsolateral prefrontal cortices (DLPFC) and lie within the frontoparietal network, which has a general role in planning, organizing, and executive function. Brain regions in the frontoparietal network such as the DLPFC exhibit marked surface area expansion in humans (Hill et al., 2010) and allow primates to maintain and shift goal representations and associated motivational behaviors with much greater flexibility than other mammals. These regulatory regions are hypothesized to modulate activity in brain regions that are automatically engaged by the presence of a threat, such as the amygdala (Ochsner & Gross, 2005). In humans, the DLPFC may implement explicit emotion regulation strategies that can be learned through instructions, as occurs in cognitive reframing or active suppression.

Neurobiology of Behavioral Inhibition

In this section, the biology of behavioral inhibition is contextualized within the framework of the threat-related systems described above. To summarize this section, the biology of behavioral inhibition can be conceptualized as hypersensitivity in systems that support threat reactions, which include the amygdala and BNST, in combination with altered development of regulatory systems. Open questions include whether individuals high in behavioral inhibition have dysfunction in multiple regulatory systems simultaneously, as well as how dysfunctions evolve with development among individuals who mature to be free of psychopathology.

Threat Reactions

Several pieces of evidence suggest that individuals high in behavioral inhibition have structural and functional alterations in brain systems that support threat reactions. Schwartz et al. provided some of the first evidence to support this idea. This group used functional magnetic resonance imaging (fMRI) to examine amygdala reactivity to novel stimuli (Schwartz, Wright, Shin, Kagan, & Rauch, 2003). In the first such study, adults who had previously been identified during early childhood as high in behavioral inhibition were found to have higher amygdala activity compared to adults who had not had high behavioral inhibition. The same group later extended this finding by demonstrating that infants with a high reactive negative phenotype, a precursor of behavioral inhibition, also had increased amygdala reactivity as adults (Schwartz et al., 2012).

Pérez-Edgar et al. (2007) similarly found that 10-year old children who had previously been identified as high in behavioral inhibition had higher amygdala activity while passively viewing a fearful face relative to children without high behavioral inhibition. Interestingly, this basic result appears to have some parallels across species, as monkeys with high anxious temperament, related to the construct of behavioral inhibition, manifest increased metabolism in the amygdala following an intruder task (Birn et al., 2014). Other studies reported alterations in amygdala structure or functional connectivity in individuals previously identified as high in behavioral inhibition (Clauss et al., 2014; Roy et al., 2014) or in neonates who go on to develop high levels of behavioral inhibition (Rogers et al., 2017).

Despite the promising nature of these initial findings, considerably more work is needed. In general, concerns have arisen in the brain imaging literature about Type I errors and failures to replicate initial findings. These concerns clearly apply to the above-noted studies on behavioral inhibition as sample sizes remain small, and few studies adopt identical methods in attempts to replicate initial findings. This concern is shared with other brain imaging studies on individual differences. Moreover, the few studies that have adopted an imaging approach generally fail to replicate initial findings (Schwartz et al., 2010; Sylvester et al., 2016). Nevertheless, progress is evident in brain imaging as studies among humans examine structure and functions in biological systems that can be probed through highly similar methodology across species. This brings a level of rigor to studies of brain imaging that were not possessed by earlier biological research in psychology and psychiatry.

Subgenual Anterior Cingulate Cortex (sgACC)

In addition to alterations in the amygdala, behavioral inhibition has also been linked to deficits in each of the regulatory systems described above. Several studies reported differences in the structure and function of a region at or near the sgACC, a region described above that is important for implicit emotion regulation and

extinction-based fear reduction. Schwartz et al. (2010) reported that adults previously identified as high in behavioral inhibition during early children had greater thickness of a right ventromedial prefrontal cortex region near the sgACC compared to adults who had been low in behavioral inhibition as children. Additional studies reported differences in functional connectivity of the sgACC: in individuals with high versus low behavioral inhibition as children (Clauss, Benningfield, Rao, & Blackford, 2016; Roy et al., 2014; Taber-Thomas, Morales, Hillary, & Pérez-Edgar, 2016) as well as alterations in sgACC activity during anticipation and viewing of fearful faces (Clauss et al., 2016). Shechner et al. (2017) recently used fear conditioning and extinction methods to directly implicate the sgACC in extinction and behavioral inhibition, as schematically illustrated in Fig. 2. Nevertheless, as noted above for studies of the amygdala, studies in this area also generally fail to adopt identical methods in attempts to replicate initial associations. While the work lays the groundwork for a rigorous approach, future studies in far larger samples with more rigorous statistical approaches are needed.

Ventrolateral Prefrontal Cortex (VLPFC)

Additional work examines functions of the right VLPFC and associated components of ventral attention network in behavioral inhibition. This brain system may modulate initial reactions to threats by shifting attention toward or away from threatening stimuli. Several studies have reported increased right lateralized brain activity, as measured with electroencephalography (EEG), in infants or young children high in behavioral inhibition in response to novel stimuli (Calkins, Fox, & Marshall, 1996; Fox et al., 1995; Fox, Henderson, Rubin, Calkins, & Schmidt, 2001). The poor spatial resolution of EEG precludes precise localization of the anatomical source of this brain activity. Nevertheless, increased right lateralized activity in frontal regions could reflect increased activity in the right VLPFC and ventral attention network, given other relevant evidence. This includes evidence that the ventral attention network is right lateralized and is involved in the involuntary, automatic direction of attention to new stimuli (Corbetta et al., 2008). Additional evidence includes recent findings suggesting that variation during the neonatal period in functional connectivity between the right VLFPC and right temporal-parietal junction, another node in the ventral attention network, predicts behavioral inhibition at age 2 years (Sylvester et al., 2017).

Dorsal Anterior Cingulate Cortex (dACC)

Several lines of evidence implicate a regulatory system that includes the dACC in the physiology of behavioral inhibition. As mentioned above, the dACC and insula function as part of both the cingulo-opercular network, involved in error detection,

and salience network, involved in assessing salience (Dosenbach et al., 2006; Seeley et al., 2007). Most studies of behavioral inhibition do not precisely localize the portion of the dACC involved in fear regulation. Nevertheless, several studies have reported abnormalities in activity (Clauss et al., 2016; Clauss, Cowan, & Blackford, 2011), functional connectivity (Clauss et al., 2016; Taber-Thomas et al., 2016), and cortical thickness (Sylvester et al., 2016) of the dACC in individuals with prior histories of high behavioral inhibition. In addition, individuals with behavioral inhibition as children, relative to those with no such history, express increased error-related negativity (ERN) (Lahat et al., 2014), an EEG signal thought to reflect, in part, dACC function (Moser, Moran, Schroder, Donnellan, & Yeung, 2013). The increase in the ERN is consistent with increased activity in the dACC reported with fMRI in some studies (Clauss et al., 2016).

Dorsolateral Prefrontal Cortex (DLPFC)

Compared to work on the sgACC, VLPFC, and dACC, less research targets the DLPFC in behavioral inhibition. The DLPFC functions as part of a system that matures later than the other systems (Hill et al., 2010). This late-maturing system enables flexible deployment of regulatory strategies, which can be learned through explicit emotion regulation techniques such as cognitive reframing. Clauss et al. (2016) recently compared children with low behavioral inhibition to children who were high in behavioral inhibition, using a threat anticipation task. Clauss et al. (2016) reported increased activity in the DLPFC while viewing faces in children with high behavioral inhibition compared to children with low behavioral inhibition. These results were interpreted as a failure to engage appropriate proactive emotion regulation strategies during an anticipatory phase of the task. As a result, children high in behavioral inhibition used a maladaptive, reactive emotion regulation strategy involving the DLPFC once the faces appeared (see also the chapter "The Neurobiology of Behavioral Inhibition as a Developmental Mechanism" by Blackford et al.). As with other work, future studies are required to replicate these using comparable methods and in order to explore the proposed mechanism in more detail.

Brain system research applying current imaging methods to behavioral inhibition is only beginning. Hence, the available research possesses many limitations. One concern is that many of the studies described above examine brain structure and function in adolescents or adults who had high versus low behavioral inhibition as young children. Thus, it is not clear which results are related to causes versus consequences of having high behavioral inhibition (see the chapter "Behavioral Inhibition as a Precursor to Psychopathology" by Klein and Mumper). To begin to address this concern, we recently examined associations between functional connectivity near birth and symptoms of behavioral inhibition at age 2 years as measured by parent report using the Infant Toddler Social Emotional Assessment (ITSEA).

In a first study, we established that resting-state functional connectivity between the amygdala and several regions in the frontal and temporal cortices differed between neonates who would go on to develop high versus low behavioral inhibition as 2-year-olds (Rogers et al., 2017). In a second study, we further established that decreased neonatal connectivity of the VLPFC and sgACC, but not the dACC, was related to behavioral inhibition at age 2 years (Sylvester et al., 2017). If these findings are replicated in additional longitudinal studies, they suggest that the first alterations associated with behavioral inhibition occur in the amygdala and in the regulatory systems centered on the sgACC and VLPFC. A speculative possibility is that alterations in the dACC and potentially the DLPFC either occur later in development or are adaptive compensations in children with high behavioral inhibition.

Beyond studies of threat-responsive circuitry, other research examines alterations in distinct brain regions, related to other information-processing functions, among children with behavioral inhibition. These alterations may interact with alterations in threat-responsive circuitry to shape risk. For example, behavioral inhibition has been linked to increased striatal response to reward (Guyer, et al., 2006, 2014), which could result from either hypersensitivity to reward or motivation to avoid errors (Lahat, Benson, Pine, Fox, & Ernst, 2016).

In summary, the biology of behavioral inhibition may involve hypersensitivity in brain regions, such as the amygdala, that detect threatening stimuli. This hypersensitivity may manifest in tandem with alterations in associated regulatory systems. These include systems encompassing the sgACC, associated with implicit emotion regulation; the VLPFC, associated with attention to novel and threatening stimuli; the dACC, associated with upregulation of the fear response; and the DLFPC, associated with explicit emotion regulation strategies.

Neurobiology of Anxiety Disorders

Similar to behavioral inhibition, the neurobiology of anxiety disorders is often contextualized within the basic neuroscience of threat-sensitive circuitry (Blackford & Pine, 2012; Etkin, 2010; Shin & Liberzon, 2010; Sylvester et al., 2012). Given the relation between behavioral inhibition and anxiety disorders, it is not surprising that there is substantial overlap in the biology of these two constructs. As reviewed below, there is evidence for dysfunction in anxiety disorders in brain systems that detect and make the initial interpretation of stimuli as threatening, such as the amygdala and BNST. In addition, there is evidence for alterations in the same regulatory systems described above for behavioral inhibition, including systems centered on the sgACC, the VLFPC, the dACC, and the DLPFC. In contrast to behavioral inhibition, however, studies in anxiety disorders find a somewhat more replicable pattern of results across age groups. In addition, there is more evidence for deficits in explicit emotion regulatory systems centered on the DLPFC in anxiety disorders compared to behavioral inhibition. These overlaps and potential discrepancies inform attempts to bridge these conditions.

Similar to behavioral inhibition, there are many studies in children and adolescents with anxiety disorders that demonstrate alterations in activity, functional connectivity, and volume of the amygdala (Birn et al., 2014; Blackford & Pine, 2012; McClure et al., 2007; Monk et al., 2008; Thomas et al., 2001). These data suggest that children with anxiety disorders have amygdalae that are overactive in response to threat. This notion is consistent with the hypothesis that the automatic brain systems that detect threats are overactive in both anxiety disorders and behavioral inhibition.

There is also ample evidence for similar alterations in regulatory systems in anxiety disorders and behavioral inhibition. These alterations have been the subject of prior reviews and are described here briefly (Blackford & Pine, 2012; Etkin, 2010; Shin & Liberzon, 2010; Sylvester et al., 2012). Many studies have reported altered activity in the medial prefrontal cortex in a region near the sgACC in individuals with anxiety disorders (Casey et al., 2011; Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010; Evans et al., 2009). Activity is usually decreased in the sgACC in anxiety disorders, but directionality depends on the specific paradigm used in the study. These sgACC activity differences sometimes have been linked to alterations in implicit emotion regulation or variation in extinction-based fear reduction mechanisms (Casey et al., 2011; Delgado, Nearing, Ledoux, & Phelps, 2008). This hypothesis is further supported by studies demonstrating alterations in strength and directionality of functional connectivity of the sgACC in individuals with anxiety disorders (Etkin et al., 2010; Hahn et al., 2011). The direction of altered sgACC connectivity appears to depend critically on whether connectivity is measured during a specific task versus during rest periods.

Another consistent set of findings reveals alterations in the right VLPFC in individuals with anxiety disorders. Several studies have reported increased activity in the VLPFC in children with anxiety disorders in response to angry faces relative to children without anxiety disorders (Monk et al., 2006, 2008). Moreover, such findings often encompass the proximal insula cortex, which may account for overlapping functions shared by networks engaging these regions. Indeed, among primates, VLPFC may represent an expansion of the earlier evolving insula cortex (Murray, Wise, & Graham, 2017). Given the role of the right VLPFC in attention, one possibility is that this increased activity reflects increased attention for threats and possibly other salient stimuli, such as various types of evocative faces. An alternative hypothesis is that this increased activity represents a compensatory mechanism to decrease anxiety. This hypothesis is supported by the finding that among children with anxiety disorders, children with higher VLPFC activity have lower anxiety (Monk et al., 2006). An additional study reported alterations in functional connectivity of the right VLPFC and the ventral attention network among children with a prior history of an anxiety disorder (Sylvester et al., 2013).

In addition to alterations in the sgACC and VLPFC, many studies implicate dysfunction in the dACC in the pathophysiology of anxiety disorders. These studies include reports of increased activity in the dACC in individuals with anxiety disorders during the viewing of emotional faces (Amir et al., 2005; McClure et al., 2007) as well as reports of differences in functional connectivity of this region

(Etkin et al., 2010; Liao et al., 2010). As in the case of behavioral inhibition, another line of evidence comes from EEG studies of the ERN, which may localize in part to the dACC. A consistent finding has been increased ERN in subjects with anxiety disorders compared to healthy controls (Moser et al., 2013; Weinberg, Olvet, & Hajcak, 2010), consistent with the studies discussed above reporting increased dACC activity as measured with fMRI.

Finally, anxiety disorders have been associated with dysfunction in the DLFPC, generally in the context of disordered explicit emotion regulation. These studies have generally reported increased activity in the DLPFC in tasks that have incorporated emotionally laden stimuli (Bruhl, Delsignore, Komossa, & Weidt, 2014; Etkin, Prater, Schatzberg, Menon, & Greicius, 2009; Goldin, Manber-Ball, Werner, Heimberg, & Gross, 2009). Interestingly, a few studies have also reported altered DLPFC activity in individuals with high trait activity in tasks that use neutral, non-emotional stimuli (Bishop, 2009; Bishop, Jenkins, & Lawrence, 2007). These results open the possibility that anxiety is associated with deficits in DLPFC function even outside the realm of emotion regulation. As with the other regulatory regions, anxiety has also been associated with variation in functional connectivity of the DLPFC (Liao et al., 2010).

Trajectories from Behavioral Inhibition to Anxiety

The preceding sections connect the biology of behavioral inhibition and anxiety disorders through research on threat-responsive circuitry. Although it is useful to compare studies that examine behavioral inhibition to studies that examine anxiety disorders, there are several pitfalls to this approach. First, few studies directly compare individuals with behavioral inhibition and anxiety disorders. As a result, the extant work does not directly compare the nature of deficits in the two phenotypes. Second, it is not clear from the above work how deficits in the different regulatory systems interact in behavioral inhibition versus anxiety disorders. For example, both behavioral inhibition and anxiety disorders represent heterogenous conditions. It is possible that similar appearing behavioral phenotypes reflect the downstream effects of highly variable brain functions, an example of equifinality. Finally, findings in studies reviewed above derive largely from work with a single brain imaging data point. Thus, correlates of anxiety disorders and behavioral inhibition could evolve with development, showing distinct patterns with each other at particular ages.

To address these concerns, several studies have assessed anxiety symptoms and brain function in children with behavioral inhibition. In these longitudinal studies, the interaction between early childhood behavioral inhibition and variation in one of the regulatory systems in later childhood is examined in relation to symptoms of anxiety. Specific regulatory systems studied in this manner include those that modulate threat-response behavior through attention, potentially involving the VLPFC, and sensitivity to errors, potentially involving the dACC. Each of these studies has obtained a similar pattern of results: high early childhood behavioral inhibition in

combination with deficits in attention- or error-related systems later in childhood is associated with anxiety symptoms at a third, later, timepoint.

Several studies have examined the relations among early childhood behavioral inhibition, attention-related mechanisms later in childhood, and symptoms or diagnosis of an anxiety disorder. For example, White et al. (2017) studied the relations among early childhood behavioral inhibition, attention to threatening stimuli at ages 5 and 7 years, and symptoms of anxiety at age 7 years. This study revealed that children with high behavioral inhibition who also had an attention bias toward threat, away from positive stimuli, or no bias, had the greatest symptoms of anxiety at age 7 years. In contrast, behavioral inhibition was not related to anxiety in children who had attention bias away from threatening stimuli or toward positive stimuli at age 7 years. Critically, it was the combination of high behavioral inhibition and maladaptive attention that was associated with symptoms of anxiety, either behavioral inhibition or maladaptive attention alone was not associated with later symptoms of anxiety.

Reeb-Sutherland et al. (2009) measured the P300 event-related potential (ERP) in response to novel stimuli in adolescents. The P300 may index the involuntary capture of attention by salient stimuli. Children with high behavioral inhibition who also had a strong P300 ERP response to novel stimuli were most likely to have had a history of an anxiety disorder. Finally, Perez-Edgar et al. (2010) examined relations among sustained attention in 9-month-old infants, behavioral inhibition in early childhood, and symptoms of social discomfort at age 14 years. In this study, early childhood behavioral inhibition was related to later symptoms of social discomfort exclusively in children who had low sustained attention as infants. Together, the studies of White et al. (2017), Reeb-Sutherland et al. (2009), and Perez-Edgar et al. (2010) support a link between early childhood behavioral inhibition, later variation in attention, and subsequent symptoms of anxiety.

In addition to attention-related mechanisms, another set of studies has examined the relations among early childhood behavioral inhibition, behavioral or neural markers of error-detection brain systems in later childhood, and subsequent symptoms of anxiety (see the chapter "Relations Between Behavioral Inhibition, Cognitive Control and Anxiety: Novel Insights Provided by Parsing Subdomains of Cognitive Control" by Buzzell et al.). Lahat et al. (2014) used longitudinal data to study the relations between early childhood behavioral inhibition, the ERN at age 7 years, and social anxiety symptoms at age 9 years. As discussed above, the ERN is a neuronal response to errors and may at least partly reflect dACC activity. In this study, the ERN and correct related negativity (CRN) were measured in a group of children classified on the basis of having high or low behavioral inhibition over early childhood. Consistent with prior work (McDermott et al., 2009), the children with high behavioral inhibition had a higher ERN at age 7 years compared to children with low behavioral inhibition.

In addition, children with high behavioral inhibition who had a large difference between the ERN and CRN at age 7 tended to have higher social phobia symptoms at age 9. Children with low behavioral inhibition, regardless of the difference between their ERN and CRN, and children with high behavioral inhibition who had

a small difference between the ERN and CRN tended to have lower symptoms of social phobia at age 9 years. In other words, only the combination of both high behavioral inhibition in early childhood and a large difference between the ERN and CRN at age 7 years was associated with high social phobia symptoms at age 9 years. In another study, Hardee et al. (2013) reported that functional connectivity between the insula and amygdala during an attention task was more strongly related to symptoms of anxiety in adults previously classified as high in behavioral inhibition compared to adults that had been classified as low in behavioral inhibition. Given that the dACC and insula reside in the same functional brain network, it is possible that this result provides further evidence for error-related brain systems moderating relations between early behavioral inhibition and later anxiety symptoms. Further studies are needed to test this hypothesis.

