

Stable Early Maternal Report of Behavioral Inhibition Predicts Lifetime Social Anxiety Disorder in Adolescence

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ABSTRACT

Objective: Behavioral inhibition (BI), a temperamental style identifiable in early childhood, is considered a risk factor for the development of anxiety disorders, particularly social anxiety disorder (SAD). However, few studies examining this question have evaluated the stability of BI across multiple developmental time points and followed participants into adolescence—the developmental period during which risk for SAD onset is at its peak. The current study used a prospective longitudinal design to determine whether stable early BI predicted the presence of psychiatric disorders and continuous levels of social anxiety in adolescents. It was hypothesized that stable BI would predict the presence of adolescent psychiatric diagnoses, specifically SAD. **Method:** Participants included 126 adolescents aged 14 to 16 years who were first recruited at 4 months of age from hospital birth records. Temperament was measured at multiple time points between the ages of 14 months and 7 years. In adolescence, diagnostic interviews were conducted with parents and adolescents, and continuous measures of adolescent- and parent-reported social anxiety were collected. **Results:** Stable maternal-reported early BI was associated with 3.79 times increased odds of a lifetime SAD diagnosis, but not other diagnoses, during adolescence (95% confidence interval 1.18–12.12). Stable maternal-reported early BI also predicted independent adolescent and parent ratings of ongoing social anxiety symptoms. **Conclusions:** Findings suggesting that stable maternal-reported early BI predicts lifetime SAD have important implications for the early identification and prevention of SAD. *J. Am. Acad. Child Adolesc. Psychiatry*, 2009;48(9):928–935. **Key Words:** temperament, behavioral inhibition, social anxiety disorder.

Approximately 15% to 20% of children can be classified as behaviorally inhibited during early childhood. This temperamental style involves the tendency to show signs

of fear, reticence, or wariness in response to unfamiliar situations and to withdraw from unfamiliar peers.^{1,2} Approximately half of all children categorized as extremely behaviorally inhibited continue to show signs of wariness across childhood.³ Children showing consistent behavioral inhibition (BI) are characterized by greater autonomic reactivity,⁴ elevated morning cortisol levels,⁵ heightened startle responses,⁶ and more vigilant attention styles.⁷ As well, adolescents or young adults who were characterized in childhood with BI were found, using functional imaging studies, to show heightened amygdala activation to novel neutral faces⁸ or to threatening emotion faces,⁹ findings similar to those documented in patients with anxiety disorders. Together, these findings suggest that BI may be a possible risk factor for anxiety disorders.¹⁰ Although accumulating findings do support this possibility,^{11,12} few

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studies have evaluated the stability of early BI across multiple developmental time points and followed participants into the period of greatest risk for social anxiety using comprehensive diagnostic assessment protocols.

A number of studies examining the association between early BI and anxiety psychopathology have used cross-sectional designs,¹³ retrospective measures of early temperament,^{14–16} and/or questionnaire data assessing anxiety problems or personality traits.^{17,18} For instance, Biederman and colleagues¹³ reported increased risk for social anxiety disorder (SAD) among 2- to 6-year-old offspring of parents with panic disorder who were concurrently classified as high BI. In a mixed sample of high-risk and unselected children, children classified as high BI were at increased risk for concurrent multiple anxiety disorders, overanxious disorder, and phobias.^{19,20} Seventy-six of these children were reassessed at 3-year follow-up; children initially classified as high and low BI differed in rates of multiple psychiatric diagnoses, multiple anxiety disorders, avoidant disorder, separation anxiety, and agoraphobia.²¹ Similarly, Hirshfeld-Becker and colleagues²² reported on a mixed sample of children assessed for BI once between the ages of 21 months and 6 years who were reevaluated with the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) parent and child interviews 5 years later (mean age 9.6 years). In this sample, BI specifically predicted the onset of SAD (odds ratio 2.37; 95% confidence interval 1.10–5.10) within the at-risk group; however, these findings were limited to children at risk for anxiety by virtue of parental anxiety and mood disorders. The extent to which these results generalize to an unselected sample have yet to be established.

Data bearing most directly on risk for anxiety disorders among individuals with early BI emerge from prospective longitudinal studies. Three prospective longitudinal studies followed samples into adolescence or adulthood. Schwartz and colleagues²³ found a specific association between age-2 BI and lifetime SAD assessed during adolescence; however, when impairment was required for diagnosis, this finding held only for girls. Moreover, interviews with parents were not conducted, an approach which calls into question the validity of lifetime diagnoses.^{24,25} Prior and colleagues¹² conducted psychiatric assessments with a subset of their epidemiological sample ($n = 59$) at ages 13 to 14 years and found that adolescents meeting current criteria for anx-

ety disorders did not evidence extreme or stable shy/inhibited temperament (based on maternal report) in earlier assessments. Finally, Caspi and colleagues²⁶ reported that participants characterized by extreme low or high BI at age 3 years were at increased risk for multiple current psychiatric disorders, particularly depression, at age 21 years; however, they found no specific association between early BI and adult anxiety. Existing studies therefore provide mixed support for the relations between early BI and anxiety disorders during adolescence and adulthood. Furthermore, of these studies, only Prior and colleagues^{12,27,28} reported multiple early assessments of BI and no strong evidence emerged of relations between early shyness and current anxiety diagnoses in adolescence.

In understanding the link between early temperament and later psychopathology, it is important to consider that BI is only moderately stable across development.³ Perez-Edgar and Fox¹⁰ reported stability over 1 to 6 years ranging from 0.24 to 0.64, with greater stability among extreme groups. However, there is also a great deal of temporal variability in BI. For instance, Kagan and Snidman¹⁷ reported that only 18% of inhibited infants were classified as inhibited at every laboratory evaluation from 1 to 7 years of age. Individuals with stable BI may represent a distinct subgroup with a biological or genetic predisposition to negatively react to novel situations. Indeed, findings from a small study suggested that children who consistently fell into the high BI group at 21 months, 4 years, 5.5 years, and 7.5 years had higher rates of anxiety disorders at age 7.5 years than those who were not consistently inhibited at each of these time points.²⁹ We therefore hypothesized that it is stable BI, rather than BI measured at a single time point, which places individuals at increased risk for developing anxiety disorders.

The current study examines the degree to which stable BI, measured at four time points from infancy through childhood using maternal reports and/or behavioral observations, predicts anxiety disorders in adolescence. In adolescence, we conducted semistructured diagnostic interviews with the parent and adolescent to assess a broad range of *DSM-IV* psychiatric disorders, as well as a continuous measure of adolescent- and parent-reported social anxiety symptoms. Of note, these three measures were completed independently to generate three independent sources of information about social anxiety symptoms.

METHOD

Participants

Families with young infants were initially contacted by mail using birth records of local hospitals. They were asked to return surveys to ensure that infants were full term and normally developing and that parents were right handed (because of the aims of the larger study). Infants ($n = 443$) were screened at 4 months of age to assess their reactivity to novel auditory and visual stimuli. Videotapes of the screening procedure were coded for positive and negative affect and motor activity during the presentation of novel stimuli. A complete description of the stimuli, coding procedures, and intercoder reliability is presented elsewhere.^{19,30,31} One hundred seventy-eight (92 female subjects and 86 male subjects) primarily white infants from two-parent middle-class homes were selected to provide a wide range of temperamental reactivity to novelty. Specifically, 37% of the selected infants showed high negative/high motor reactivity, 29% showed high positive/high motor reactivity, and 34% showed low reactivity. These infants were followed across childhood and into adolescence as part of the larger longitudinal study.