While this chapter has focused on relations between behavioral inhibition and anxiety disorders, Lahat et al. (2012) examined substance use as an additional outcome. More specifically, Lahat et al. (2012) examined relations among early childhood behavioral inhibition, striatal hypersensitivity to reward during adolescence, and substance use 5 years later. Hypersensitivity to reward was measured with functional magnetic resonance imaging (fMRI) by comparing conditions in which subjects received a cue indicating that the upcoming trial would have high reward or loss (high reward expectation) versus conditions in which there was no expectation of reward. Results indicated that hypersensitivity to reward predicted later substance use among individuals who had had high but not low behavioral inhibition as children. Again, the combination of high behavioral inhibition and striatal hypersensitivity related to later psychopathology.

Proposed Framework

Available data suggest a preliminary framework to bridge behavioral inhibition and anxiety disorders, which can be examined in future work. Behavioral inhibition appears to involve a lowered threshold for deploying rapid, automatic threat-reactive brain systems, as suggested by imaging studies. These hypersensitive systems appear to manifest in the context of additional alterations in brain systems that regulate threat reactions. These other alterations encompass at least four separate regulatory systems, centered on the sgACC (implicit emotion regulation), VLPFC (attention), dACC (error detection and/or salience), and possibly the DLPFC (explicit emotion regulation). Importantly, we do not know how this set of brain alterations maps on to behavior in any one individual. Previously demonstrated alterations appear early in development in individuals with high behavioral inhibition, but the stability over development is an important area of future work.

Work on the basic biology and development of threat-responsive brain systems suggest that the biology of behavioral inhibition evolves with development into the biology of anxiety disorders. This evolution may occur when alterations in later-maturing regulatory systems manifest stably over development. An intriguing

but untested hypothesis is that behavioral inhibition evolves into anxiety disorders with the stable expression of perturbations in multiple regulatory systems. These perturbations include decreased functioning of systems that typically downregulate the threat system as well as increased functioning of systems that typically upregulate the threat system. As detailed in the next section, there are likely many genetic and environmental factors that may influence this evolving developmental picture.

Progression from Behavioral Inhibition to Anxiety Disorders

Behavioral inhibition may generate risk for anxiety disorders when early alterations in circuits regulating threat-responsive circuitry stabilize over development. In this section, we review environmental factors that are associated with risk of progression from behavioral inhibition to symptoms of anxiety disorders (Degnan & Fox, 2007), as well as factors associated with continuity of anxiety symptoms present early in life to symptoms present later in life. Factors that modulate behavioral risk may exert their effect by impacting the stabilization of regulatory circuitry. Future work is needed to test this hypothesis.

One set of environmental factors associated with risk for developing an anxiety disorder pertains to parents. These factors include parental psychopathology, parental response to their own anxiety, and parental response to their child's anxiety (see the chapter "The Social World of Behaviorally Inhibited Children: A Transactional Account" by Henderson et al. and the chapter "Behavioral Inhibition as a Precursor to Psychopathology" by Klein and Mumper). It should be noted from the outset that the degree to which certain parenting styles cause symptoms of anxiety remains unclear. This causal relation represents one of many possible routes connecting parental and child behavior. For example, children with behavioral inhibition who go on to develop anxiety disorders might elicit certain parenting behaviors, which relate to risk. Alternatively, shared genetic effects could underlie the association. Nevertheless, parenting styles linked to the development of anxiety disorders have been reported in parents of children high in behavioral inhibition (Dougherty et al., 2013; Lewis-Morrarty et al., 2012) and can be altered through therapies, reducing the risk for anxiety (see the chapter "Behavioural Inhibition and the Prevention of Internalising Distress in Early Childhood" by Rapee and Bayer).

Risk for anxiety in children high in behavioral inhibition might be mitigated by parenting that is high in warmth but also firmly encouraging of behaviors in the child designed to overcome fear through gradual exposure. In contrast, allowing behaviors to persist that facilitate a child's avoidance of feared scenarios may increase risk for anxiety disorders. Overprotective parenting, especially, has been consistently associated with increased risk for developing an anxiety disorder (Edwards, Rapee, & Kennedy, 2010; Hudson, Dodd, Lyneham, & Bovopoulous, 2011; Vreeke, Muris, Mayer, Huijding, & Rapee, 2013).

There are many reasons why some parenting practices might reduce risk. A leading hypothesis is that sensitive practices might give children opportunities to learn how to master fear in a controlled, supportive, and nurturing environment. In contrast,

when children are shielded from fear, they may learn to avoid feared stimuli, which can reinforce avoidance as a coping skill and potentially increase the risk of an anxiety disorder. Consistent with this hypothesis, early socialization appears to be a protective factor against the evolution from high behavioral inhibition to an anxiety disorder (Degnan & Fox, 2007). Children with frequent exposure to peers at an early age may have the opportunity to practice and develop mature coping skills to manage anxiety surrounding interaction with peers, lessening their chance for developing a future anxiety disorder (see the chapter "Peer Relations and the Behaviorally Inhibited Child" by Rubin et al.).

Shielding children from stimuli that they fear, such as peers, might increase the risk of the progression from high behavioral inhibition to a later anxiety disorder through specific effects on brain circuitry. As detailed above, regulatory systems centered around the sgACC may lead to fear extinction by reducing amygdala activity to previously feared stimuli. Children who are not given the opportunity to reduce fear through exposure may not engage sgACC-related mechanisms during childhood, which could result in reduced efficacy of this circuitry through lack of use. In contrast, preliminary data suggest that resilient behaviorally inhibited children demonstrate enhanced levels of function in this sgACC-related circuitry (Shechner et al., 2017). Repeated practice of exposure-based fear reduction may strengthen these pathways, such that they develop into a more adaptive mechanism, which may prevent the onset of an anxiety disorder later in life. Again, further work is needed to test this speculative hypothesis.

Early environmental influences may also affect other brain regions. As reviewed above, adaptive control of attention may involve the VLPFC and provide an important mechanism for regulating fear. Parents may teach their children to attend to or ignore mildly threatening stimuli. Thus, environmental influences may impact the development of VLPFC-related circuitry. Theoretical work suggests that children acquire fears through direct experience with threatening stimuli, witnessing others experience threatening stimuli, and through verbal transmission of information about potential threats (Rachman, 1991). Children learn to fear and avoid stimuli about which they are told negative information (Field & Lawson, 2003), consistent with verbal transmission (see the chapter "Behavioral Inhibition and the Associative Learning of Fear" by Reynolds et al.). Each of these mechanisms may involve engage VLPFC-related circuitry. One possibility is that children learn through experience to attend to mildly threatening stimuli because of witnessing their parent's responses to these stimuli. By repeatedly attending to these stimuli, the children train VLPFC-related circuitry to automatically attend to negative stimuli, stabilizing this regulatory circuitry in a maladaptive state and increasing risk for an anxiety disorder.

As described above, the DLFPC is a central regulatory region thought to support explicit strategies for emotion regulation, such as cognitive reframing. Cognitive behavioral therapy (CBT) represents the best-established psychotherapy for anxiety disorders, and it directly teaches children the practice of explicit emotion regulation strategies. Versions of CBT designed for children often include parental involvement in the therapy, especially for younger children (Hirshfeld-Becker et al., 2010). It is possible that parents who are able to teach their children how to adaptively use

explicit emotion regulation strategies may help prevent the progression from high behavioral inhibition to an anxiety disorder by training DLPFC-related regulation mechanisms. Interestingly, although the automatic capture of attention by negative stimuli appears to involve the VLPFC, as reviewed above, the DLPFC may be involved in learning how to explicitly override this automatic capture of attention by negative stimuli (Clarke, Browning, Hammond, Notebaert, & MacLeod, 2014). Thus, DLPFC-related circuitry may also be trained in an adaptive manner as children learn to voluntarily override automatic captures of attention by fearful stimuli.

It is unclear whether parents or other environmental factors can similarly affect dACC-related circuitry. As discussed above, regulatory systems that include the dACC appear to upregulate the fear response by increasing sensitivity to errors or by enhancing salience of external stimuli. In either case, it is possible that through repeated exposure to frightening events in a supportive, safe environment, the dACC-related circuitry becomes less active and attributes less salience to all stimuli. This hypothesis is speculative and requires future testing.

To summarize, many factors predict the progression from a behaviorally inhibited temperament to symptoms of an anxiety disorder. Each factor operates in a developmental context, and they could thereby influence maturation in fear regulating mechanisms. These mechanisms are supported by functions supported by many brain regions, including sgACC (implicit emotion regulation), VLPFC (attention-based regulation), DLPFC (explicit emotion regulation), and dACC (upregulation of fear).

Future Directions

This chapter described a framework for using neuroscience to bridge behavioral inhibition and psychopathology, primarily anxiety disorders, while charting the development of particular brain networks. In brief, behavioral inhibition is framed as involving hypersensitivity in an automatically deployed threat-reactive circuitry, encompassing the amygdala. This hypersensitivity is thought to interact with alterations in other brain systems that support regulatory capacities. These systems engage multiple interconnected brain regions, to support diverse psychological processes. This includes the dACC (upregulation), sgACC (implicit downregulation), VLPFC (attention-related regulation), and DLFPC (explicit regulation). The biology of behavioral inhibition may evolve into the biology of an anxiety disorder when regulation systems become stably dysfunctional over the course of development. Environmental influences such as dysfunctional parenting behaviors and limited interactions with peers may influence the progression from early behavioral inhibition to later anxiety disorders by stabilizing circuits that regulate fear in a maladaptive state.

An important strength of the reviewed studies of behavioral inhibition and anxiety disorders is that most are from samples followed longitudinally. Two separate sets of cohorts, one set from Kagan and colleagues and another set from Fox and colleagues, have been followed from infancy through young adulthood. This strategy,

unparalleled in most other areas in the study of psychopathology, provides unique opportunities to assess progression from behavioral inhibition to anxiety disorders in individuals. Despite the longitudinal nature of these studies, however, most of the studies reviewed above examine a single biological mechanism or system (e.g., amygdala reactivity or attention systems) at a time, and results are generally presented in the aggregate.

One particularly important next step in developing a deeper understanding of the biological bridge between behavioral inhibition and psychopathology is to extend these previous longitudinal studies. This may be possible through studies that start from birth and use brain imaging to assess directly the multiple regulatory systems discussed in the chapter. Another important step is to improve on the methodology of prior imaging studies, both in anxiety disorders and behavioral inhibition. This will require larger sample sizes, multiple sites using identical methods, and more rigorous statistical thresholds. Such work may support a deeper understanding of the biological systems that allow behavioral inhibition to create risk for an anxiety disorder.

Although the data reviewed above indicate that, on average, children with high behavioral inhibition have deficits in at least four regulatory systems, it is unclear exactly when over the course of development these deficits emerge. It is also unknown whether any one individual with high behavioral inhibition has deficits in all four of these regulatory systems, as opposed to just one or two. One possibility is that individual children with high behavioral inhibition have dysfunction in one or two regulatory systems early in development, and then these children develop an anxiety disorder when all four regulatory systems become dysfunctional. Additionally, the regulatory systems may interact with one another to manifest specific symptoms. These possibilities could be tested by measuring all four systems at each assessment in future longitudinal assessments of behavioral inhibition and anxiety disorders.

Another important direction for future work is to precisely define the biological systems that are associated with fear regulation in behavioral inhibition and anxiety disorders. Prior studies have made progress by reporting brain regions with differential activity or connectivity during particular tasks. The next step to better define these systems is to precisely define the larger functional brain networks in which these regions reside. Many of the brain regions discussed above and reported in studies of behavioral inhibition are from parts of the brain in which there are many different functional brain areas in close proximity to one another. These differing functional brain areas have separable functions, connections, and functional brain network relationships. The VLPFC, for example, includes at least four or five closely juxtaposed regions that are involved in the involuntary capture of attention, self-referential processes, top-down executive control, and error detection (Power et al., 2011).

This problem is compounded by the recent finding that there is substantial heterogeneity in the anatomical location of borders between these different regions from subject to subject (Gordon, Laumann, Adeyemo, & Petersen, 2017). The precise identity of the VLPFC region detected in, say, a study of behavioral inhibition can be determined by additional analyses of resting-state functional connectivity

data or by including "localizer" task-based fMRI scans. Understanding the basic biology of the specific regions highlighted in studies of behavioral inhibition and anxiety disorders will yield greater insights into these conditions as well as provide a framework to guide the development of novel interventions.

Another important area for future work is to determine the impact of interventions on the biological progression from behavioral inhibition to anxiety disorders. The framework in this chapter identifies potential targets in regulatory circuits for such interventions. However, far more work is needed before such interventions might be considered. This reflects the limited state of current knowledge in neuroscience as it relates to clinical problems, which increases the possibility for unintended harmful consequences from well-intended interventions in a maladaptive state.

Attention bias modification training (ABMT) provides an interesting example for discussing the clinical translation of neuroscience to patients and at-risk individuals. This therapy is designed to retrain anxious individuals to attend to neutral or happy stimuli. This intervention retrains attention and improves symptoms of anxiety in both children and adults (Beard, Sawyer, & Hofmann, 2012; Hakamata et al., 2010). One study suggests that ABMT operates by engaging DLPFC-related circuitry, perhaps indicating a voluntary shift of attention that overrides a more automatic engagement of attention by threatening stimuli (Clarke et al., 2014). An important goal of future work is to design training tasks in addition to ABM that train other brain systems (Sylvester et al., 2012). These interventions could then be tested for their ability to alter the trajectory of the specific circuits discussed in this chapter and possibly prevent the progression from behavioral inhibition to an anxiety disorder.

Interventions such as ABMT are justifiable among children who are currently affected, since the risk for harmful unintended consequences is offset by the presence of impairment in these children. Recent work suggests that some forms of ABMT might not only treat anxiety disorders but also prevent the onset of mental illness in selected high-risk individuals (Badura-Brack et al., 2015; Wald et al., 2016). However, such interventions are not without risk. ABMT emerged following work that suggested some alterations in attention could increase anxiety and stress sensitivity in humans (MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002). Moreover, in one context, forms of ABMT can be beneficial, but in another context, the same form may be harmful. Because children with behavioral inhibition often are at-risk but unaffected clinically, the threshold for intervention is higher than in children with anxiety disorders.

Beyond child interventions, another important area for future work is to test the effects of parent-based interventions on the biological progression of a child from high behavioral inhibition to an anxiety disorder. While the evidence above implies that altering parental behavior might reduce the risk of progression to an anxiety disorder, the biological basis of this risk reduction is not understood. For example, it could be tested whether the children of parents who encourage gentle and supportive exposure to feared events have improved sgACC regulation of the fear reaction.

An additional, more speculative, possibility would be to test whether interventions aimed at reducing parental anxiety have an indirect influence on their children's brain circuitry, mediated through changes in parenting behaviors. For example, if a parent undergoes ABM and has reduced attention to threat, this may alter the parent's behavior in a way that reduces the child's own attention bias to threat. This altered attention in the child could be associated with either VLPFC- or DLPFC-related brain circuitry. By understanding the impact of current treatments, novel child-directed brain training regimens, and parent interventions, it may be possible in the future to direct a suite of interventions at a child with high behavioral inhibition in order to help prevent the progression to an anxiety disorder.

Finally, this review has focused on anxiety disorders, but future work should also examine the bridge between behavioral inhibition and other forms of psychopathology. Although the link is less tight, behavioral inhibition may be a risk factor for conditions beyond anxiety disorders such as depression and substance use problems (Fox et al., 2005). This risk is likely to be exacerbated by specific environmental risk factors that may be overlapping or distinct from factors that increase risk for developing problematic anxiety. In addition, anxiety disorders themselves are a risk factor for developing many future disorders including additional anxiety disorders, depression, and substance use disorders (Benjamin, Harrison, Settipani, Brodman, & Kendall, 2013). Thus, behavioral inhibition may also indirectly be a bridge to these other disorders. An important line for future work is to follow individuals with high behavioral inhibition and anxiety disorders longitudinally into adulthood and delineate the biological bridge for symptoms of these other disorders beyond anxiety.

Conclusions

In summary, the focus of this chapter was on the biological bridge between behavioral inhibition and psychopathology, with an emphasis on anxiety disorders. We stressed that both behavioral inhibition and anxiety disorders include alterations in the brain systems that automatically detect threatening stimuli as well as in the regulatory systems that modify this initial, automatic response. We presented a framework in which the biological bridge between behavioral inhibition and anxiety disorders involves the developmental stabilization of the fear regulatory pathways in a way that serves to amplify rather than lessen fear. An untested possibility is that behavioral inhibition involves early dysfunction of one or two regulatory systems and that in cases in which the biology evolves to have dysfunction in more regulatory systems, an anxiety disorder develops.

We also highlighted specific environmental influences that seem to moderate relations between early appearing behavioral inhibition and later development of an anxiety disorder and how these environmental influences may impact circuitry in a way that increases or lessens the risk for a future anxiety disorder. The work on behavioral inhibition and the biological bridge to anxiety disorders is valuable not

only for understanding anxiety disorders but also providing a feasible biological model for how early temperamental variation can evolve over time into psychopathology. Given that most psychopathology may represent disorders of brain development, this model system may have a broad impact on our understanding of psychopathology.

References

Amir, N., Klumpp, H., Elias, J., Bedwell, J. S., Yanasak, N., & Miller, L. S. (2005). Increased activation of the anterior cingulate cortex during processing of disgust faces in individuals with social phobia. *Biological Psychiatry, 57*(9), 975–981. https://doi.org/10.1016/j.biopsych.2005.01.044

Badura-Brack, A. S., Naim, R., Ryan, T. J., Levy, O., Abend, R., Khanna, M. M., … Bar-Haim, Y. (2015). Effect of attention training on attention bias variability and PTSD symptoms: Randomized controlled trials in Israeli and U.S. combat veterans. *The American Journal of Psychiatry, 172*(12), 1233–1241. https://doi.org/10.1176/appi.ajp.2015.14121578

Barrett, L. F. (2017). *How emotions are made: The secret life of the brain*. New York, NY: Houghton Mifflin Harcourt.

Beard, C., Sawyer, A. T., & Hofmann, S. G. (2012). Efficacy of attention bias modification using threat and appetitive stimuli: A meta-analytic review. *Behavior Therapy, 43*(4), 724–740. https://doi.org/10.1016/j.beth.2012.01.002

Benjamin, C. L., Harrison, J. P., Settipani, C. A., Brodman, D. M., & Kendall, P. C. (2013). Anxiety and related outcomes in young adults 7 to 19 years after receiving treatment for child anxiety. *Journal of Consulting and Clinical Psychology, 81*(5), 865–876. https://doi.org/10.1037/a0033048

Birn, R. M., Shackman, A. J., Oler, J. A., Williams, L. E., McFarlin, D. R., Rogers, G. M., … Kalin, N. H. (2014). Evolutionarily conserved prefrontal-amygdalar dysfunction in early-life anxiety. *Molecular Psychiatry, 19*(8), 915–922. https://doi.org/10.1038/mp.2014.46

Bishop, S. J. (2009). Trait anxiety and impoverished prefrontal control of attention. *Nature Neuroscience, 12*(1), 92–98. https://doi.org/10.1038/nn.2242

Bishop, S. J., Jenkins, R., & Lawrence, A. D. (2007). Neural processing of fearful faces: Effects of anxiety are gated by perceptual capacity limitations. *Cerebral Cortex, 17*(7), 1595–1603. https://doi.org/10.1093/cercor/bhl070

Blackford, J. U., & Pine, D. S. (2012). Neural substrates of childhood anxiety disorders: A review of neuroimaging findings. *Child and Adolescent Psychiatric Clinics of North America, 21*(3), 501–525. https://doi.org/10.1016/j.chc.2012.05.002

Bruhl, A. B., Delsignore, A., Komossa, K., & Weidt, S. (2014). Neuroimaging in social anxiety disorder-a meta-analytic review resulting in a new neurofunctional model. *Neuroscience and Biobehavioral Reviews, 47*, 260–280. https://doi.org/10.1016/j.neubiorev.2014.08.003

Calhoon, G. G., & Tye, K. M. (2015). Resolving the neural circuits of anxiety. *Nature Neuroscience, 18*(10), 1394–1404. https://doi.org/10.1038/nn.4101

Calkins, S. D., Fox, N. A., & Marshall, T. R. (1996). Behavioral and physiological antecedents of inhibited and uninhibited behavior. *Child Development, 67*(2), 523–540.

Casey, B. J., Ruberry, E. J., Libby, V., Glatt, C. E., Hare, T., Soliman, F., … Tottenham, N. (2011). Transitional and translational studies of risk for anxiety. *Depression and Anxiety, 28*(1), 18–28. https://doi.org/10.1002/da.20783

Clarke, P. J., Browning, M., Hammond, G., Notebaert, L., & MacLeod, C. (2014). The causal role of the dorsolateral prefrontal cortex in the modification of attentional bias: Evidence from transcranial direct current stimulation. *Biological Psychiatry, 76*(12), 946–952. https://doi.org/10.1016/j.biopsych.2014.03.003

Clauss, J. A., Benningfield, M. M., Rao, U., & Blackford, J. U. (2016). Altered prefrontal cortex function marks heightened anxiety risk in children. *Journal of the American Academy of Child and Adolescent Psychiatry, 55*(9), 809–816. https://doi.org/10.1016/j.jaac.2016.05.024

Clauss, J. A., & Blackford, J. U. (2012). Behavioral inhibition and risk for developing social anxiety disorder: A meta-analytic study. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*(10), 1066–1075.e1. https://doi.org/10.1016/j.jaac.2012.08.002

Clauss, J. A., Cowan, R. L., & Blackford, J. U. (2011). Expectation and temperament moderate amygdala and dorsal anterior cingulate cortex responses to fear faces. *Cognitive, Affective, & Behavioral Neuroscience, 11*(1), 13–21. https://doi.org/10.3758/s13415-010-0007-9

Clauss, J. A., Seay, A. L., VanDerKlok, R. M., Avery, S. N., Cao, A., Cowan, R. L., … Blackford, J. U. (2014). Structural and functional bases of inhibited temperament. *Social Cognitive and Affective Neuroscience, 9*(12), 2049–2058. https://doi.org/10.1093/scan/nsu019

Corbetta, M., Patel, G., & Shulman, G. L. (2008). The reorienting system of the human brain: From environment to theory of mind. *Neuron, 58*(3), 306–324. https://doi.org/10.1016/j.neuron.2008.04.017

Davis, M., Walker, D. L., Miles, L., & Grillon, C. (2010). Phasic vs sustained fear in rats and humans: Role of the extended amygdala in fear vs anxiety. *Neuropsychopharmacology, 35*(1), 105–135. https://doi.org/10.1038/npp.2009.109

Degnan, K. A., & Fox, N. A. (2007). Behavioral inhibition and anxiety disorders: Multiple levels of a resilience process. *Development and Psychopathology, 19*(3), 729. https://doi.org/10.1017/S0954579407000363

Delgado, M. R., Nearing, K. I., Ledoux, J. E., & Phelps, E. A. (2008). Neural circuitry underlying the regulation of conditioned fear and its relation to extinction. *Neuron, 59*(5), 829–838. https://doi.org/10.1016/j.neuron.2008.06.029

Dosenbach, N. U., Visscher, K. M., Palmer, E. D., Miezin, F. M., Wenger, K. K., Kang, H. C., … Petersen, S. E. (2006). A core system for the implementation of task sets. *Neuron, 50*(5), 799–812. https://doi.org/10.1016/j.neuron.2006.04.031

Dougherty, L. R., Tolep, M. R., Bufferd, S. J., Olino, T. M., Dyson, M., Traditi, J., … Klein, D. N. (2013). Preschool anxiety disorders: Comprehensive assessment of clinical, demographic, temperamental, familial, and life stress correlates. *Journal of Clinical Child & Adolescent Psychology, 42*(5), 577–589. https://doi.org/10.1080/15374416.2012.759225

Edwards, S. L., Rapee, R. M., & Kennedy, S. (2010). Prediction of anxiety symptoms in preschool-aged children: Examination of maternal and paternal perspectives. *Journal of Child Psychology and Psychiatry, 51*(3), 313–321. https://doi.org/10.1111/j.1469-7610.2009.02160.x

Etkin, A. (2010). Functional neuroanatomy of anxiety: A neural circuit perspective. *Current Topics in Behavioral Neurosciences, 2*, 251–277.

Etkin, A., Buchel, C., & Gross, J. J. (2015). The neural bases of emotion regulation. *Nature Reviews Neuroscience, 16*(11), 693–700. https://doi.org/10.1038/nrn4044

Etkin, A., Prater, K. E., Hoeft, F., Menon, V., & Schatzberg, A. F. (2010). Failure of anterior cingulate activation and connectivity with the amygdala during implicit regulation of emotional processing in generalized anxiety disorder. *The American Journal of Psychiatry, 167*(5), 545–554. https://doi.org/10.1176/appi.ajp.2009.09070931

Etkin, A., Prater, K. E., Schatzberg, A. F., Menon, V., & Greicius, M. D. (2009). Disrupted amygdalar subregion functional connectivity and evidence of a compensatory network in generalized anxiety disorder. *Archives of General Psychiatry, 66*(12), 1361–1372. https://doi.org/10.1001/archgenpsychiatry.2009.104

Evans, K. C., Simon, N. M., Dougherty, D. D., Hoge, E. A., Worthington, J. J., Chow, C., … Rauch, S. L. (2009). A PET study of tiagabine treatment implicates ventral medial prefrontal cortex in generalized social anxiety disorder. *Neuropsychopharmacology, 34*(2), 390–398. https://doi.org/10.1038/npp.2008.69

Field, A. P., & Lawson, J. (2003). Fear information and the development of fears during childhood: Effects on implicit fear responses and behavioural avoidance. *Behaviour Research and Therapy, 41*(11), 1277–1293.

Fox, A. S., & Kalin, N. H. (2014). A translational neuroscience approach to understanding the development of social anxiety disorder and its pathophysiology. *The American Journal of Psychiatry, 171*(11), 1162–1173. https://doi.org/10.1176/appi.ajp.2014.14040449

Fox, N. A., Henderson, H. A., Rubin, K. H., Calkins, S. D., & Schmidt, L. A. (2001). Continuity and discontinuity of behavioral inhibition and exuberance: Psychophysiological and behavioral influences across the first four years of life. *Child Development, 72*(1), 1–21.

Fox, N. A., Henderson, H. A., Marshall, P. J., Nichols, K. E., & Ghera, M. M. (2005). Behavioral inhibition: Linking biology and behavior within a developmental framework. *Annual Review of Psychology, 56*(1), 235–262. https://doi.org/10.1146/annurev.psych.55.090902.141532

Fox, N. A., Rubin, K. H., Calkins, S. D., Marshall, T. R., Coplan, R. J., Porges, S. W., … Stewart, S. (1995). Frontal activation asymmetry and social competence at four years of age. *Child Development, 66*(6), 1770–1784.

Goldin, P. R., Manber-Ball, T., Werner, K., Heimberg, R., & Gross, J. J. (2009). Neural mechanisms of cognitive reappraisal of negative self-beliefs in social anxiety disorder. *Biological Psychiatry, 66*(12), 1091–1099. https://doi.org/10.1016/j.biopsych.2009.07.014

Gordon, E. M., Laumann, T. O., Adeyemo, B., & Petersen, S. E. (2017). Individual variability of the system-level organization of the human brain. *Cerebral Cortex, 27*(1), 386–399. https://doi.org/10.1093/cercor/bhv239

Guyer, A. E., Benson, B., Choate, V. R., Bar-Haim, Y., Perez-Edgar, K., Jarcho, J. M., … Nelson, E. E. (2014). Lasting associations between early-childhood temperament and late-adolescent reward-circuitry response to peer feedback. *Development and Psychopathology, 26*(1), 229–243. https://doi.org/10.1017/S0954579413000941

Guyer, A. E., Nelson, E. E., Perez-Edgar, K., Hardin, M. G., Roberson-Nay, R., Monk, C. S., … Ernst, M. (2006). Striatal functional alteration in adolescents characterized by early childhood behavioral inhibition. *The Journal of Neuroscience, 26*(24), 6399–6405. https://doi.org/10.1523/JNEUROSCI.0666-06.2006

Hahn, A., Stein, P., Windischberger, C., Weissenbacher, A., Spindelegger, C., Moser, E., … Lanzenberger, R. (2011). Reduced resting-state functional connectivity between amygdala and orbitofrontal cortex in social anxiety disorder. *Neuroimage, 56*(3), 881–889. https://doi.org/10.1016/j.neuroimage.2011.02.064

Hakamata, Y., Lissek, S., Bar-Haim, Y., Britton, J. C., Fox, N. A., Leibenluft, E., … Pine, D. S. (2010). Attention bias modification treatment: A meta-analysis toward the establishment of novel treatment for anxiety. *Biological Psychiatry, 68*(11), 982–990. https://doi.org/10.1016/j.biopsych.2010.07.021

Hardee, J. E., Benson, B. E., Bar-Haim, Y., Mogg, K., Bradley, B. P., Chen, G., … Perez-Edgar, K. (2013). Patterns of neural connectivity during an attention bias task moderate associations between early childhood temperament and internalizing symptoms in young adulthood. *Biological Psychiatry, 74*(4), 273–279. https://doi.org/10.1016/j.biopsych.2013.01.036

Henderson, H. A., Pine, D. S., & Fox, N. A. (2015). Behavioral inhibition and developmental risk: A dual-processing perspective. *Neuropsychopharmacology, 40*, 207–224. https://doi.org/10.1038/npp.2014.189

Hill, J., Inder, T., Neil, J., Dierker, D., Harwell, J., & Van Essen, D. (2010). Similar patterns of cortical expansion during human development and evolution. *Proceedings of the National Academy of Sciences of the United States of America, 107*(29), 13135–13140. https://doi.org/10.1073/pnas.1001229107

Hirshfeld-Becker, D. R., Masek, B., Henin, A., Blakely, L. R., Pollock-Wurman, R. A., Mcquade, J., … Biederman, J. (2010). Cognitive behavioral therapy for 4- to 7-year-old children with anxiety disorders: A randomized clinical trial. *Journal of Consulting and Clinical Psychology, 78*(4), 498–510. https://doi.org/10.1037/a0019055

Hudson, J. L., Dodd, H. F., Lyneham, H. J., & Bovopoulous, N. (2011). Temperament and family environment in the development of anxiety disorder: Two-year follow-up. *Journal of the American Academy of Child and Adolescent Psychiatry, 50*(12), 1255–1264.e1. https://doi.org/10.1016/j.jaac.2011.09.009

Kagan, J., Reznick, J. S., Snidman, N., Gibbons, J., & Johnson, M. O. (1988). Childhood derivatives of inhibition and lack of inhibition to the unfamiliar. *Child Development, 59*(6), 1580–1589.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*(6), 593–602. https://doi.org/10.1001/archpsyc.62.6.593

Lahat, A., Benson, B. E, Pine, D. S., Fox, N. A., & Ernst, M.. (2016). Neural responses to reward in childhood: Relations to early behavioral inhibition and social anxiety. *Social Cognitive and Affective Neuroscience*. https://doi.org/10.1093/scan/nsw122

Lahat, A., Lamm, C., Chronis-Tuscano, A., Pine, D. S., Henderson, H. A., & Fox, N. A. (2014). Early behavioral inhibition and increased error monitoring predict later social phobia symptoms in childhood. *Journal of the American Academy of Child and Adolescent Psychiatry, 53*(4), 447–455. https://doi.org/10.1016/j.jaac.2013.12.019

Lahat, A., Pérez-Edgar, K., Degnan, K. A., Guyer, A. E., Lejuez, C. W., Ernst, M., … Fox, N. A. (2012). Early childhood temperament predicts substance use in young adults. *Translational Psychiatry, 2*(9), e157. https://doi.org/10.1038/tp.2012.87

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annual Review of Neuroscience, 23*, 155–184. https://doi.org/10.1146/annurev.neuro.23.1.155

LeDoux, J. E., & Pine, D. S. (2016). Using neuroscience to help understand fear and anxiety: A two-system framework. *The American Journal of Psychiatry, 173*(11), 1083–1093. https://doi.org/10.1176/appi.ajp.2016.16030353

Lewis-Morrarty, E., Degnan, K. A., Chronis-Tuscano, A., Rubin, K. H., Cheah, C. S. L., Pine, D. S., … Fox, N. A. (2012). Maternal over-control moderates the association between early childhood behavioral inhibition and adolescent social anxiety symptoms. *Journal of Abnormal Child Psychology, 40*(8), 1363–1373. https://doi.org/10.1007/s10802-012-9663-2

Liao, W., Chen, H., Feng, Y., Mantini, D., Gentili, C., Pan, Z., … Zhang, W. (2010). Selective aberrant functional connectivity of resting state networks in social anxiety disorder. *Neuroimage, 52*(4), 1549–1558. https://doi.org/10.1016/j.neuroimage.2010.05.010

MacLeod, C., Rutherford, E., Campbell, L., Ebsworthy, G., & Holker, L. (2002). Selective attention and emotional vulnerability: Assessing the causal basis of their association through the experimental manipulation of attentional bias. *Journal of Abnormal Psychology, 111*(1), 107–123.

McClure, E. B., Monk, C. S., Nelson, E. E., Parrish, J. M., Adler, A., Blair, R., … Pine, D. S. (2007). Abnormal attention modulation of fear circuit function in pediatric generalized anxiety disorder. *Archives of General Psychiatry, 64*(1), 97–106. https://doi.org/10.1001/archpsyc.64.1.97

McDermott, J. M., Perez-Edgar, K., Henderson, H. A., Chronis-Tuscano, A., Pine, D. S., & Fox, N. A. (2009). A history of childhood behavioral inhibition and enhanced response monitoring in adolescence are linked to clinical anxiety. *Biological Psychiatry, 65*(5), 445–448. https://doi.org/10.1016/j.biopsych.2008.10.043

Merikangas, K. R., He, J.-P., Burstein, M., Swanson, S. A., Avenevoli, S., Cui, L., … Swendsen, J. (2010). Lifetime prevalence of mental disorders in U.S. adolescents: Results from the National Comorbidity Survey Replication—Adolescent Supplement (NCS-A). *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(10), 980–989. https://doi.org/10.1016/j.jaac.2010.05.017

Milad, M. R., Wright, C. I., Orr, S. P., Pitman, R. K., Quirk, G. J., & Rauch, S. L. (2007). Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. *Biological Psychiatry, 62*(5), 446–454. https://doi.org/10.1016/j.biopsych.2006.10.011

Monk, C. S., Nelson, E. E., McClure, E. B., Mogg, K., Bradley, B. P., Leibenluft, E., … Pine, D. S. (2006). Ventrolateral prefrontal cortex activation and attentional bias in response to angry faces in adolescents with generalized anxiety disorder. *The American Journal of Psychiatry, 163*(6), 1091–1097. https://doi.org/10.1176/appi.ajp.163.6.1091

Monk, C. S., Telzer, E. H., Mogg, K., Bradley, B. P., Mai, X., Louro, H. M. C., … Pine, D. S. (2008). Amygdala and ventrolateral prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. *Archives of General Psychiatry, 65*(5), 568–576. https://doi.org/10.1001/archpsyc.65.5.568

Moser, J. S., Moran, T. P., Schroder, H. S., Donnellan, M. B., & Yeung, N. (2013). On the relationship between anxiety and error monitoring: A meta-analysis and conceptual framework. *Frontiers in Human Neuroscience, 7*, 466. https://doi.org/10.3389/fnhum.2013.00466

Murray, E., Wise, S., & Graham, K. (2017). *The evolution of memory systems*. Oxford, England: Oxford University Press.

Ochsner, K. N., & Gross, J. J. (2005). The cognitive control of emotion. *Trends in Cognitive Sciences, 9*(5), 242–249. https://doi.org/10.1016/j.tics.2005.03.010

Perez-Edgar, K., McDermott, J. N., Korelitz, K., Degnan, K. A., Curby, T. W., Pine, D. S., & Fox, N. A. (2010). Patterns of sustained attention in infancy shape the developmental trajectory of social behavior from toddlerhood through adolescence. *Developmental Psychology, 46*(6), 1723–1730. https://doi.org/10.1037/a0021064

Pérez-Edgar, K., Roberson-Nay, R., Hardin, M. G., Poeth, K., Guyer, A. E., Nelson, E. E., … Ernst, M. (2007). Attention alters neural responses to evocative faces in behaviorally inhibited adolescents. *Neuroimage, 35*(4), 1538–1546. https://doi.org/10.1016/j.neuroimage.2007.02.006

Pine, D. S. (2007). Research review: A neuroscience framework for pediatric anxiety disorders. *Journal of Child Psychology and Psychiatry, 48*(7), 631–648. https://doi.org/10.1111/j.1469-7610.2007.01751.x

Pine, D. S., & Fox, N. A. (2015). Childhood antecedents and risk for adult mental disorders. *Annual Review of Psychology, 66*, 459–485. https://doi.org/10.1146/annurev-psych-010814-015038

Power, J. D., Cohen, A. L., Nelson, S. M., Wig, G. S., Barnes, K. A., Church, J. A., … Petersen, S. E. (2011). Functional network organization of the human brain. *Neuron, 72*(4), 665–678. https://doi.org/10.1016/j.neuron.2011.09.006

Rachman, S. (1991). Neo-conditioning and the classical theory of fear acquisition. *Clinical Psychology Review, 11*, 155–173.

Raichle, M. E. (2011). The restless brain. *Brain Connectivity, 1*(1), 3–12. https://doi.org/10.1089/brain.2011.0019

Raichle, M. E. (2015). The brain's default mode network. *Annual Review of Neuroscience, 38*, 433–447. https://doi.org/10.1146/annurev-neuro-071013-014030

Reeb-Sutherland, B. C., Vanderwert, R. E., Degnan, K. A., Marshall, P. J., Perez-Edgar, K., Chronis-Tuscano, A., … Fox, N. A. (2009). Attention to novelty in behaviorally inhibited adolescents moderates risk for anxiety. *Journal of Child Psychology and Psychiatry, 50*(11), 1365–1372. https://doi.org/10.1111/j.1469-7610.2009.02170.x

Rogers, C. E., Sylvester, C. M., Mintz, C., Kenley, J. K., Shimony, J. S., Barch, D. M., & Smyser, C. D. (2017). Neonatal amygdala functional connectivity at rest in healthy and preterm infants and early internalizing symptoms. *Journal of the American Academy of Child and Adolescent Psychiatry, 56*(2), 157–166. https://doi.org/10.1016/j.jaac.2016.11.005

Roy, A. K., Benson, B. E., Degnan, K. A., Perez-Edgar, K., Pine, D. S., Fox, N. A., & Ernst, M. (2014). Alterations in amygdala functional connectivity reflect early temperament. *Biological Psychology, 103*, 248–254. https://doi.org/10.1016/j.biopsycho.2014.09.007

Schwartz, C. E., Kunwar, P. S., Greve, D. N., Kagan, J., Snidman, N. C., & Bloch, R. B. (2012). A phenotype of early infancy predicts reactivity of the amygdala in male adults. *Molecular Psychiatry, 17*(10), 1042–1050. https://doi.org/10.1038/mp.2011.96

Schwartz, C. E., Kunwar, P. S., Greve, D. N., Moran, L. R., Viner, J. C., Covino, J. M., … Wallace, S. R. (2010). Structural differences in adult orbital and ventromedial prefrontal cortex predicted by infant temperament at 4 months of age. *Archives of General Psychiatry, 67*(1), 78–84. https://doi.org/10.1001/archgenpsychiatry.2009.171

Schwartz, C. E., Wright, C. I., Shin, L. M., Kagan, J., & Rauch, S. L. (2003). Inhibited and uninhibited infants "grown up": Adult amygdalar response to novelty. *Science, 300*(5627), 1952–1953. https://doi.org/10.1126/science.1083703

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., … Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *The Journal of Neuroscience, 27*(9), 2349–2356. https://doi.org/10.1523/JNEUROSCI.5587-06.2007

Shechner, T., Fox, N. A., Mash, J. A., Jarcho, J. M., Chen, G., Leibenluft, E., … Britton, J. C. (2017). Differences in neural response to extinction recall in young adults with or without

history of behavioral inhibition. *Development and Psychopathology, 30*, 179–189. https://doi.org/10.1017/S0954579417000554

Shin, L. M., & Liberzon, I. (2010). The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology, 35*(1), 169–191. https://doi.org/10.1038/npp.2009.83

Sylvester, C. M., Barch, D. M., Corbetta, M., Power, J. D., Schlaggar, B. L., & Luby, J. L. (2013). Resting state functional connectivity of the ventral attention network in children with a history of depression or anxiety. *Journal of the American Academy of Child and Adolescent Psychiatry, 52*(12), 1326–1336.e5. https://doi.org/10.1016/j.jaac.2013.10.001

Sylvester, C. M., Barch, D. M., Harms, M. P., Belden, A. C., Oakberg, T. J., Gold, A. L., … Pine, D. S. (2016). Early childhood behavioral inhibition predicts cortical thickness in adulthood. *Journal of the American Academy of Child and Adolescent Psychiatry, 55*(2), 122–129.e1. https://doi.org/10.1016/j.jaac.2015.11.007

Sylvester, C. M., Corbetta, M., Raichle, M. E., Rodebaugh, T. L., Schlaggar, B. L., Sheline, Y. I., … Lenze, E. J. (2012). Functional network dysfunction in anxiety and anxiety disorders. *Trends in Neurosciences, 35*(9), 527–535. https://doi.org/10.1016/j.tins.2012.04.012

Sylvester, C. M., & Pine, D. S. (2016). Anxiety disorders. In J. L. Luby (Ed.), *Handbook of preschool mental health* (2nd ed.). New York, NY: Guilford Press.