Procedure

When the infants were 14 months, 24 months, 4 years, and 7 years of age, the mothers were asked to complete temperament surveys, and the children were invited to participate in laboratory tasks assessing BI.^{19,30,31} Of the original selected sample, 159 mothers of child participants (78 female subjects and 81 male subjects) completed a temperament questionnaire at least one of the assessment points across infancy and childhood ($n = 139$ at 14 months; $n = 133$ at 24 months; $n = 133$ at 4 years; and $n = 116$ at 7 years). Those with temperament data at any time point were not significantly different by sex (all p 's $> .07$).

When participants were between the ages of 14 and 16 years (mean 15.05 years, SD 1.82 years), the original selected sample was invited back to the laboratory, at which time consent and assent were obtained from parents and adolescents, respectively, and measures of psychiatric symptoms were administered. Of those that participated across childhood, 129 (66 female subjects and 63 male subjects; 81% of the 159 seen during childhood) were assessed by questionnaires and/or psychiatric interviews in adolescence; 122 completed psychiatric interviews. Those that participated in adolescence were not significantly different from those who did not participate by sex, BI measures, or adolescent psychiatric symptoms/diagnosis (all p 's $> .10$).

This project was approved by the institutional review board at the University of Maryland.

Measures

Temperament Assessment. At 14 and 24 months, the infants' reactions to unfamiliar stimuli in the laboratory were coded to provide an index of BI (a complete description of these procedures is presented elsewhere^{19,30,31}). Maternal reports of temperament were gathered at these same time points using the Toddler Behavior Assessment Questionnaire,³² a 111-item measure on which parents rate the frequency of specific behaviors as they occurred in the past month. For this study, the Social Fearfulness scale, consisting of 19 items ($\alpha = .87$) measuring inhibition, distress, withdrawal, and shyness, was used. Examples of items included are as follows: "When s/he saw other children while in the park or playground, how often did your

child approach and immediately join in play?"; "When one of the parents' friends who does not have daily contact with your child visited the home, how often did your child talk much less than usual?"; "When your child was approached by a stranger when you and she/he were out, how often did your child show distress or cry?" Items were averaged, and scores ranged from 1.00 to 7.00 (14 months: mean 4.05, SD 1.09; 24 months: mean 4.09, SD .95), with higher scores indicating greater distress to novelty.

Mothers completed the Colorado Children's Temperament Inventory^{33,34} when their children were 4 and 7 years old. The Colorado Children's Temperament Inventory measures maternal perceptions of child temperament (e.g., emotionality, activity level, shyness). The subscale of Shyness/Sociability was used, which included five items rated from 1 to 5, such as "child makes friends easily" or "child takes a long time to warm up to strangers" ($\alpha = .88$). Items were averaged, and scores ranged from 1.00 to 4.00 (age 4 years: mean 2.54, SD .84; age 7 years: mean 2.24, SD .76), with higher scores indicating greater shyness.

Adolescent Psychiatric Assessment. K-SADS diagnostic interview. Adolescents and their parent (typically mothers) were separately administered the K-SADS,^{35,36} a semistructured diagnostic interview assessing *DSM-IV* disorders. The K-SADS was supplemented with probe questions from the Anxiety Disorders Interview Schedule for Children,³⁷ which included items assessing degree of interference rated on a scale of 0 to 8, where "4" was designated as the point at which the symptom resulted in impaired functioning and/or need for services. Interviews were conducted by advanced clinical psychology doctoral students under the close supervision of a licensed clinical psychologist and a board-certified child and adolescent psychiatrist, all of whom were uninformed regarding both early temperament data and ratings on all scales completed by parents and adolescents. Detailed safety protocols were developed to address reports of abuse and suicidal ideation. In cases for which there was disagreement between parent and adolescent, interviewers continued to probe until a final determination was made. Final diagnoses were discussed by the clinical team and made by expert consensus based on information from both adolescent and parent, consistent with studies reviewed herein.²² Audiotapes of 59 interviews were reviewed by the supervising psychiatrist or psychologist to monitor reliability. Kappas between diagnoses made by interviewers and expert clinicians were .84 for any disorder, .92 for anxiety disorders; and .90 for disruptive behavior disorders.