Sylvester, C. M., Smyser, C. D., Smyser, T., Kenley, J., Ackerman, J. J., Jr., Shimony, J. S., … Rogers, C. E. (2017). Cortical functional connectivity evident after birth and behavioral inhibition at age 2. *The American Journal of Psychiatry, 175*, 180. https://doi.org/10.1176/appi.ajp.2017.17010018

Taber-Thomas, B. C., Morales, S., Hillary, F. G., & Pérez-Edgar, K. E. (2016). Altered topography of intrinsic functional connectivity in childhood risk for social anxiety. *Depression and Anxiety, 33*(11), 995–1004. https://doi.org/10.1002/da.22508

Thomas, K. M., Drevets, W. C., Dahl, R. E., Ryan, N. D., Birmaher, B., Eccard, C. H., … Casey, B. J. (2001). Amygdala response to fearful faces in anxious and depressed children. *Archives of General Psychiatry, 58*(11), 1057–1063.

Tovote, P., Fadok, J. P., & Luthi, A. (2015). Neuronal circuits for fear and anxiety. *Nature Reviews Neuroscience, 16*(6), 317–331. https://doi.org/10.1038/nrn3945

Uddin, L. Q. (2015). Salience processing and insular cortical function and dysfunction. *Nature Reviews Neuroscience, 16*(1), 55–61. https://doi.org/10.1038/nrn3857

Vreeke, L. J., Muris, P. E. T. E. R., Mayer, B., Huijding, J., & Rapee, R. M. (2013). Skittish, shielded, and scared: Relations among behavioral inhibition, overprotective parenting, and anxiety in native and non-native Dutch preschool children. *Journal of Anxiety Disorders, 27*(7), 703–710. https://doi.org/10.1016/j.janxdis.2013.09.006

Wald, I., Fruchter, E., Ginat, K., Stolin, E., Dagan, D., Bliese, P. D., … Bar-Haim, Y. (2016). Selective prevention of combat-related post-traumatic stress disorder using attention bias modification training: A randomized controlled trial. *Psychological Medicine, 46*(12), 2627–2636. https://doi.org/10.1017/S0033291716000945

Weinberg, A., Olvet, D. M., & Hajcak, G. (2010). Increased error-related brain activity in generalized anxiety disorder. *Biological Psychology, 85*(3), 472–480. https://doi.org/10.1016/j.biopsycho.2010.09.011

White, L. K., Degnan, K. A., Henderson, H. A., Pérez-Edgar, K., Walker, O. L., Shechner, T., … Fox, N. A. (2017). Developmental relations among behavioral inhibition, anxiety, and attention biases to threat and positive information. *Child Development, 88*(1), 141–155. https://doi.org/10.1111/cdev.12696

Behavioural Inhibition and the Prevention of Internalising Distress in Early Childhood

Ronald M. Rapee and Jordana K. Bayer

Abstract An inhibited temperamental style has been identified as one of the core risks for the later development of anxiety and related disorders. Several additional risks are believed to interact with child inhibition, including parent emotionality, parental rearing style, and poor social skills. These factors lend themselves to modification, opening the door to prevention of emotional disorders. To date there has been surprisingly little focus on the prevention of emotional disorder through identification of early child inhibition. The current chapter briefly summarises the current literature. It then moves on to consider several relevant issues including the best target for intervention, the most relevant population, and novel intervention strategies. Finally, the chapter describes some attempts to apply prevention at a population level and discusses barriers and future directions.

The pioneering work of Kagan and colleagues (Kagan, Reznick, Clarke, Snidman, & Garcia-Coll, 1984) opened the door to the systematic study of the temperamental origins of internalising distress. As initially described, behavioural inhibition refers to consistently shy, quiet, or timid behaviours in reaction to unfamiliar events (Kagan, Reznick, & Snidman, 1988). While behavioural inhibition has received probably the most extensive research evidence, a number of closely related constructs have been described in the literature including shyness (Prior, Smart, Sanson, & Oberklaid, 2000), social withdrawal (Rubin, Coplan, & Bowker, 2009), and anxious solitude (Gazelle & Ladd, 2003). Each of these temperamental styles is characterised by some unique features, but they all share a number of common characteristics.

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Throughout the rest of this chapter, we will use the broad term 'inhibition' to refer collectively to this group of related temperamental constructs.

As outlined by chapters in this volume, early inhibition has been identified as a key risk factor for anxiety and related internalising disorders (see the chapter "The Neurobiology of Behavioral Inhibition as a Developmental Mechanism" by Blackford et al. and the chapter "Behavioral Inhibition as a Precursor to Psychopathology" by Klein and Mumper and the chapter "The Biological Bridge Between Behavioral Inhibition and Psychopathology" by Sylvester and Pine). Several models of the development of anxiety disorders propose a central role for temperamental inhibition. For example, we have previously argued that withdrawal and inhibition, especially characterised by a fundamental avoidant style of dealing with the world, underpin vulnerability to later anxiety (Rapee, Schniering, & Hudson, 2009). This temperamental avoidant style lies at the heart of additional risks.

For example, we argue that parents commonly react to their child's inhibited nature by protecting the child and facilitating avoidance. In turn, this temperament-environment correlation exacerbates the child's anxiousness and further increases risk for disorder (see the chapter "The Social World of Behaviorally Inhibited Children: A Transactional Account" by Henderson et al.). Parent characteristics may contribute additional risk. Parents of anxious children are themselves more vulnerable to emotional distress (higher neuroticism), potentially increasing the likelihood of overly protective reactions to their child's distress. In a similar fashion, avoidant characteristics in the child can elicit threat-based stressors from the broader environment such as peer victimisation, which contribute further risk for anxiety disorder (see the chapter "Peer Relations and the Behaviorally Inhibited Child" by Rubin et al.).

Empirical evidence has broadly supported these predictions. For example, using data from the Longitudinal Study of Australian Children (LSAC), Bayer, Ukoumunne, et al. (2011) showed that parental harsh discipline and overprotection along with maternal emotional distress predicted child internalising symptoms into middle childhood. Additional evidence was demonstrated in a longitudinal study by Edwards, Rapee, and Kennedy (2010) that surveyed parents of 3–4-year-old children. Data from mothers supported a model in which the child's anxiety at age 4 (after controlling for stability of anxiety over time) was predicted by maternal protection, child inhibition, and maternal negative affect along with negative life events when the child was 3 years of age. Data from fathers showed fewer predictors, although there was markedly less power. Nonetheless, children's anxiety at 4 years was predicted by 3-year-old paternal protection along with negative life events.

Across the literature, considerable evidence has supported the prediction of anxiety (especially social anxiety) from early inhibition (Clauss & Blackford, 2012) as well as from parent emotional distress or disorder (Micco et al., 2009). Support for the role of parental overprotection has been demonstrated, but less consistently (McLeod, Wood, & Weisz, 2007; Rapee, 1997). Perhaps one reason for the less consistent evidence for parent overprotection lies in inconsistencies by which this construct has been defined and measured. As defined in our models, the key construct relates to parental support for the child's avoidance, yet overprotection in many studies is assessed far more broadly. Further, most studies assess parent protection through self-report, and it is possible that parents will either not have

good insight to their parenting or not be completely honest. So we are left with good evidence that early child inhibition and parent emotional reactivity are strong predictors of later anxiety (and related disorders) in children, while the role of parental support of avoidance is emerging but is currently less consistent. As we will consider in this chapter, addressing these known risk factors should lead to reductions in the development of anxiety and related constructs (Rapee, 2002). More powerful prevention programs will require greater understanding of factors underpinning the development of anxiety.

Prevention of Emotional Disorders Using Behavioural Inhibition: Empirical Evidence

As noted, current theory predicts that providing interventions around the construct of behavioural inhibition should lead to prevention or reduction in later emotional disorders, especially anxiety disorders. This prediction holds regardless of whether inhibition is seen as an independent precursor to disorder or an early indicator or form of the disorder (see the chapter "Behavioral Inhibition as a Precursor to Psychopathology" by Klein and Mumper; Rapee & Coplan, 2010). Despite the development of this theory over the past three decades (Kagan et al., 1984), there have been surprisingly few attempts to prevent emotional disorders in this way.

In an early small (pilot) trial, LaFreniere and Capuano (1997) identified 43 preschool-aged children (31–70 months; $M = 53$ months) who scored 1 standard deviation or more above the mean on a measure of anxiety/withdrawal. These children displayed trait-like characteristics reflecting shyness, social withdrawal, and solitary play. They were randomly allocated to either treatment or no treatment (control). Treatment lasted 20 sessions over 6 months, involving detailed assessment of maternal and family characteristics, caregiver education, parental skills and child interaction training, and provision of social support. At the end of 6 months, there were small, significant differences (one-tailed) between the two groups on maternal control, child motivation, and social competence. However, the groups did not differ significantly on parenting stress, maternal affect, or, most critically, anxiety withdrawal.

It is unfortunate that these researchers did not take this work further since it remains the most detailed and extensive attempt to alter parent/child interactions in this population of highly inhibited young children. However, due to its resource requirements, the likely value of the program as an applied and publicly supported intervention had to be limited. This early study, along with Kagan's seminal observations, provided the impetus for our own research into the prevention of emotional disorders. Our own work began by targeting behaviourally inhibited preschool-aged children, initially selected following a detailed laboratory observation along the lines developed by Jerome Kagan and Nancy Snidman (see the chapter "The History and Theory of Behavioral Inhibition" by Kagan). The children we selected were characterised by extensive silence in the face of unfamiliarity, close proximity to their caregiver, and avoidance of novel people and toys (Rapee, 2002). Our primary longitudinal cohort included 146 inhibited children, originally aged 36–59 months

(M = 47 months) who were randomly allocated to either parent education or no intervention (Rapee, Kennedy, Ingram, Edwards, & Sweeney, 2005).

The intervention we developed is now referred to as the Cool Little Kids program (Rapee, Lau, & Kennedy, 2010). Cool Little Kids is a six-session, group-based parent education program aimed at reducing and preventing the development of anxiety and related emotional disorders. Six sessions is unusually brief, but we were heavily influenced by the length and likely expense of the LaFreniere and Capuano program and so wanted to create a program that had low resource requirements and therefore stood a better chance of being implemented in public health settings. The program is primarily aimed at (a) directly reducing child withdrawal and (b) reducing a key moderator of inhibition, parent protectiveness. Hence the core components include teaching parents to reduce their protective behaviours and to stop supporting their child's avoidance and teaching parents how to systematically promote active approach behaviours in their child.

The outcome results from our primary longitudinal cohort have been excellent. When we began this research, we had no idea whether preventing anxiety was possible nor whether this very brief program would have any effects. Our lack of prior expectation allowed us to have a control group that never received intervention (aside from referrals to mental health professionals when warranted). It is difficult to ethically justify such a situation again, but in this first trial, this unusual control group allowed long-term comparison. At our first assessment point (12 months after baseline), 50% of the children whose parents had received education met DSM criteria for an anxiety disorder compared with 64% of those in the control group (Rapee et al., 2005). We next reported results from both 24 and 36 months after baseline (when the children were around 6 and 7 years old) (Rapee, Kennedy, Ingram, Edwards, & Sweeney, 2010). At those points, 38% and 40% of those in the intervention group had an anxiety disorder compared with 68% and 69% of the controls. We finally followed these children again 11 years after they first entered the study, when they were in their mid-teens (Rapee, 2013). At that stage we were able to assess both anxiety and mood disorders. Interestingly, there were no significant differences in adolescent outcomes for boys. However, fewer girls whose parents had been through Cool Little Kids (when the children were in preschool) demonstrated either an anxiety disorder (39%) or a mood disorder (0%) compared with girls in the control condition (61% and 16%, respectively). The results across all these years are nicely summarised by showing the average number of anxiety disorders (to age 7) or anxiety and mood disorders (at age 15) across assessment points in Fig. 1.

The efficacy of Cool Little Kids to reduce emotional disorders has not yet been widely replicated, although a few positive results have been reported. In one follow-up study, we wanted to look at effects in children who were at especially high risk for psychopathology. We therefore selected preschool-aged children who scored 2 standard deviations above the norm on a measure of social withdrawal and who also had at least 1 parent meeting DSM criteria for an anxiety disorder (Kennedy, Rapee, & Edwards, 2009). Six months after baseline, fewer children whose parents had been through the program had an anxiety disorder (53%) versus children in the control condition (93%). In an independent evaluation in Hong Kong, parents of 57 inhibited preschoolers were randomly allocated to Cool Little Kids or no interven-

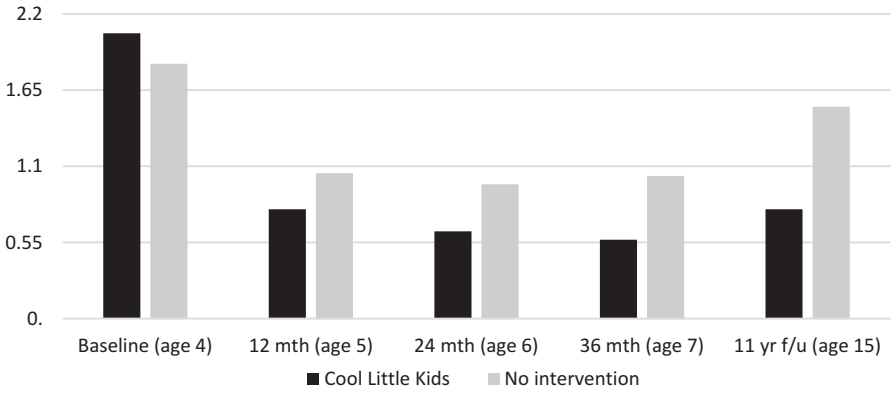

Fig. 1 Mean number of anxiety disorders in children whose parents did Cool Little Kids vs no intervention across age. Note that the final data point (age 15) refers to both anxiety and mood disorders and only to girls. Reported from Rapee, Kennedy, Ingram, Edwards, & Sweeney (2010) and Rapee (2013)

tion (Luke, Chan, Au, & Lai, 2017). Six months after baseline, children in the active condition showed lower scores on anxious shyness rated by teachers, although the groups did not differ significantly on internalising symptoms.

The interventions described above to reduce or prevent emotional distress among inhibited young children all have in common a focus on teaching parents different methods of handling or helping their child. A different method of intervention is for therapists, teachers, or other professionals to directly work with children to teach them relevant skills. Some emerging research, coming from a social skills deficits perspective, is beginning to use this strategy. Coplan, Schneider, Matheson, and Graham (2010) developed the Social Skills Facilitated Play program, which includes eight, 60-min sessions in which children are taught core social skills related to initiating and maintaining peer interactions. The background to the program came from evidence that shy and inhibited young children are socially reticent and demonstrate poor social competence and interaction skills (Coplan, Prakash, O'Neill, & Armer, 2004; Rubin et al., 2009).

The first evaluation reported a pilot trial with 22 inhibited preschool children aged 48–66 months (M = 56 months) who were randomly allocated to intervention or no treatment (control) (Coplan et al., 2010). Three months after baseline, relative to those in the control, children in the social skills program showed lower levels of observed reticence-wariness and higher social competence, although the groups did not differ on teacher-rated anxiety. A second small pilot was conducted in China among 16 shy preschool children aged 4–5 years (Li et al., 2016). Six months after baseline, compared to control children, children who completed the Social Skills Facilitated Play program showed greater improvements in peer interactions and prosocial behaviours, but effects on anxiety or internalising problems were not reported.

Following from the two foci of intervention described above (parent-focused vs child-focused), a logical question may be whether better effects can be obtained

by combining these directions. Chronis-Tuscano and colleagues developed the Turtle program, comprising eight, 90-min sessions separately for both children and parents, each of which is led by two therapists (Chronis-Tuscano et al., 2015). Parents are taught detailed parenting strategies to build confidence and approach behaviours in their child, while children are taught social and anxiety management skills. In a pilot trial, 32 inhibited preschool children aged 42–60 months (M = 52 months) were randomly assigned to Turtle or no treatment (control). After 8 weeks, compared to control children, children in the Turtle program scored lower on measures of anxiety and internalising symptoms. Following a similar perspective, we completed a small trial in which we combined the parent components from Cool Little Kids with the social skills components from Social Skills Facilitated Play (Lau, Rapee, & Coplan, 2017). Seventy-two inhibited, preschool-aged children aged 36–65 months (M = 52 months) were randomly allocated to either the combined intervention or waitlist. After 6 months, the combined parent and child intervention led to greater reductions relative to waitlist on anxiety diagnoses, anxiety symptoms, and life interference.

In summary, although data are still relatively limited, evidence is beginning to accumulate to suggest that psychological interventions can be addressed toward preschool-aged children who are at risk for later internalising disorders due to their high levels of social withdrawal and inhibition. The most extensive research to date has focused on intervention addressed directly to parents. However, programs directly targeting intervention to the withdrawn child or to both the parents and the child are beginning to emerge. In addition to the need for replication and extension of the research described above, the evidence and theory to date raises several conceptual issues that should be considered in order to advance the field. The following sections will address these issues.

Constructs to Be Targeted

As has been discussed, childhood inhibition is a clear risk factor for the later development of anxiety and related internalising disorders. Consequently, most prevention programs focused on inhibition have used this temperamental characteristic as a marker to identify at-risk young children as targets for intervention, in other words, selective prevention (Lyneham, Hudson, & Rapee, 2014). The identification of young children who are highly inhibited points to two possible targets for intervention. First, high inhibition might be seen purely as a risk marker, and the intervention itself might be targeted at changing other factors that interact with inhibition to create later distress. Second, interventions could be targeted at directly reducing child inhibition. To date, most programs are aimed at altering additional risk factors related to emotional disorders.

For example, Cool Little Kids and Turtle both address parenting factors that have been linked to child emotional disorders. Social Skills Facilitated Play addresses children's social interaction skills that are believed to underpin the later development

of disorders. At this stage of our knowledge, the extent to which this is successful is largely unknown. As noted earlier, the pilot trials of Social Skills Facilitated Play have shown improvements in social competence, but the extent to which this leads to reductions in later emotional disorders is unknown. Similarly, the extent to which interventions targeted at parenting actually alter parental behaviour has not been extensively evaluated and has received mixed results. The Turtle pilot demonstrated large reductions in anxiety along with moderate improvements in maternal positive affect. However, there was no change in maternal negative control. Cool Little Kids has demonstrated reductions in anxiety and, in one trial, concomitantly showed significant reductions in maternally reported overprotection (Lau et al., 2017). On the other hand, in a recent online intervention trial, we showed reductions in diagnosed anxiety disorders in the absence of significant effects on parent overprotection (Morgan et al., 2017).

Preventive interventions may also directly address children's inhibition. It is possible that improving social competence in Social Skills Facilitated Play, for example, directly reduces children's inhibition. This possibility has not yet been evaluated, although reductions in social wariness were reported (Coplan et al., 2010). On the other hand, maternally reported behavioural inhibition did show marked reduction in the Turtle pilot (Chronis-Tuscano et al., 2015). The extensive in vivo exposure in Cool Little Kids might directly reduce child inhibition, but there is mixed evidence for this. In our first large cohort, we assessed inhibition through both parent report and laboratory observation at baseline, 1-year, and 2-year follow-up (Rapee et al., 2005). The results showed large decreases in behavioural inhibition in both groups, but no significant difference between treatment and control groups, despite marked differences in the number of anxiety disorders.

These results highlighted the conceptual distinction between disorder and temperamental inhibition (Rapee & Coplan, 2010), and we concluded that the intervention reduced risk for anxiety disorders without changing behavioural inhibition (see the chapter "Behavioral Inhibition as a Precursor to Psychopathology" by Klein and Mumper). However, we also noted a large reduction in inhibition among untreated children and speculated that group differences may have been obscured by large regression to the mean. Therefore, in a later trial, we selected inhibited children who were especially extreme and also had a second risk factor, parent emotional disorder (Kennedy et al., 2009). In contrast to our previous trial, in this later trial, we managed to show group differences at 6 months on levels of actual inhibition, assessed by both parent report and also through direct laboratory observation. In a more recent trial that included moderately inhibited children with a parent scoring high on emotional distress, we similarly showed a trend toward group differences in maternally reported child inhibition (Lau et al., 2017).

Similar results have been reported in related areas. For example, in a large universal trial of the prevention of anxiety in preschool children, outcomes showed significantly greater reduction among intervention children relative to controls on maternally reported inhibition (Anticich, Barrett, Silverman, Lacherez, & Gillies, 2013). So it appears that it is possible to directly target temperamental inhibition within prevention programs, although effects are not large. Of course conceptually,

anxiety and inhibited temperament are highly related constructs with marked overlapping variance (Rapee & Coplan, 2010), and so it is possible that what is being altered is the more transient expression of anxiety, while the true temperament is left unaltered. However, developmental evidence showing natural fluctuations in temperamental inhibition (Kagan, Snidman, Arcus, & Reznick, 1994; Kerr, 2000; Prior et al., 2000) suggests that this temperament may be less immutable than many believe.

Population for Intervention

A related question of interest is whether interventions are best addressed directly to the child, to the parents, or to both. Social Skills Facilitated Play is aimed at directly teaching social skills to inhibited young children, while Cool Little Kids has focused its intervention through parents. The Turtle program has combined these foci and works with parents while simultaneously teaching skills directly to children in parallel sessions. Whether this combination leads to larger effects than working with either the child or parent alone is yet to be determined. In one trial, as described above, we combined Cool Little Kids (for parents) with Social Skills Facilitated Play (for children) in parallel sessions (Lau et al., 2017). Further, following intervention, the parents in the waitlist condition were given the standard Cool Little Kids program, which allowed us to quasi-experimentally compare outcomes between Cool Little Kids with and without Social Skills Facilitated Play. When comparing reductions from baseline to 6 months in the combined condition with 6 months to 12 months reductions in the parent-only condition, the combined intervention showed significantly stronger effects on clinicians' ratings of anxiety, but the groups did not differ significantly on maternal ratings. Of course, the quasi-experimental design means that firm conclusions are not possible. Even if combined treatment does produce larger effects than single-focus treatment, a key consideration from a public health perspective is the resource requirements to deliver each form of intervention. Cool Little Kids alone has shown very good cost-efficacy (Mihalopoulos, Vos, Rapee, Pirkis, & Carter, 2015), so any effects from a combined program would need to be considerably larger to offset the additional costs.

A final consideration worth noting is whether prevention for inhibited children could be conducted through preschool teachers (Jitlina, Shumka, Miller, & Rapee, 2015). Preschool teachers may be especially well placed to train children in social skills given their regular opportunities to observe children and the amount of time they spend with them. They are also in a good position to conduct in vivo exposure, given the large range of potential cues within and around preschools that could form the basis for exposure. Future research adopting this model would help to flesh out the range of available options.

Key Intervention Strategies

Ideally, prevention should follow understanding of causal mechanisms. As noted in the introduction, models of the development of anxiety and related internalising distress have identified inhibited temperament, overinvolved parenting, and parental distress as key risk factors (Degnan, Almas, & Fox, 2010; Rapee et al., 2009; see the chapter "Peer Relations and the Behaviorally Inhibited Child" by Rubin et al.). Other work has focused on the role of peer relationships, in particular rejection or neglect by other children as key to the development of emotional disorder (Gazelle & Ladd, 2003; Rubin et al., 2009). Interestingly, some research has suggested that not all inhibited children are socially unskilled but that poor social skills combined with an inhibited temperament makes children especially vulnerable (Gazelle & Shell, 2017). Based on these considerations, prevention programs to date have focused on changing inhibition/withdrawal, social skills, and parental protectiveness. As we have already discussed, whether the various interventions actually alter these core constructs and whether it is the change in these constructs that mediates prevention of internalising disorder are not yet known.

Focusing on aetiological processes and risk factors may identify additional strategies of relevance to prevention interventions. Directly addressing parents' own emotional disorders should, in turn, prevent child disorder, if parents' mental health is a direct mechanism underpinning the child's disorder rather than simply reflecting a marker of genetic risk. Treatment of adult internalising disorders is well established, but whether successful treatment confers protection from mental disorder among offspring is not known.

Another risk factor that has received increasing interest in recent years is effortful control or, more specifically, attentional control. Inhibited children who are also low in the temperamental style of effortful control are at particular risk for mental disorder (Degnan et al., 2010). More detailed evidence has shown that inhibited children who have greater difficulty in focusing attentional resources and who focus preferentially toward threatening stimuli are more likely to develop later anxiety disorders relative to inhibited children who are able to control and modulate their focus of attention (Nozadi et al., 2016; White, McDermott, Degnan, Henderson, & Fox, 2011). This evidence suggests that training inhibited young children to improve their attentional control and to focus more consistently away from threatening information should prevent later anxiety. Attention training strategies along these lines have been extensively evaluated among adults with anxiety disorders, resulting in mixed results, although benefits are more apparent in certain contexts (Linetzky, Pergamin-Hight, Pine, & Bar-Haim, 2015). Nevertheless, these strategies have shown some promise, suggesting that evaluating their use among inhibited young children, either in isolation or as part of a more comprehensive intervention, may have some benefits.

Intervening with Inhibited Children Across Populations

From a public health perspective, there are strong arguments for improving mental health outcomes among temperamentally inhibited children early in life. The World Health Organization (WHO) recognises that internalising problems are high in burden of disease internationally (Mathers & Loncar, 2006; www.who.int/mediacentre/factsheets/fs369/en/). Prevalence data for youth show that internalising problems affect around one in five to one in ten children from 4 to 17 years of age (Lawrence et al., 2015; Merikangas et al., 2010). Cost-benefit studies demonstrate that intervening earlier in the life course is cheaper and more effective than later treatment (Heckman, 2000). Mrazek and Haggerty (1994) developed a theoretical model from prevention through treatment and continuing care to conceptualise population strategies for mental health. 'Universal' prevention approaches are for the general public or a whole population group that has not been identified based on individual risk. 'Targeted-selective' prevention approaches are offered to individuals or a subgroup of the population whose risk of developing mental disorders is significantly higher than average. 'Targeted-indicated' preventive interventions are for high-risk individuals identified as having minimal but detectable signs and symptoms foreshadowing mental disorder without current diagnostic levels. Targeting behaviourally inhibited children is classified as a targeted-selective approach within this framework.

Bayer et al. (2009) reviewed programs that held potential for a population approach to preventing internalising problems early in life. This systematic review focused on evidence-based interventions for internalising problems of young children aged 0–8 years. The review identified universal or targeted prevention programs, excluding treatment trials for diagnosed child mental health disorders or children receiving clinical mental health services. This revealed a paucity of preventive interventions for young children's internalising problems. Overall at that time, the Cool Little Kids parenting group program targeted to parents with inhibited preschool children had the best balance of evidence in the field. However, population-relevant conclusions were precluded by sample bias (university location and self-selection by advertisement) and labour-intensive laboratory observation methods used for selection. A larger population trial was therefore recommended, as Cool Little Kids had advantages of being brief (3 months) and demonstrated efficacy to prevent young children from developing later anxiety and internalising disorders. Determining effectiveness across an entire population was an unaddressed challenge.

In response to this need, we commenced an evaluation of the Cool Little Kids parenting group program using a population screening paradigm as a step toward public health implementation (Bayer, Rapee, et al., 2011). Extending Cool Little Kids to a population-level trial required a universal service system attended by all or almost all 4-year-olds and an acceptable screening tool to systematically identify inhibited children at risk for internalising problems. Primary health care was not considered an appropriate setting for this screening as in many countries health practitioners lack the time and resources to screen for this type of problem. Brief universal screening for behavioural inhibition was better placed in the preschool

setting. Preschool services are accessed by most 4-year-olds (95% in Australia), at a time when parents and early childhood teachers are concerned about the academic and socioemotional skills children need for school readiness (Schor, Abrams, & Shea, 2007; Wake et al., 2008).

Our population-based trial was based in the state of Victoria, Australia, and we selected preschool services across eight government areas to span the sociodemographic spectrum. After briefing preschools in the local government areas, recruitment took place over the first few months of the preschool year. All preschools offering a government-funded 4-year-old program in these districts were invited to take part, and 78% took up the offer. The participating preschools distributed an information package with inhibition screening to all parents of children enrolled in their year prior to starting school. The brief inhibition screen was the Short Temperament Scales approach subscale (Pedlow, Sanson, Prior, & Oberklaid, 1993). Parents returned the completed screen confidentially to the study team, who notified parents by letter of their child's inhibition status. The study team telephoned parents with inhibited children to explain the population trial. Preschool enrolment records included 17,661 children in the year before starting school, of which 36% of parents returned inhibition screening questionnaires. Eleven percent of children were behaviourally inhibited, and enrolment into the population trial was 78% (Beatson et al., 2014).

The population trial offered the Cool Little Kids parenting group program at local preschool services in the community to families randomly allocated to the intervention arm. Intervention was six, 90-min parenting group sessions with after-hours timing to facilitate attendance by working parents. The first two groups were a week apart. The next three sessions were biweekly to allow parents time to practise at home with their child, implementing strategies and encountering challenges. The final session was a month after the fifth session, to review progress and plan ahead for future challenges as children grew older. Trained clinical psychologists and postgraduate clinical psychology interns who followed the published therapist and 'parent activity book' manuals facilitated the groups. The population trial's control arm was 'usual care' access for families to available support services in the community. Most young children with socioemotional problems in Australia do not receive any help from professional services (Oh, Mathers, Hiscock, Wake, & Bayer, 2015).

Parents' feedback at post-intervention in the population trial was that Cool Little Kids was 'useful' and 'helpful' with their inhibited young child. Most parents found the process of inhibition screening was helpful when paired with the offer for assistance (87%). Most parents reported that the parenting group program was 'quite' to 'extremely' useful for understanding their young child's shyness, inhibition, and anxiety (86%), learning what leads to anxiety in young children (89%), encouraging brave child behaviour (91%), reducing child anxious behaviour (91%), and changing their own personal anxious and fearful thinking patterns (80%). In overall endorsement, 95% of parents said they would recommend this early intervention program to other families with inhibited children (Beatson et al., 2014).

While parents in the population trial described Cool Little Kids as useful for their inhibited children, the 1-year outcomes showed little impact on child anxiety

disorders over the population. On the Strengths and Difficulties Questionnaire, there was a significant effect for internalising problems with 24% of intervention versus 33% of control children scoring in the 'abnormal' range on the emotional difficulties subscale. But on most other measures, reductions were similar in both conditions, and the two groups did not differ significantly on the percentage of children at 12 months who met criteria for an anxiety disorder (44% intervention vs 50% control). However, the results demonstrated a significant interaction, such that the intervention reduced risk of anxiety disorders among inhibited children who also had an anxious parent compared to controls (Bayer et al., 2018).

Overall in this population trial, level of engagement was quite low when parenting groups were offered at no direct cost to parents. Only a third of parents took up the offer of screening at preschools to determine their child's inhibition status. Only a third of parents with inhibited children in the intervention arm participated in most of the program (5–6 groups). Then, only 20% continued to practise the program skills frequently with their inhibited child in the year following the program. In contrast, parents enrolled in our previous university-based trial appeared to be highly motivated with 73% attending most of the program (5–6 groups) (Rapee, Kennedy et al., 2010). Significant motivation was required for the university trial since parents needed to commit to intensive direct observation assessments pre- and post-intervention. In contrast, the population trial made it easy for parents to participate with relatively little effort via a brief child shyness screen and free parenting groups in the local community setting. This may have created a context for lower parent motivation and thereby weaker trial outcomes. The population trial's outcomes will be followed into mid-childhood (age 9–10 years).

Lessons Learned

From these results we might predict that successful prevention programs that are run broadly across the community will greatly benefit from techniques to ensure that parents enrolling in the program are sufficiently motivated to attend the majority of sessions and to continue practising with their young children as they grow. Mian (2014) recently emphasised that 'the greatest challenges to dissemination and establishing effectiveness of early childhood anxiety interventions for high-risk children will likely be related to parents' interest, willingness, or ability to engage in these programs' (p. 90). Consistent with this claim, we recently showed that the frequency of home practice was the primary predictor of beneficial outcomes from an online version of Cool Little Kids (Morgan, Rapee, Salim, & Bayer, 2018). One way forward could be to offer parenting groups only for those parents in the community who demonstrate commitment to participation and engagement. Consistent with our finding that inhibited children with an anxious parent did appear to benefit from the program, it is possible that parents with a personal history of anxiety may be particularly motivated to enrol and prevent their inhibited children from suffering

in a similar way. Another option to attract only the more motivated parents might be inclusion of a financial payment to enrol, although this would need to be balanced to maximise equity.

A recent study on Cool Little Kids offered with a service fee in the community took this approach. The literature tends to overlook implementation evaluations in real-world settings, although this oversight warrants attention in relation to adopting programs into practice (Graeff-Martins et al., 2008; Sanders & Kirby, 2015). La Trobe University's Psychology Clinic offered Cool Little Kids as a low-cost clinical psychology service at preschools in the Victorian community. An evaluation was conducted of this service in 2015 (Jarosz & Bayer, 2017). The psychology service informed preschool directors in six metropolitan districts that the Cool Little Kids parenting group program was available in their community. Preschools were provided with information flyers to distribute to parents of children enrolled in their year before starting school. The flyer included the behavioural inhibition questions for parents to self-screen their child and invited parents of inhibited children to contact the service for further details.

Parents of 86 children booked into the Cool Little Kids community service by paying $A50 to cover the parent activity book and group refreshments. Postgraduate clinical psychology interns attended an intervention workshop led by a clinical psychologist experienced with Cool Little Kids. After training, the intern clinicians facilitated the parenting group program in the evenings under regular supervision. At the first group session, parents received a service evaluation information pack to consider at home. Thirty-eight parents consented to take part in the service evaluation, and 92% provided post-intervention feedback.

At the beginning of the Cool Little Kids program, the service evaluation sample scored high on child internalising problems and overinvolved/protective parenting in comparison to community norms. Two thirds of the service evaluation sample attended most of the program (5–6 groups) with the remainder attending at least half (3–4 groups)—hence, motivation in the sample appeared to be considerably higher than in our population trial. Parents gave feedback that the Cool Little Kids service was 'quite' to 'extremely' useful for learning what contributes to child anxiety (94%), strategies to encourage child bravery (97%), strategies to reduce child anxiety (91%), and in managing their own personal anxieties (87%). Almost all (94%) would recommend Cool Little Kids for other families. Child internalising problems improved significantly across all measures after the intervention. To illustrate, on the Strengths and Difficulties Questionnaire emotional difficulties scale, the service evaluation sample moved from 37% 'abnormal' on commencing the service to 14% 'abnormal' after the service ($p = 0.008$). Significant improvements from the start to the end of the service were also found on overinvolved/protective and nurturing parenting, as well as parent stress. It appears that maximising parent motivation to engage in Cool Little Kids in the community, in this case through the use of a service fee, can lead to clinically meaningful benefits for families. Future research will need to determine whether this efficacy is greater than running the intervention in the absence of motivational enhancement.

Barriers to the Implementation of Early Intervention in the Community

Although Cool Little Kids is a brief parenting group program, there are substantial barriers to offering it widely for families in the population. At the service level, a scarcity of mental health professionals trained in this early intervention limits its availability. In addition, families themselves face barriers to attending parenting groups, including time, transportation, and childcare (Axford, Lehtonen, Kaoukji, Tobin, & Berry, 2012).

Recently, Internet delivery has been considered as a way to overcome some of the barriers to population implementation. In response to this need, we developed an online adaptation of Cool Little Kids (Morgan, Rapee, & Bayer, 2016) and then conducted a randomised controlled trial offering the program Australia-wide (Morgan et al., 2017). The online trial was promoted with paid advertisements on Facebook and Google, advertisements on parenting and mental health-related websites, and flyers distributed to preschools. A Cool Little Kids Online website provided study information and an enrolment link to recruit parents with 3- to 6-year-old children. For eligibility, parents filled in an online inhibition screening questionnaire, and then those with inhibited children were randomly allocated to the online intervention or waitlist control.

The online adaptation comprises eight modules with written information, videos, audio narration, interactive worksheets and activities, and parent stories. The online modules mirror content in the original parenting group program, covering psychoeducation about the nature, development, and risks for child anxiety disorders, and practical ways to reduce child anxiety through graded exposure, contingency management, reducing overprotective behaviours, and managing parents' own fears and worries. A new module was released each week, encouraging parents to complete one module per week, although they could work at their own pace as preferred. Parents had access to the online program for 6 months and could request telephone support from a psychologist to troubleshoot implementing the intervention techniques if required. Randomised trial results supported efficacy for this online mode of delivery in the population. Children in the intervention arm had greater reductions in child anxiety symptoms, anxiety disorders, and life interference from anxiety, compared to the waitlist controls. However, similar improvements did not emerge for child internalising symptoms or overprotective parenting (Morgan et al., 2017).

Wide dissemination of preventive programs into the population poses considerable challenges to researchers and service providers. Giesen, Searle, and Sawyer (2007) have suggested a number of important principles to consider. Services need to have properly trained staff who adhere to the program content. Intervention dosage (such as attendance at sessions) should be maximised by providing out-of-hours sessions for working parents and on-site childcare where possible. Intervention delivery should be sensitive to different cultures and at-risk populations. It is more likely that an intervention will be accepted by service providers and taken up in the population when it has proven effective or cost-effective outcome data; synchronises with the

adopter's values, past experience, and perceived needs; is simple to understand; is easy to adapt into the organisation; has transferable knowledge to other contexts; and supplies training and a help desk (Giesen et al., 2007). For adaptation into new settings, it is essential that a professional consultant who is experienced with the program works closely with the new providers, to ensure that components essential for effectiveness are maintained, while less critical aspects of the program are being tailored to local needs. As noted earlier, the cost-effectiveness of Cool Little Kids has been modelled and shown to represent very good value for money (Mihalopoulos et al., 2015). Nevertheless, uptake and adherence across the population will need to be addressed before widespread implementation reflects the modelled cost-benefits.

Dissemination approaches for Cool Little Kids can continue to be explored in the future. One direction could involve a two-stage screening process. Cool Little Kids could be offered to higher-risk children in the population who have dual risks of behavioural inhibition as well as parental anxiety. Inhibition screening could take place at preschools. Then parents of inhibited children who are interested in Cool Little Kids could complete an anxiety questionnaire to determine family risk as a second aspect for eligibility. An issue to consider for this approach in the population would be parent concern about stigma. Parents appear to be comfortable with identifying their young child as shy/inhibited via screening at preschool. However, they might be less comfortable about identifying personal anxiety as a family risk to a clinician at the second stage of screening. Methods for dual screening would need to be carefully developed and piloted.