Screen for Child Anxiety-Related Emotional Disorders-Revised. The 66-item Screen for Child Anxiety-Related Emotional Disorders-Revised (SCARED-R) is a psychometrically sound questionnaire for measuring a broad range of *DSM*-defined anxiety disorder symptoms.³⁸ Parent and adolescent reports on the SCARED-R Social Phobia (parent: $\alpha = .83$, adolescent: $\alpha = .74$) and Total Anxiety (parent: $\alpha = .94$, child: $\alpha = .93$) scales were used. The parents and adolescents completed the scales independently, uninformed regarding the other's ratings. Items were averaged for each scale and scores ranged from 0 to 14.00 for Social Phobia (parent: mean 3.91, SD 3.68; adolescent: mean 3.81, SD 3.35) and 0 to 50.00 for Total Anxiety (parent: mean 10.72, SD 9.72; adolescent: mean 14.43, SD 11.46), with higher scores indicating a greater number of anxiety symptoms.

Data Analytic Strategy

Latent Class Analysis. To generate longitudinal profiles of BI, latent class analysis (LCA) was performed using V4.1 of Mplus.^{39,40} This type of analysis seeks to identify unmeasured (i.e., latent) class

membership among the participants using both categorical and/or continuous observed indicator variables, as in structural equation modeling. Although similar to cluster analysis, LCA offers many advantages over traditional cluster techniques. First, use of LCA's maximum likelihood (ML) method assumes that the data are missing at random, which allows the model parameters to be informed by all cases that contribute a portion of the data. An analysis of the temperament data across infancy and childhood suggests that patterns of missing data did not violate the assumption that it was missing completely at random, Little's missing completely at random $\chi^2_{26} = 22.17, p = .68$. In addition, ML has been recently recommended by methodologists as an appropriate way to accommodate missing data.⁴¹ Second, unlike traditional cluster analysis algorithms that group cases near each other by some definition of distance (e.g., Euclidean distance for k-means cluster analysis), the LCA approach relies on a formal statistical model based on probabilities to classify cases. This formal statistical model allows for flexibility in the model.^{42,43} The parameters of latent class models entail estimates of conditional response probabilities and the estimated proportion of cases in each latent class (which sums to 1.0). The ML method estimation iteratively calculates model parameters to be those which are most likely to account for observed results. Then, classification is based on Bayes' theorem, which computes a posterior probability (based on a function of the model's parameters) of membership for each latent class. Cases are then assigned into a latent class for which the posterior probability is highest.⁴³⁻⁴⁵

Latent classes were analyzed using maternal report of BI, behavioral observation of BI, and composites of maternal report and behavioral observation of BI. However, the classes based on behavioral observation and classes based on the maternal report/behavioral composites were not significantly related to any adolescent diagnoses or report of psychopathology. Therefore, only the findings using the maternal report BI classes are presented in the "Results" section. Specifically, maternal report of social fear at 14 and 24 months and shyness at 4 and 7 years were used to form the longitudinal profiles of maternal-reported BI in the current sample. Given the skewed nature of the data, dichotomized versions of the maternal report measures were used where "0" denoted a child rated in the lower two thirds of the sample at that time point and "1" denoted a child rated in the top one third of the sample at that time point. Also, because different temperament questionnaires were used across time, the average level of BI at each age was estimated independently within each class (i.e., latent profile analysis).⁴⁶ Models with two through four profiles were estimated. Best model fit was assessed using Bayesian information criteria (BIC), where the smallest negative number indicates best fit. This index has been shown to identify the appropriate number of groups in finite mixture models⁴⁷ and penalizes the model for the number of parameters, thus guarding against models overfitting the data. The Lo-Mendell-Rubin Likelihood ratio test (LMRL) was also used, which tests the significance of the -2 Log-likelihood difference between models with k and $k-1$ profiles.⁴⁸