Another future direction to consider for Cool Little Kids in the population is stepped care. Cool Little Kids Online could be offered as a first self-directed step for families with inhibited young children. At the end of the online program, parents could complete an outcome assessment online. Augmented face-to-face care could then be offered for children who still have clinical levels of anxiety or internalising problems. Augmented care could consist of the parenting group program (e.g. Cool Little Kids) or another recently developed alternative. The Turtle program, described earlier, is one such possible alternative intervention with likely value for extremely inhibited children. Other programs have also demonstrated efficacy in the treatment of clinical anxiety disorders among preschool-aged children (Anticich et al., 2013; Cartwright-Hatton et al., 2011; Hirshfeld-Becker et al., 2010). It will be important in future population application to develop funding models for preventive services that accompany different approaches.

Conclusion

In conclusion, behavioural inhibition affects around one in ten preschool children in the population. Inhibited young children are at significant risk of developing anxiety disorders and internalising problems as they grow. Families use various different terms to describe their inhibited child (shy, sensitive, reserved, anxious). Early intervention with inhibited young children focuses on teaching parents how to

encourage children to face and overcome their fears, rather than promoting avoidance behaviours and/or teaching children more effective social engagement skills. In university trials with motivated parents who engage strongly with early intervention, positive mental health outcomes for inhibited young children have been found. Research to date exploring wider population application of early intervention indicates that parents' degree of motivation and engagement is important for effectiveness. Future directions to explore in population application include dual-gate screening for inhibition plus parent anxiety, stepped care from a self-directed online intervention followed by face-to-face clinical care for children still in need, and sustainable early intervention funding models.

References

Anticich, S. A., Barrett, P. M., Silverman, W., Lacherez, P., & Gillies, R. (2013). The prevention of childhood anxiety and promotion of resilience among preschool-aged children: A universal school based trial. *Advances in School Mental Health Promotion, 6*(2), 93–121.

Axford, N., Lehtonen, M., Kaoukji, D., Tobin, K., & Berry, V. (2012). Engaging parents in parenting programs: Lessons from research and practice. *Children and Youth Services Review, 34*, 2061–2071.

Bayer, J. K., Beatson, R., Bretherton, L., Hiscock, H., Wake, M., Gilbertson, T., … Rapee, R. M. (2018). Translational delivery of Cool Little Kids to prevent child internalising problems: Randomised controlled trial. *Australian and New Zealand Journal of Psychiatry, 52*, 181. https://doi.org/10.1177/0004867417726582

Bayer, J. K., Hiscock, H., Scalzo, K., Mathers, M., McDonald, M., Morris, A., … Wake, M. (2009). Systematic review of preventive interventions for children's mental health: What would work in Australian contexts? *Australian and New Zealand Journal of Psychiatry, 43*(8), 695–710.

Bayer, J. K., Rapee, R. M., Hiscock, H., Ukoumunne, O. C., Mihalopoulos, C., Clifford, S., & Wake, M. (2011). The Cool Little Kids randomised controlled trial: Population-level early prevention for anxiety disorders. *BMC Public Health, 11*, 11.

Bayer, J. K., Ukoumunne, O. C., Lucas, N., Wake, M., Scalzo, K., & Nicholson, J. M. (2011). Risk factors for childhood mental health symptoms: National longitudinal study of Australian children. *Pediatrics, 128*, e865–e879.

Beatson, R. M., Bayer, J. K., Perry, A., Mathers, M., Hiscock, H., Wake, M., … Rapee, R. M. (2014). Community screening for preschool child inhibition to offer the 'Cool Little Kids' anxiety prevention programme. *Infant and Child Development, 23*(6), 650–661.

Cartwright-Hatton, S., McNally, D., Field, A. P., Rust, S., Laskey, B., Dixon, C., … Woodham, A. (2011). A new parenting-based group intervention for young anxious children: Results of a randomized controlled trial. *Journal of the American Academy of Child & Adolescent Psychiatry, 50*(3), 242–251.

Chronis-Tuscano, A., Rubin, K. H., O'Brien, K. A., Coplan, R. J., Thomas, S. R., Dougherty, L. R., … Wimsatt, M. (2015). Preliminary evaluation of a multimodal early intervention program for behaviorally inhibited preschoolers. *Journal of Consulting and Clinical Psychology, 83*(3), 534–540.

Clauss, J. A., & Blackford, J. U. (2012). Behavioral inhibition and risk for developing social anxiety disorder: A meta-analytic study. *Journal of the American Academy of Child & Adolescent Psychiatry, 51*(10), 1066–1075.

Coplan, R. J., Prakash, K., O'Neill, K., & Armer, M. (2004). Do you "want" to play? Distinguishing between conflicted shyness and social disinterest in early childhood. *Developmental Psychology, 40*(2), 244–258.

Coplan, R. J., Schneider, B. H., Matheson, A., & Graham, A. (2010). 'Play skills' for shy children: Development of a social skills facilitated play early intervention program for extremely inhibited preschoolers. *Infant and Child Development, 19*(3), 223–237.

Degnan, K. A., Almas, A. N., & Fox, N. A. (2010). Temperament and the environment in the etiology of childhood anxiety. *Journal of Child Psychology and Psychiatry, 51*(4), 497–517.

Edwards, S. L., Rapee, R. M., & Kennedy, S. (2010). Prediction of anxiety symptoms in preschool-aged children: Examination of maternal and paternal perspectives. *Journal of Child Psychology & Psychiatry, 51*(3), 313–321.

Gazelle, H., & Ladd, G. W. (2003). Anxious solitude and peer exclusion: A diathesis-stress model of internalizing trajectories in childhood. *Child Development, 74*(1), 257–278.

Gazelle, H., & Shell, M. D. (2017). Behavioral profiles of anxious solitary children: Predicting peer relations trajectories from third to fifth grade. *Merrill-Palmer Quarterly, 63*(2), 237.

Giesen, F., Searle, A., & Sawyer, M. (2007). Identifying and implementing prevention programmes for childhood mental health problems. *Journal of Paediatrics and Child Health, 43*, 785–789.

Graeff-Martins, A. S., Flament, M. F., Fayyad, J., Tyano, S., Jensen, P., & Rohde, L. A. (2008). Diffusion of efficacious interventions for children and adolescents with mental health problems. *Journal of Child Psychology and Psychiatry, 49*, 335–352.

Heckman, J. (2000). *Invest in the very young*. Chicago, IL: Ounce of Prevention Fund and the University of Chicago Harris School of Public Policy Analysis.

Hirshfeld-Becker, D. R., Masek, B., Henin, A., Blakely, L. R., Pollock-Wurman, R. A., McQuade, J., … Biederman, J. (2010). Cognitive behavioral therapy for 4- to 7-year-old children with anxiety disorders: A randomized clinical trial. *Journal of Consulting and Clinical Psychology, 78*(4), 498–510.

Jarosz, E., & Bayer, J. K. (2017). Service evaluation of the Cool Little Kids parenting program delivered in the community. *Advances in Mental Health*, 1. https://doi.org/10.1080/18387357.2017.1418630

Jitlina, K., Shumka, E., Miller, L. D., & Rapee, R. M. (2015). *Disseminating evidence-based anxiety prevention strategies into the schools: Capitalizing on existing clinical anxiety treatment programs*. Paper presented at the 49th ABCT Convention, Chicago, November 12–15.

Kagan, J., Reznick, J. S., Clarke, C., Snidman, N., & Garcia-Coll, C. (1984). Behavioral inhibition to the unfamiliar. *Child Development, 55*, 2212–2225.

Kagan, J., Reznick, J. S., & Snidman, N. (1988). Biological bases of childhood shyness. *Science, 240*, 167–171.

Kagan, J., Snidman, N., Arcus, D., & Reznick, J. S. (1994). *Galen's prophecy: Temperament in human nature*. New York, NY: Basic Books.

Kennedy, S. J., Rapee, R. M., & Edwards, S. L. (2009). A selective intervention program for inhibited preschool-aged children of parents with an anxiety disorder: Effects on current anxiety disorders and temperament. *Journal of the American Academy of Child & Adolescent Psychiatry, 48*(6), 602–609.

Kerr, M. (2000). Childhood and adolescent shyness in long-term perspective. In W. R. Crozier (Ed.), *Shyness: Development, consolidation and change* (pp. 65–87). London, England: Routledge.

LaFreniere, P. J., & Capuano, F. (1997). Preventive intervention as a means of clarifying direction of effects in socialization: Anxious-withdrawn preschoolers case. *Development and Psychopathology, 9*, 551–564.

Lau, E. X., Rapee, R. M., & Coplan, R. J. (2017). Combining child social skills training with a parent early intervention program for inhibited preschool children. *Journal of Anxiety Disorders, 51*, 32–38.

Lawrence, D., Johnson, S., Hafekost, J., Boterhoven De Haan, K., Sawyer, M. G., Ainley, J., & Zubrick, S. (2015). *The mental health of children and adolescents*. Report on the second Australian Child and Adolescent Survey of Mental Health and Wellbeing. Retrieved from Canberra, Australia.

Li, Y., Coplan, R. J., Wang, Y., Yin, J., Zhu, J., Gao, Z., & Li, L. (2016). *Preliminary evaluation of a social skills training and facilitated play early intervention programme for extremely shy young children in china* (Vol. 25, p. 565). Infant and Child Development.

Linetzky, M., Pergamin-Hight, L., Pine, D. S., & Bar-Haim, Y. (2015). Quantitative evaluation of the clinical efficacy of attention bias modification treatment for anxiety disorders. *Depression and Anxiety, 32*(6), 383–391.

Luke, F., Chan, C. C., Au, A., & Lai, S. M. K. (2017). Adaptive parenting for alleviating young children's shyness: A randomized controlled trial of an early intervention program. *Infant and Child Development, 26*, e2030.

Lyneham, H. J., Hudson, J. L., & Rapee, R. M. (2014). Prevention of anxiety disorders. In T. Ehring & P. M. Emmelkamp (Eds.), *International handbook of anxiety disorders* (pp. 625–642). Chichester, England: Wiley.

Mathers, C. D., & Loncar, D. (2006). Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Medicine, 3*(11), e442. https://doi.org/10.1371/journal.pmed.0030442

McLeod, B. D., Wood, J. J., & Weisz, J. R. (2007). Examining the association between parenting and childhood anxiety: A meta-analysis. *Clinical Psychology Review, 27*, 155–172.

Merikangas, K. R., He, J.-P., Burstein, M., Swanson, S. A., Avenevoli, S., Cui, L., … Swendsen, J. (2010). Lifetime prevalence of mental disorders in U.S. adolescents: Results from the National Comorbidity Survey Replication-Adolescent Supplement (NCS-A). *Journal of the American Academy of Child & Adolescent Psychiatry, 49*(10), 980–989.

Mian, N. D. (2014). Little children with big worries: Addressing the needs of young, anxious children and the problem of parent engagement. *Clinical Child and Family Psychology Review, 17*, 85–96.

Micco, J. A., Henin, A., Mick, E., Kim, S., Hopkins, C. A., Biederman, J., & Hirshfeld-Becker, D. R. (2009). Anxiety and depressive disorders in offspring at high risk for anxiety: A meta-analysis. *Journal of Anxiety Disorders, 23*(8), 1158–1164.

Mihalopoulos, C., Vos, T., Rapee, R. M., Pirkis, J., & Carter, R. (2015). The population cost-effectiveness of a parenting intervention designed to prevent anxiety disorders in children. *Journal of Child Psychology & Psychiatry, 56*(9), 1026–1033.

Morgan, A. J., Rapee, R. M., & Bayer, J. K. (2016). Prevention and early intervention of anxiety problems in young children: A pilot evaluation of Cool Little Kids Online. *Internet Interventions, 4*, 105–112.

Morgan, A. J., Rapee, R. M., Salim, A., & Bayer, J. K. (2018). Predicting response to an internet-delivered parenting program for anxiety in early childhood. *Behavior Therapy, 49*, 237.

Morgan, A. J., Rapee, R. M., Salim, A., Goharpey, N., Tamir, E., McLellan, L. F., & Bayer, J. K. (2017). Internet-delivered parenting program for early intervention of anxiety problems in young children: A randomized controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry, 56*, 417.

Mrazek, P. J., & Haggerty, R. J. (1994). In P. J. Mrazek & R. J. Haggerty (Eds.), *Reducing risks for mental disorders*. Washington, DC: National Academy Press.

Nozadi, S. S., Troller-Renfree, S., White, L. K., Frenkel, T. I., Degnan, K. A., Bar-Haim, Y., … Fox, N. A. (2016). The moderating role of attention biases in understanding the link between behavioral inhibition and anxiety. *Journal of Experimental Psychopathology, 7*(3), 451–465.

Oh, E., Mathers, M., Hiscock, H., Wake, M., & Bayer, J. K. (2015). Professional help seeking for young children with mental health problems. *Australian Journal of Psychology, 67*, 187–195.

Pedlow, R., Sanson, A., Prior, M., & Oberklaid, F. (1993). Stability of maternally reported temperament from infancy to 8 years. *Developmental Psychology, 29*(6), 998–1007.

Prior, M., Smart, D., Sanson, A., & Oberklaid, F. (2000). Does shy-inhibited temperament in childhood lead to anxiety problems in adolescence? *Journal of the American Academy of Child and Adolescent Psychiatry, 39*(4), 461–468.

Rapee, R. M. (1997). Potential role of childrearing practices in the development of anxiety and depression. *Clinical Psychology Review, 17*, 47–67.

Rapee, R. M. (2002). The development and modification of temperamental risk for anxiety disorders: Prevention of a lifetime of anxiety? *Biological Psychiatry, 52*, 947–957.

Rapee, R. M. (2013). The preventative effects of a brief, early intervention for preschool-aged children at risk for internalising: Follow-up into middle adolescence. *Journal of Child Psychology and Psychiatry, 54*(7), 780–788.

Rapee, R. M., & Coplan, R. J. (2010). Conceptual relations between anxiety disorder and fearful temperament. In H. Gazelle & K. H. Rubin (Eds.), *Social anxiety in childhood: Bridging developmental and clinical perspectives. New directions for child and adolescent development* (Vol. 127, pp. 17–31). San Francisco, CA: Jossey-Bass.

Rapee, R. M., Kennedy, S., Ingram, M., Edwards, S. L., & Sweeney, L. (2005). Prevention and early intervention of anxiety disorders in inhibited preschool children. *Journal of Consulting and Clinical Psychology, 73*(3), 488–497.

Rapee, R. M., Kennedy, S., Ingram, M., Edwards, S. L., & Sweeney, L. (2010). Altering the trajectory of anxiety in at-risk young children. *American Journal of Psychiatry, 167*, 1518–1525.

Rapee, R. M., Lau, E. X., & Kennedy, S. J. (2010). *The Cool Little Kids anxiety prevention program –s therapist manual*. Sydney, NSW, Australia: Centre for Emotional Health, Macquarie University.

Rapee, R. M., Schniering, C. A., & Hudson, J. L. (2009). Anxiety disorders during childhood and adolescence: Origins and treatment. *Annual Review of Clinical Psychology, 5*, 311–341.

Rubin, K. H., Coplan, R. J., & Bowker, J. C. (2009). Social withdrawal in childhood. *Annual Review of Psychology, 60*, 141–171. https://doi.org/10.1146/annurev.psych.60.110707.163642

Sanders, M. R., & Kirby, J. N. (2015). Surviving or thriving: Quality assurance mechanisms to promote innovation in the development of evidence-based parenting interventions. *Prevention Science, 16*, 421–431.

Schor, E. L., Abrams, M., & Shea, K. (2007). Medicaid: Health promotion and disease prevention for school readiness. *Health Affairs, 26*, 420–429.

Wake, M., Sanson, A., Berthelsen, D., Hardy, P., Mission, S., Smith, K., Ungerer, J., & LSAC Research Consortium. (2008). How well are Australian infants and children aged 4 to 5 years doing? *Findings from the Longitudinal Study of Australian Children Wave 1* (Social Policy Research Paper No. 36). Canberra, Australia: Department of Families, Housing, Community services and Indigenous Affairs, Australian Government.

White, L. K., McDermott, J. M., Degnan, K. A., Henderson, H. A., & Fox, N. A. (2011). Behavioral inhibition and anxiety: The moderating roles of inhibitory control and attention shifting. *Journal of Abnormal Child Psychology, 39*(5), 735–747.

Next Steps: Behavioral Inhibition as a Model System

Koraly Pérez-Edgar and Nathan A. Fox

Abstract The current volume brings together a complex network of research that stemmed from the initial observation of individual variation in infants and toddlers. Since then, the last three decades of work has morphed the initial definition of behavioral inhibition, the systems associated with the temperamental trait, and the trajectories that we have associated with early profiles. The current chapter first outlines some of the core lessons that can be drawn from the extant literature. We then ask five questions that still puzzle researchers and may point to the "developmental arc" of the studies that will emerge in the decades to come.

In his essay, *Follow the Evidence, Not the Words,* Jerome Kagan (2016) suggests that psychologists should view Charles Darwin, not Albert Einstein, as a role model for the field. This exhortation is fitting as behavioral inhibition (BI) illustrates the triumph of observation and description in identifying, and then carving out, a unique phenomenon for further study. As noted in chapter the "The History and Theory of Behavioral Inhibition" by Kagan, and in other writings, the initial formulation of behavioral inhibition arose from the careful observation of infant reactivity and behavior, which in turn relied on the repeated viewing of videotapes. Keen observation allowed Kagan to extract the signal from the surrounding noise. While not predicted, the signal was nonetheless robust, supporting over three decades of research. This volume represents only a selection of the work that has emerged from the initial discovery (Kagan, 2012) of behavioral inhibition (García Coll, Kagan, & Reznick, 1984; Kagan, Reznick, Clarke, Snidman, & García-Coll, 1984). Even so, the volume illustrates the many ways in which researchers have come to build on, transform, and expand upon the initial observation.

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The different sections of the book were designed to reflect some important areas of inquiry that build on or help us better understand the phenomenon of behavioral inhibition, beginning in childhood and expanding through the life span. This included animal models of behavioral inhibition, biological underpinnings, social relationships, cognitive mechanisms, and psychopathology. The diversity of these topics supports our contention that behavioral inhibition can be seen as a model system for the study of development. Here, we briefly touch on six ways in which behavioral inhibition research reflects and advances important approaches to developmental research.

First, as noted, research began with the initial observation and *description* of the phenomenon of interest. This is crucial, as it allowed researchers to begin their work with a shared understanding of the entity *out in nature* that they wish to better understand through further observation and experimental manipulation (Pérez-Edgar & Hastings, 2018). Behavioral inhibition is observed in toddlers when they are confronted with novel objects, contexts, and people. All of the work builds from this foundation. Of course, this is not to say that the definition that emerges from observation is rigid or immutable. Anyone who has read this literature, or the previous 15 chapters, can quickly see that multiple operationalizations and labels have come to sit under the umbrella of behavioral inhibition. But fundamentally, behavior is the cornerstone for identifying and describing this temperament. We touch on this a bit more later in this chapter.

Second, behavioral inhibition emerges over *time,* as it is an epiphenomenon of a more basic pattern of reactivity, which is itself identified by observing behavior in early infancy. Negative reactivity is a core antecedent of the behaviorally inhibited behavior seen later in the first and second years of life. Indeed, Kagan would argue that high reactive infants exhibit the temperamental type that then manifests as the pattern of behaviors known as behavioral inhibition (Fox, Henderson, Rubin, Calkins, & Schmidt, 2001; Fox, Snidman, Haas, Degnan, & Kagan, 2015). Going forward in time, behavioral inhibition is related to social reticence in early childhood and then, for some adolescents, clinically significant social anxiety (Chronis-Tuscano et al., 2009; Rapee, Kennedy, Ingram, Edwards, & Sweeney, 2005).

Behavioral inhibition is one of the best characterized and most potent individual predictors of social anxiety (Clauss & Blackford, 2012). One of the important advances in the field was the recognition that many of the behaviors and physiological responses of behaviorally inhibited children (freezing, avoidance, elevated heart rate) were similar to those found by neuroscientists studying the origins of anxiety and fear learning in rodents (LeDoux, 1995; Phelps & LeDoux, 2005). Indeed, the reactivity that Kagan first observed (back arching, distress vocalizations, motor movements) was described in the rodent literature examining the neuroscience of fear learning. Specific areas in the brain stem and limbic system (e.g., central gray, etc.) were thought to underlie these responses in both rodents and infants. In addition, child psychiatrists and child clinicians noted that the behaviors of young children who were the offspring of anxious and depressed mothers often looked similar to those described for the behaviorally inhibited child (Rosenbaum et al., 1988, 1992,

2000). Together this work ignited interest in examining patterns of reactivity and behavioral inhibition as potential precursors of anxiety disorders.

Much of the current work linking behavioral inhibition and anxiety focuses on the progression from behavioral inhibition to varying levels of social reticence and inhibition, as outlined by the chapter "The Temperamentally Shy Child as the Social Adult: An Exemplar of Multifinality" by Poole and colleagues. The task is no easier if we are focused on more extreme trajectories that lead to clinical disorder. Indeed the chapter "Behavioral Inhibition as a Precursor to Psychopathology" by Klein and Mumper outline *seven* different models that may account for the documented relation between early behavioral inhibition and the later emergence of anxiety.

Equally important is the fact that while many behaviorally inhibited children go on to exhibit social anxiety, the majority do not (Degnan & Fox, 2007). In addition, not all anxious individuals were previously behaviorally inhibited (Clauss & Blackford, 2012). Shyness and clinical anxiety are not dependent on having had extreme negative reactivity in infancy nor behavioral inhibition as a toddler. In addition, problematic trajectories need not only lead to anxiety as we have data linking behavioral inhibition multiple outcomings, including depression (Gladstone & Parker, 2006) and substance use (Lahat et al., 2012; Williams et al., 2010).

Third, researchers built on the complexity of initial descriptions to examine potential underlying *mechanisms.* The dogged search for processes and mechanisms often set developmental psychologists apart from colleagues in the other subdisciplines. Mechanisms arise from functional influences on a child's current state that can lawfully direct change over time (van der Molen & Molenaar, 1994). Given the central focus on change, it is natural for developmental psychologists to want to capture and explain the causes of this change. To ask this question, we often rely on experimental methods that manipulate a potential mechanism of interest and then carefully track any and all changes in the outcome. This is a mechanistic approach to the developmental question.

Each of the sections in this volume illustrates work that, to varying extents, attempts to isolate and (quasi-) manipulate potential mechanisms of change. The chapters "Behavioral Inhibition in Nonhuman Primates: The Elephant in the Room" by Capitanio and "Behavioral Inhibition in Rodents: A Model to Study Causes and Health Consequences of Temperament" by Cavigelli, for example, use animal models to document and manipulate experiences that influence social and health-related functions. As another example, the chapter "Behavioral Inhibition and the Associative Learning of Fear" by Reynolds and colleagues build on animal models, and our understanding of basic learning processes, to show how behaviorally inhibited children acquire (learn) fears through both direct experience and vicarious observation.

Historically, there has been some concern that an overly mechanistic approach may isolate developmentalists for the very phenomenon that first interested them. Wohlwill (1973), for example, argued that if developmental psychology opened itself up to "the invasion of the experimentalists," the field would lose its place as a distinct contributor to psychology. Rather, it would devolve into a paler branch of general

psychology defined simply by the age of the participants. However, the last few decades of behavioral inhibition research clearly show that you can marry a careful description of children's natural trajectories with systematic study (and manipulation) of potential mechanisms without becoming "mechanistic tinkerers." Indeed, it was careful observation that suggested that behavioral inhibition morphed over time due to the emergence of cognitive and emotional self-evaluation (see the chapter "Relations Between Behavioral Inhibition, Cognitive Control and Anxiety: Novel Insights Provided by Parsing Subdomains of Cognitive Control" by Buzzell et al.), as well as decreased influence from parents and increasing importance of peers (see the chapter "The Social World of Behaviorally Inhibited Children: A Transactional Account" by Henderson et al. and the chapter "Peer Relations and the Behaviorally Inhibited Child" by Rubin et al.).

Fourth, behavioral inhibition research exemplifies the importance of isolating and examining *individual differences*. One core goal of developmental research is to document and understand the expected sequence of change over time, linking antecedent events to subsequent change. This work sets the foundation for more specialized study. However, there are inherent tensions between outlining nomothetic laws that focus on universal sequences and their contexts versus identifying idiographic patterns that are unique to individuals (Scarr, 1992; Scarr & McCartney, 1983).

In studying individual differences, we have to make space for the realization that the environment, and experiences encountered within an environment, does not have the same meaning for all children. Scarr (1992) argued that a child constructs a unique reality for him- or herself. Behavioral inhibition research shines a light on clear differences in how children react to ostensibly identical social contexts. Some children rush to embrace the novelty of the social world, while others pull back from ambiguous and unexpected threats. These variations appear early and shape the child's "experienced environment." In this way, fairly subtle individual differences can impact socioemotional functioning from infancy by creating cascading and self-reinforcing biases in social cognition and behavior (see the chapter "The Social World of Behaviorally Inhibited Children: A Transactional Account" by Henderson et al. and the chapter "Attention Mechanisms in Behavioral Inhibition: Exploring, and Exploiting, the Environment" by Pérez-Edgar).

Taking an individual difference approach can also expand our methodological toolbox. Petrill and Brody (2002) argued that experimental psychology creates variability by manipulating the environment, while researchers interested in individual differences study naturally occurring variation. To do so we use using statistical methods to "partition sources of variance in a measure." We are lucky, as a science, that individual differences are likely to be lawful rather than a random assortment of disconnected and independent traits. As a result, we can shift from a focus on variance across conditions to variance among individuals. This change in focus is then coupled by a shift from a variable-centered analytic approach to a person-centered approach. Thus, the focus is not on how a variable behaves across context or time but on how individuals, or groups of individuals, react in response to maturational forces and the surrounding environment.

Fifth, often more by necessity than desire, research in behavioral inhibition has incorporated *multiple levels of analysis.* As noted, the initial work in behavioral inhibition was rooted in carefully describing behavior in response to standardized experiences. However, this description was also closely tied to a proposed mechanism that suggested that underlying hyper-reactivity in the amygdala generated the behavioral inhibition phenotype (Kagan, Reznick, & Snidman, 1987). So, from the start, there was the challenge of tying together neural functioning with observed behavior, despite the many intervening layers of processing and activity.

This was a particularly tricky proposition in the mid-1980s since there were both developmental and technological barriers to examining the limbic correlates of behavioral inhibition. First, neuroimaging techniques were not readily available to researchers interested in human behavior. Indeed, the initial studies demonstrating the feasibility of capturing the blood oxygen level dependent (BOLD) signal associated with neural functioning were not published until the early 1990s (Kwong et al., 1992; Ogawa et al., 1992). Second, the specific parameters of neuroimaging require participants to remain very still (at the level of millimeters) and require specific task parameters and responses (except in the case of resting state measures). Keeping still and following directions have never been strengths of the toddler population.

As a result, researchers first proceeded by systematically measuring secondary, peripheral, measures that both reflect "deeper" neural structures and can track variation in observed behavior. Creative studies examined electroencephalogram (EEG) activity at rest and in response to challenge, stimulus-locked EEG responses via event-related potentials (ERPs), startle responses to expected and unexpected stimuli, resting and reactive cardiac patterns, and skin conductance responses (Fox, Hane, & Pérez-Edgar, 2006). As the chapter "Psychobiological Processes in the Development of Behavioral Inhibition" by Buss and Qu points out, psychophysiological measures can both help find heterogeneity underlying surface level homogeneity in behavior and track the functional antecedents of observed behaviors. Then, as neuroimaging technology became more widely available, we saw the first functional imaging study directly examining limbic activity in adults with a history of behavioral inhibition (Schwartz, Wright, Shin, Kagan, & Rauch, 2003). This work triggered a rapid succession of studies that worked to capture the normative (see the chapter "The Neural Mechanisms of Behavioral Inhibition" by Jarcho and Guyer), developmental (see the chapter "The Neurobiology of Behavioral Inhibition as a Developmental Mechanism" by Blackford et al.), and clinical (see the chapter "The Biological Bridge Between Behavioral Inhibition and Psychopathology" by Sylvester and Pine) antecedents and consequences of behavioral inhibition.

In doing so, the most comprehensive studies (Fox, Henderson, Marshall, Nichols, & Ghera, 2005; Kagan, 2012; Klein, Dyson, Kujawa, & Kotov, 2012) incorporated observed behavior, cognitive functioning, social interactions, self-report, biological measures, genetic variation, clinical diagnoses, and adult outcomes. Multiple measures, of course, also mean greater complexity—complexity in methodology, analytics,

and interpretation. This is reflected in entire volumes that have attempted to capture the ins and outs of this approach, as in the *Handbook of Multimethod Measurement in Psychology* (Eid & Diener, 2006). When you gather these multiple measures, you are then confronted with the daunting question of how to best aggregate these measures—if at all—and how to interpret the inevitably highly complex relations that will emerge or, worse, how to explain when the relations do not emerge.

Indeed, while we work to choose measures that theoretically reflect a shared underlying construct, our actual results often have correlations that likely could have been achieved by drawing measures out of a hat. For example, Nesse et al. (1985) examined measures of distress during in vivo exposure therapy in phobic individuals. Although they noted increases in subjective anxiety, pulse, blood pressure, plasma norepinephrine, epinephrine, insulin, cortisol, and growth hormone, there was only modest convergence in the "magnitude, consistency, timing, and concordance" (p320) of their measures. And this is with a well-understood, relatively straightforward mechanism. Clearly, more work is needed to better understand the shared and unique information provided across measures of interest.

Sixth, behavioral inhibition helps illustrate how basic research can spur *application*, which looks to intervene for children potentially on a path to negative outcomes. The initial description of behavioral inhibition identified children of interest (e.g., the chapter "The History and Theory of Behavioral Inhibition" by Kagan) and documented the trajectory to social anxiety (e.g., the chapter "The Neurobiology of Behavioral Inhibition as a Developmental Mechanism" by Blackford et al. and the chapter "Behavioral Inhibition as a Precursor to Psychopathology" by Klein and Mumper). Follow-up research then documented the mechanisms that could alter this trajectory for children (e.g., interactions with peers, the chapter "Peer Relations and the Behaviorally Inhibited Child" by Rubin et al.; fear-learning, "Behavioral Inhibition and the Associative Learning of Fear" by Reynolds et al.). The next piece of the chain is then to target, and manipulate, these mechanisms in order to modify risk. In this volume, the chapter "Behavioural Inhibition and the Prevention of Internalising Distress in Early Childhood" by Rapee and Bayer outline a systematic line of research that has worked to ameliorate risk by either targeting parental behaviors (e.g., overprotectiveness) or the child herself (e.g., engendering "bravery" in the face of uncertainty). Additional approaches, such as the Turtle Program (Chronis-Tuscano et al., 2015), are working to divert maladaptive trajectories as early as preschool, leveraging the power of social interaction. Indeed, prior work showed that simply attending a preschool, which exposes children to novel teachers and peers, was enough to lessen shyness and anxiety for many children (Almas et al., 2011; Phillips, Fox, & Gunnar, 2011).

Even with the breadth and depth of research carried out over the last three decades, we continue to face open questions that still puzzle researchers in behavioral inhibition and/or point to potential avenues for future work. Surprisingly, some of the questions are rather basic (what is behavioral inhibition?). Luckily for us, the breadth and depth of the remaining questions should keep researchers busy for the next three decades as well. Here we note only five of the many questions left to debate and solve.

We Say We Study Behavioral Inhibition, But Are We All Studying the Same Thing?

We would argue that the wide range of studies described and discussed in the current volume reflects the strength of behavioral inhibition as a construct of study. This volume suggests that behavioral inhibition is pervasive as a developmental phenomenon and it is prominent in the developmental literature. This may also mean that the term "behavioral inhibition" has come to be used for a number of constructs that are only partially overlapping. Recruiting 5-year-old children assessed through maternal report of behavioral inhibition is not the equivalent of directly assessing behavior at age 2. Initially assessing behavior at age 2 is likely also not the equivalent of constraining the label to children who displayed negative reactivity in infancy. The use of multiple assessment measures under the same label may dilute the collective strength of the knowledge generated across studies.

In addition, there are constructs and behaviors that appear quite similar to "behavioral inhibition" but are labeled as shyness, temperamental shyness, social reticence, social withdrawal, social anxiety, and so on. Indeed, this equifinality and multifinality of labeling, to borrow a term, is evident within and across all of the chapters in the current volume. We present here animal models, direct observation, self- and parent-report, infant antecedents, adult sequelae, and cognitive and biological underpinnings. Then we layer on the correlates of behavioral inhibition.

Thus, the construct and its correlates are reflected in data generated by a rat who did not explore an enclosure, a monkey who became immobile upon seeing a human approach the cage, a college student who showed a potentiated eye blink startle to a loud sound while looking at unpleasant pictures, an adolescent's verbal report of reluctance to attend parties, a rise in salivary cortisol during the Trier Stress Test, less alpha-band power in the right than the left frontal lobe, or a large BOLD signal in the amygdala to social pictures. In all likelihood, were we to repeat these measures in the same individual, we may not see them "hang together" in the way we expect.

As such, there are a number of issues that must be kept in mind when reading the literature. When you move beyond the initial direct observation of behavior in toddlers, can we continue to use the term behavioral inhibition? Even if we do see behaviors that we all agree are "inhibited," how do we determine that these are not simply phenotypic copies of the construct of interest? Is heterogeneity in outcomes linked to behavioral inhibition due to the influence of the environment and maturation, or due to the fact that we have swept up multiple traits (e.g., dysregulated fear, Buss et al., 2013), under the umbrella of behavioral inhibition? Are we examining categorically distinct individuals or individuals that reside at the extreme of a temperamental spectrum?

It seems clear that the emerging strategy of observing children at multiple levels of analysis, across contexts (see point 5, below), over time, will be central to answering these questions. This may help us understand if observed changes reflect changes in underlying temperament, or the manifestation of this trait. We may be able to

better understand if constructs of interest are mechanisms of behavioral inhibition, that is, they generate the behavioral profile we see in the laboratory, or if they are independent moderators of behavioral inhibition.

What Is the "Allostatic Load" of Being Behaviorally Inhibited?

Much of the focus on the long-term outcomes and impact of early behavioral inhibition has been on socioemotional concerns and psychiatric diagnoses. This reflects the profiles that emerged over time with observation. It also reflects the scientific interests and expertise of many of the researchers studying behavioral inhibition. After all, the person doing the science may be just as important as the subject of study as they will be the ones determining which questions go to the front of the line to be asked first, what answers are interesting and worth following up, and which data points should be allowed to influence the ongoing conversation.

Clearly, the socioemotional processes associated with behavioral inhibition are central to how we understand the construct. However, there is growing recognition of the basic health consequences of stable high behavioral inhibition in humans (the chapter "The Temperamentally Shy Child as the Social Adult: An Exemplar of Multifinality" by Poole et al.), nonhuman primates (the chapter "Behavioral Inhibition in Nonhuman Primates: The Elephant in the Room" by Capitanio), and rodents (the chapter "Behavioral Inhibition in Rodents: A Model to Study Causes and Health Consequences of Temperament" by Cavigelli). We see signs of increases in early perinatal risk, asthma and allergies, cardiovascular disease, and, in the case of Cavigelli's rodent model, early mortality.

The wide-ranging health-related outcomes reflect the multitude of systems that have been either linked directly to individual variation in behavioral inhibition or are altered when risk factors are assessed in the context of behavioral inhibition: gene expression, glucocorticoid production and function, hormone levels, and central and peripheral nervous system function. Thus, it may be helpful to base work on the position that behavioral inhibition increases the overall allostatic load an individual carries (the chapter "The Temperamentally Shy Child as the Social Adult: An Exemplar of Multifinality" by Poole et al.). Through allostasis, the body's set points are altered in order to deal with pressing challenges to the child in the moment. High, or repeated, levels of challenge may overwhelm the behaviorally inhibited child's ability to flexibly respond and then downregulate to a point of homeostasis (Susman, Schmeelk, Ponirakis, & Gariepy, 2001). The downstream impact of chronically high allostatic loads is then seen in a cascade of deteriorating neurodevelopmental systems and psychological distress. In the case of behavioral inhibition, a general hypersensitivity to stress and distress may be particularly difficult when embedded in a harsh environment. However, as Chronis-Tuscano and colleagues note (Chronis-Tuscano, Danko, Rubin, Coplan, & Novick, 2018), "there are

virtually no studies of BI/SW [behaviorally inhibited/socially withdrawn] young children who are growing up in stressful, dangerous community and family settings" (p. 9).

How Central Is Self-Referential Processing to Observed Patterns and Trajectories of Behavioral Inhibition?

The initial characterization of behavioral inhibition focused on the outward. That is, children were exposed to novel social and nonsocial experiences, and researchers coded their behavioral responses. Parental measures of behavioral inhibition, such as the Behavioral Inhibition Questionnaire (Bishop, Spence, & McDonald, 2003), have a similar approach.

Although the initial formulation of infant reactivity and behavioral inhibition was not dependent on social context, subsequent studies quickly found that many concerns were most evident in social contexts (Kagan, 2001). The reasons for the shift from sensory novelty to social novelty are still an open question. However, it is clear that the concern with a social environment may be a deep-seated mechanism of behavioral inhibition. For example, both the chapter "Behavioral Inhibition in Rodents: A Model to Study Causes and Health Consequences of Temperament" by Cavigelli and the chapter "Behavioral Inhibition in Nonhuman Primates: The Elephant in the Room" by Capitanio found that behavioral and health outcomes of their animal models were dependent on whether they characterized neophobia (a marker of behavioral inhibition) with or without the presence of conspecifics.

Recent work in children and adolescents also suggests that many of the processes generally linked to behavioral inhibition are specifically amplified when placed in a social—or self-referential—context. At age 7, children with a history of behavioral inhibition showed few behavioral or electrophysiological (EEG and ERP) differences relative to non-inhibited peers when completing a Posner cued attention task (Pérez-Edgar & Fox, 2005). However, when performance was then tied to having to perform an embarrassing task, behaviorally inhibited children showed faster response, greater errors, more difficulty shifting attention, larger ERP components, and more right frontal EEG activity. In adolescence, neuroimaging studies found that the same children unexpectedly showed greater striatal response to monetary reward than non-inhibited peers (Guyer et al., 2006). Follow-up work further refined this observation by noting that the increased striatal response in behavioral inhibition was most pronounced when the reward was tied to the child's performance, rather than simply provided at random (Bar-Haim et al., 2009).

In this volume, the chapter "Relations between Behavioral Inhibition, Cognitive Control and Anxiety: Novel insights provided by Parsing Subdomains of Cognitive Control" by Buzzell and colleagues noted a series of studies suggesting that self-referential monitoring of performance, particularly in the presence of others, is a strong predictor of anxiety outcomes. Previous work (Lahat et al., 2014; McDermott

et al., 2009) found that behaviorally inhibited children and adolescents who show an enhanced error-related negativity (ERN) are at increased risk for anxiety. Follow-up research noted that the relation between monitoring, behavioral inhibition, and anxiety may be most acute when errors are committed in the presence of others (Buzzell et al., 2017).

The neuroimaging and ERN data suggest that many of the trajectories of interest in behavioral inhibition reflect the child's systematic self-monitoring and his subjective evaluation of feedback. Moving beyond task measures, resting-state fMRI studies (Rogers et al., 2017; Roy et al., 2014; Sylvester et al., 2018; Taber-Thomas, Morales, Hillary, & Pérez-Edgar, 2016) suggest that neural networks associated with self-referential processing are "weighted" more heavily than task-centered networks. Future work will further disentangle how the child's sense of self, as an actor, may influence their psychosocial adjustment.

Are Regulatory Processes Necessarily a Good Thing in the Context of Behavioral Inhibition?

Typically, the emergence of regulatory processes is seen as a necessary "good" in a child's developmental trajectory. That is, regulatory processes help the child dampen reactive responses in the moment, shuffle through potential responses, choose and implement the best response, and then interpret subsequent responses (Crick & Dodge, 1994). Indeed, in many cases, maladaptive trajectories are thought to be rooted in poor or fragile regulatory processes, particularly in the case of externalizing difficulties (Eisenberg et al., 2001).

From this perspective, high levels of self-regulation would serve as a resilience factor for children. That is, at risk children would show internalizing problems and anxiety *unless* control mechanisms could come in and disrupt the trajectory (Lonigan & Vasey, 2009; Susa, Pitică, Benga, & Miclea, 2012). However, recent work suggests that high levels of control, much like monitoring, may be detrimental in the context of behavioral inhibition. Henderson and Wilson (2017) note that some regulatory processes can potentiate and sustain behavior that increase risk. In particular, response monitor can maintain a focus on contextual and self-referential cues. The effect may be particularly acute when confronting negative feedback in social realm, which further reinforces withdrawal tendencies and learning. The child is then even slower to return to goal-directed attention, which is already potentially fragile given the resting state and electrophysiology data. Overall, response monitoring works to limit flexibility, rather than allowing the child to marshal attentional and cognitive processes as needed.

Together, these findings suggest that we should treat behavioral inhibition as a unique developmental context in which core cognitive, emotional, and social processes may not respond as we would typically expect. Indeed, it has forced us to examine which aspects of cognitive control are actually activated (monitoring vs. control) and the effects of context on the consequences of deploying control mechanisms.

What Do We Really Know About Behavioral Inhibition Beyond the Laboratory?

The vast majority of behavioral inhibition studies rely on direct observation of behavior with standardized scenarios or present participants with controlled stimuli in order to capture a motor or neural response. Relatively less work has examined behaviorally inhibited children in their daily environments, as they interact with familiar adults and peers. In this volume, the chapter "Peer Relations and the Behaviorally Inhibited Child" by Rubin and colleagues make the argument that we need to better understand how behaviorally inhibited children interact with familiar peers in order to explain how early temperament traits may lead to specific developmental outcomes.

In this vein, we see that patterns of behavioral inhibition/temperamental shyness shift over the course of the school year and impact socioemotional and academic functioning (Rudasill & Rimm-Kaufman, 2009). Indeed, social components of testing, even if not directly related with the subject matter, may impact how well behaviorally inhibited children perform (Crozier & Hostettler, 2003). In addition, the chapter "Psychobiological Processes in the Development of Behavioral Inhibition" by Buss and Qu notes that we cannot assume that behaviorally inhibited children view "positive" social interactions in the same way as parents, teachers, and researchers. The authors point out that popularity may actually be associated with increasing cortisol over time for behaviorally inhibited children (Tarullo, Mliner, & Gunnar, 2011).

While we puzzle through the impact of behavioral inhibition in "traditional" social settings, we now have to layer on new and emerging contexts for social interaction. The explosion of the internet and social media means that children and adolescents now have more ways than ever to interact (or avoid interacting) with the social world. We do not know how these new experiences may interact with social tendencies linked with behavioral inhibition. In some cases, social media may allow behaviorally inhibited adolescents the opportunity to interact in a manner that feels safer and more in control. This could ease their concern with unpredictability and serve as a transition to more direct social contact. However, it could be that the Internet and social media allow the behaviorally inhibited child to retreat even further from the social world, insuring that they never confront, and overcome, their fears (the chapter "Attention Mechanisms in Behavioral Inhibition: Exploring, and Exploiting, the Environment" by Pérez-Edgar).

Ironically, these new modes of communication may actually ease our ability to carry out research. Historically, we have been concerned that the methods we use in the laboratory show poor ecological validity. This criticism is particularly sharp for tasks that are designed to be compatible with electrophysiology and neuroimaging techniques (the chapter "The Neural Mechanisms of Behavioral Inhibition" by Jarcho and Guyer). However, as children and adolescents increasingly videochat, text, and check in on social media, we see that our computer-reliant tasks and the "outside" social world are coming closer and closer together.

Closing Commentary

Two generations of researchers have followed two tracks since the introduction of behavioral inhibition as a construct of study. The first track looks to document developmental trajectories centered on the behavioral inhibition profile, beginning prenatally (DiPietro, Ghera, & Costigan, 2008; DiPietro, Hodgson, Costigan, & Johnson, 1996) through to adulthood (Poole, Van Lieshout, & Schmidt, 2017). The second (sometimes overlapping) track has worked to isolate and experimentally manipulate candidate moderators that shift prototypical developmental trajectories. Here the large portion of attention has been on social factors including parenting behaviors, peer relationships, and cultural expectations. Smaller scale individual mechanisms, such as attention to salient stimuli and interpretive mechanisms, have also been examined. Variations due to these mechanisms are evident as early as the second year of life, suggesting that even by age 2, our observations of "pure" behavioral inhibition are not quite so pure.

So where do we stand? We have identified a striking individual difference factor that is evident early in life, relatively stable, and has a broad impact on multiple levels of functioning well into adulthood. We are still trying to tease apart instances of change over time that reflect the influence of the environment versus the unspooling of somewhat predetermined trajectories. We have described the strongest, and best characterized, individual risk factor for the most common form of psychopathology, anxiety. And yet, the data imply that behavioral inhibition is a better predictor of the traits that *will not* develop rather than the profile that does emerge (see the chapter "The History and Theory of Behavioral Inhibition" by Kagan). Moving forward, the accumulation of knowledge, coupled with new technology and methods, should allow us to better situate the behaviorally inhibited child in context as we recognize the myriad of forces that both impact the child, and are deployed by the child, to shape the life course.

References

Almas, A. N., Phillips, D. A., Henderson, H. A., Hane, A. A., Degnan, K. A., Moas, O. L., & Fox, N. A. (2011). The relations between infant negative reactivity, non-maternal childcare, and children's interactions with familiar and unfamiliar peers. *Social Development, 20*, 718–740. https://doi.org/10.1111/j.1467-9507.2011.00605.x

Bar-Haim, Y., Fox, N. A., Benson, B., Guyer, A. E., Williams, A., Nelson, E. E., … Ernst, M. (2009). Neural correlates of reward processing in adolescents with a history inhibited temperament. *Psychological Science, 20*, 1009–1018. https://doi.org/10.1111/j.1467-9280.2009.02401.x

Bishop, G., Spence, S., & McDonald, C. (2003). Can parents and teachers provide a reliable and valid report of behavioral inhibition? *Child Development, 74*, 1899–1917.

Buss, K. A., Davis, E. L., Kiel, E. J., Brooker, R. J., Beekman, C., & Early, M. C. (2013). Dysregulated fear predicts social wariness and social anxiety symptoms during kindergarten. *Journal of Child Clinical & Adolescent Psychology, 42*(5), 603–616. https://doi.org/10.1080/15374416.2013.769170

Buzzell, G. A., Troller-Renfree, S. V., Barker, T. V., Bowman, L. C., Chronis-Tuscano, A., Henderson, H. A., … Fox, N. A. (2017). A neurobehavioral mechanism linking behaviorally inhibited temperament and later adolescent social anxiety. *Journal of the American Academy of Child & Adolescent Psychiatry, 56*, 1097–1105.

Chronis-Tuscano, A., Danko, C. M., Rubin, K. H., Coplan, R. J., & Novick, D. R. (2018). Future directions for research on early intervention for young children at risk for social anxiety. *Journal of Clinical Child & Adolescent Psychology, 47*, 655.

Chronis-Tuscano, A., Degnan, K. A., Pine, D. S., Pérez-Edgar, K., Henderson, H. A., Diaz, Y., … Fox, N. A. (2009). Stable behavioral inhibition during infancy and early childhood predicts the development of anxiety disorders in adolescence. *Journal of the American Academy of Child & Adolescent Psychiatry, 48*, 928–935. https://doi.org/10.1097/CHI.ob013e3181ae09df

Chronis-Tuscano, A., Rubin, K. H., O'Brien, K. A., Coplan, R. J., Thomas, S. R., Dougherty, L. R., … Menzer, M. (2015). Preliminary evaluation of a multimodal early intervention program for behaviorally inhibited preschoolers. *Journal of Consulting and Clinical Psychology, 83*, 534–540.

Clauss, J. A., & Blackford, J. U. (2012). Behavioral inhibition and risk for developing social anxiety disorder: A meta-analytic study. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*, 1066–1075. https://doi.org/10.1016/j.jaac.2012.08.002

Crick, N. R., & Dodge, K. A. (1994). A review and reformulation of social information-processing mechanisms in children's social adjustment. *Psychological Bulletin, 115*, 74–101. https://doi.org/10.1037/0033-2909.115.1.74

Crozier, W. R., & Hostettler, K. (2003). The influence of shyness on children's test performance. *British Journal of Educational Psychology, 73*, 317–328.

Degnan, K. A., & Fox, N. A. (2007). Behavioral inhibition and anxiety disorders: Multiple levels of a resilience process. *Development and Psychopathology, 19*, 729–746. https://doi.org/10.1017/S0954579407000363

DiPietro, J. A., Ghera, M. M., & Costigan, K. A. (2008). Prenatal origins of temperamental reactivity in early infancy. *Early Human Development, 84*, 569–575.

DiPietro, J. A., Hodgson, D. M., Costigan, K. A., & Johnson, T. R. (1996). Fetal antecedents of infant temperament. *Child Development, 67*, 2568–2583.

Eid, M. E., & Diener, E. E. (2006). *Handbook of multimethod measurement in psychology*. Washington, DC: American Psychological Association.

Eisenberg, N., Cumberland, A., Spinrad, T., Fabes, R. A., Shepard, S., Reiser, M., … Guthrie, I. (2001). The relations of regulation and emotionality to children's externalizing and internalizing problem behavior. *Child Development, 72*, 1112–1134.

Fox, N. A., Hane, A. A., & Pérez-Edgar, K. (2006). Psychophysiological methods for the study of developmental psychopathology. In D. Cicchetti & D. J. Cohen (Eds.), *Developmental psychopathology* (Vol. 2, pp. 381–426). Hoboken, NJ: Wiley.

Fox, N. A., Henderson, H. A., Marshall, P. J., Nichols, K. E., & Ghera, M. M. (2005). Behavioral inhibition: Linking biology and behavior within a developmental framework. *Annual Review of Psychology, 56*, 235–262.

Fox, N. A., Henderson, H. A., Rubin, K. H., Calkins, S. D., & Schmidt, L. A. (2001). Continuity and discontinuity of behavioral inhibition and exuberance: Psychophysiological and behavioral influences across the first four years of life. *Child Development, 72*, 1–21. https://doi.org/10.1111/1467-8624.00262

Fox, N. A., Snidman, N., Haas, S. A., Degnan, K. A., & Kagan, J. (2015). The relations between reactivity at 4 months and behavioral inhibition in the second year: Replication across three independent samples. *Infancy, 20*(1), 98–114.

García Coll, C., Kagan, J., & Reznick, J. S. (1984). Behavioral inhibition in young children. *Child Development, 55*, 1005–1019. https://doi.org/10.2307/1130152

Gladstone, G. L., & Parker, G. B. (2006). Is behavioral inhibition a risk factor for depression? *Journal of Affective Disorders, 95*, 85–94.

Guyer, A. E., Nelson, E. E., Perez-Edgar, K., Hardin, M. G., Roberson-Nay, R., Monk, C. S., … Ernst, M. (2006). Striatal functional alteration in adolescents characterized by early childhood behavioral inhibition. *Journal of Neuroscience, 26*(24), 6399–6405.

Henderson, H. A., & Wilson, M. J. (2017). Attention processes underlying risk and resilience in behaviorally inhibited children. *Current Behavioral Neuroscience Reports, 4*, 99–106.

Kagan, J. (2001). Temperamental contributions to affective and behavioral profiles in childhood. In S. G. Holman & P. M. DiBartolo (Eds.), *From social anxiety to social phobia: Multiple perspectives* (pp. 216–234). Needham Heights, MA: Allyn & Bacon.

Kagan, J. (2012). The biography of behavioral inhibition. In M. Zentner & R. L. Shiner (Eds.), *Handbook of temperament* (pp. 69–82). New York, NY: Guilford Press.

Kagan, J. (2016). Follow the evidence, ignore the words. In R. J. Sternberg, S. T. Fiske, & D. J. Foss (Eds.), *Scientists making a difference: One hundred eminent behavioral and brain scientists talk about their most important contributions* (pp. 260–263). New York, NY: Cambridge University Press.

Kagan, J., Reznick, J. S., Clarke, C., Snidman, N., & García-Coll, C. (1984). Behavioral inhibition to the unfamiliar. *Child Development, 55*(6), 2212–2225.

Kagan, J., Reznick, J. S., & Snidman, N. (1987). The physiology and psychology of behavioral inhibition in children. *Child Development, 58*, 1459–1473. https://doi.org/10.2307/1130685

Klein, D. N., Dyson, M. W., Kujawa, A., & Kotov, R. (2012). Temperament and internalizing disorders. In M. Zentner & R. L. Shiner (Eds.), *Handbook of temperament*. New York, NY: Guilford.

Kwong, K. K., Belliveau, J. W., Chesler, D. A., Goldberg, I. E., Weisskoff, R. M., Poncelet, B. P., … Turner, R. (1992). Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proceedings of the National Academy of Sciences, 89*, 5675–5679.

Lahat, A., Lamm, C., Chronis-Tuscano, A., Pine, D. S., Henderson, H. A., & Fox, N. A. (2014). Early behavioral inhibition and increased error monitoring predict later social phobia symptoms in childhood. *Journal of the American Academy of Child and Adolescent Psychiatry, 53*, 447–455.

Lahat, A., Pérez-Edgar, K., Degnan, K. A., Guyer, A. E., Lejuez, C. W., Ernst, M., … Fox, N. A. (2012). Early childhood temperament predicts substance use in young adults. *Translational Psychiatry, 2*, e157.

LeDoux, J. E. (1995). Emotion: Clues from the brain. *Annual Review of Psychology, 46*, 209–235.

Lonigan, C., & Vasey, M. (2009). Negative affectivity, effortful control, and attention to threat-relevant stimuli. *Journal of Abnormal Child Psychology, 37*, 387–399. https://doi.org/10.1007/s10802-008-9284-y

McDermott, J. M., Pérez-Edgar, K., Henderson, H. A., Chronis-Tuscano, A., Pine, D. S., & Fox, N. A. (2009). A history of childhood behavioral inhibition and enhanced response monitoring in adolescence are linked to clinical anxiety. *Biological Psychiatry, 65*, 445–448. https://doi.org/10.1016/j.biopsych.2008.10.043

Nesse, R. M., Curtis, G. C., Thyer, B. A., McCann, D. S., Huber-Smith, M. J., & Knopf, R. F. (1985). Endocrine and cardiovascular responses during phobic anxiety. *Psychosomatic Medicine, 47*, 320–332.

Ogawa, S., Tank, D. W., Menon, R., Ellermann, J. M., Kim, S. G., Merkle, H., & Ugurbil, K. (1992). Intrinsic signal changes accompanying sensory stimulation: Functional brain mapping with magnetic resonance imaging. *Proceedings of the National Academy of Sciences, 89*, 5951–5955.

Pérez-Edgar, K., & Fox, N. A. (2005). A behavioral and electrophysiological study of children's selective attention under neutral and affective conditions. *Journal of Cognition and Development, 6*(1), 89–118.

Pérez-Edgar, K., & Hastings, P. D. (2018). Emotion development from an experimental and individual differences lens. In J. T. Wixted & S. Ghetti (Eds.), *Stevens' handbook of experimental psychology and cognitive neuroscience* (Vol. 4, 4th ed., pp. 289–321). New York, NY: Wiley.

Petrill, S. A., & Brody, N. (2002). Personality and individual differences. In H. Pashler (Ed.), *Stevens' handbook of experimental psychology*. New York, NY: WIley.

Phelps, E. A., & LeDoux, J. E. (2005). Contributions of the amygdala to emotion processing: From animal models to human behavior. *Neuron, 48*, 175–187.

Phillips, D. A., Fox, N. A., & Gunnar, M. R. (2011). Same place, different experiences: Bringing individual differences to research in child care. *Child Development Perspectives, 5*, 44–49.

Poole, K. L., Van Lieshout, R. J., & Schmidt, L. A. (2017). Shyness and sociability beyond emerging adulthood: Implications for understanding the developmental sequelae of shyness subtypes. *Journal of Social and Clinical Psychology, 36*, 316–334.

Rapee, R. M., Kennedy, S., Ingram, M., Edwards, S., & Sweeney, L. (2005). Prevention and early intervention of anxiety disorders in inhibited preschool children. *Journal of Consulting and Clinical Psychology, 73*, 488–497.

Rogers, C. E., Sylvester, C. M., Mintz, C., Kenley, J. K., Shimony, J. S., Barch, D. M., & Smyser, C. D. (2017). Neonatal amygdala functional connectivity at rest in healthy and preterm infants and early internalizing symptoms. *Journal of the American Academy of Child & Adolescent Psychiatry, 56*, 157–166.

Rosenbaum, J. F., Biederman, J., Bolduc, E., Hirshfeld, D., Faraone, S., & Kagan, J. (1992). Comorbidity of parental anxiety disorders as risk for childhood-onset anxiety in inhibited children. *American Journal of Psychiatry, 149*, 475–481.

Rosenbaum, J. F., Biederman, J., Gersten, M., Hirshfeld, D. R., Meminger, S. R., Herman, J. B., … Snidman, N. (1988). Behavioral inhibition in children of parents with panic disorder and agoraphobia: A controlled study. *Archives of General Psychiatry, 45*, 463–470.

Rosenbaum, J. F., Biederman, J., Hirshfeld-Becker, D. R., Kagan, J., Snidman, N., Friedman, D., … Faraone, S. V. (2000). A controlled study of behavioral inhibition in children of parents with panic disorder and depression. *American Journal of Psychiatry, 157*, 2002–2010.

Roy, A. K., Benson, B., Degnan, K. A., Perez-Edgar, K., Pine, D. S., Fox, N. A., & Ernst, M. (2014). Alterations in amygdala functional connectivity reflect early temperament. *Biological Psychology, 103*, 248–254.

Rudasill, K. M., & Rimm-Kaufman, S. E. (2009). Teacher–child relationship quality: The roles of child temperament and teacher–child interactions. *Early Childhood Research Quarterly, 24*(2), 107–120.

Scarr, S. (1992). Developmental theories for the 1990s: Development and individual differences. *Child Development, 63*, 1–19.

Scarr, S., & McCartney, K. (1983). How people make their own environments: A theory of genotype-environmental effects. *Child Development, 54*, 424–435.

Schwartz, C. E., Wright, C. I., Shin, L. M., Kagan, J., & Rauch, S. L. (2003). Inhibited and uninhibited infants "grown up": Adult amygdalar response to novelty. *Science, 300*, 1952–1953.

Susa, G., Pitică, I., Benga, O., & Miclea, M. (2012). The self regulatory effect of attentional control in modulating the relationship between attentional biases toward threat and anxiety symptoms in children. *Cognition & Emotion, 26*, 1069–1083. https://doi.org/10.1080/02699931.2011.638910

Susman, E. J., Schmeelk, K. H., Ponirakis, A., & Gariepy, J. L. (2001). Maternal prenatal, postpartum, and concurrent stressors and temperament in 3-year-olds: A person and variable analysis. *Development and Psychopathology, 13*, 629–652.

Sylvester, C. M., Smyser, C. D., Smyser, T., Kenley, J. K., Ackerman, J. J., Shimony, J. S., … Rogers, C. E. (2018). Cortical functional connectivity evident after birth and behavioral inhibition at age 2. *American Journal of Psychiatry, 175*, 180–187.

Taber-Thomas, B., Morales, S., Hillary, F., & Pérez-Edgar, K. (2016). Altered topography of intrinsic functional connectivity in childhood risk for social anxiety. *Depression and Anxiety, 33*, 995–1004.

Tarullo, A. R., Mliner, S., & Gunnar, M. R. (2011). Inhibition and exuberance in preschool classrooms: Associations with peer social experiences and changes in cortisol across the preschool year. *Developmental Psychology, 47*, 1374–1388.

van der Molen, M. W., & Molenaar, P. C. M. (1994). Cognitive psychophysiology: A window to cognitive development and brain maturation. In G. Dawson & K. W. Fischer (Eds.), *Human behavior and the developing brain* (pp. 456–491). New York, NY: Guilford Press.

Williams, L. R., Fox, N. A., Lejuez, C. W., Reynolds, E. K., Henderson, H. A., Pérez-Edgar, K., … Pine, D. S. (2010). Early temperament, propensity for risk-taking and adolescent substance-related problems: A prospective multi-method investigation. *Addictive Behaviors, 35*, 1148–1151.

Wohlwill, J. F. (1973). *The study of behavioral development*. New York, NY: Academic Press.

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