The latent profile analysis was computed using all 159 participants whose mothers completed a temperament questionnaire at any of the assessment points. Model fit (BIC) for the current sample was -676.75 for one profile, -651.20 for two profiles, -659.78 for three profiles, and -673.58 for four profiles. The LMRL showed that the two-profile model was significantly better than the one-profile model ($p < .001$); the three-profile model was significantly better than the two-profile model ($p < .05$), and the four-profile model was significantly better than the three-profile model ($p < .05$). However, the four-profile model also produced problems with

reliability of the estimates. Given that the lowest BIC value was combined with a significant LMRL for the two-class model, this model was chosen as the best-fitting model. The average posterior probabilities of membership ranged from .87 to .98, reflecting a high degree of confidence in profile assignment. The "high" profile ($n = 20$) showed high average levels of maternal-reported BI at all four time points, and 13% of the sample had a higher probability of membership in this profile than the other profile. The "low" profile ($n = 139$) showed lower levels of maternal-reported BI at all four time points, and 87% of the sample had a higher probability of membership in this profile than the other profile. Mean differences on each maternal-reported BI measure across time are presented in Figure 1 for each latent class. This figure shows that the two classes were indeed distinct, and their distribution of scores was non-overlapping at each measurement point.

RESULTS

Preliminary Analyses

The 4-month temperament groupings were examined for significant relations to the adolescent psychopathology measures. None of the temperament groups were significantly related to adolescent diagnoses or anxiety symptoms (all p 's $> .25$). Therefore, these groupings were not included in any further analysis.

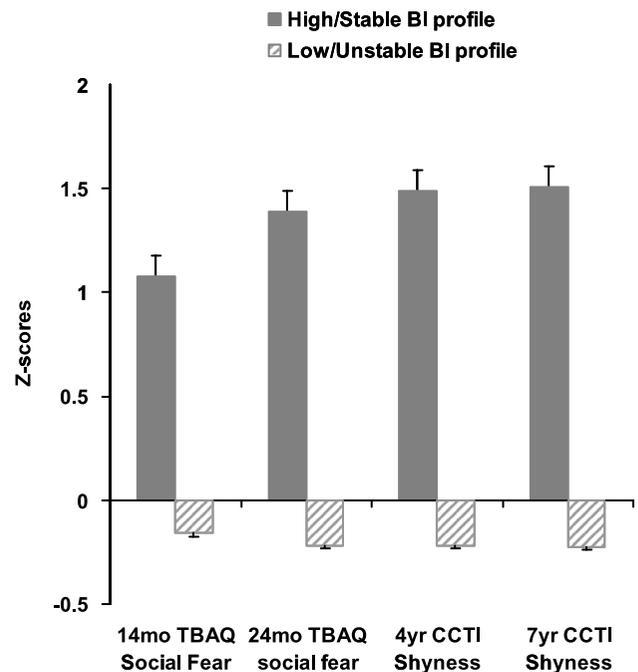


Fig. 1 Mean differences on standardized measures of behavioral inhibition (BI) across longitudinal profiles. High/stable refers to the participants with longitudinal profiles reflecting stable high BI. Low/unstable refers to the participants with longitudinal profiles reflecting unstable low BI. CCTI = Colorado Children's Temperament Inventory; TBAQ = Toddler Behavior Assessment Questionnaire.

TABLE 1

Percentage of Participants Within Each Latent Class That Met Criteria for Current *DSM-IV* Disorders

<i>DSM-IV</i> Diagnosis	Total, % (<i>n</i> = 122)	“High” BI class, % (<i>n</i> = 15)	“Low” BI Class, % (<i>n</i> = 107)	Odds Ratio (95% CI)
Any disorder	41.8 (<i>n</i> = 51)	53.3 (<i>n</i> = 8)	40.2 (<i>n</i> = 43)	1.70 (0.57–5.04)
Any anxiety disorder	24.6 (<i>n</i> = 30)	33.3 (<i>n</i> = 5)	23.4 (<i>n</i> = 25)	1.64 (0.51–5.25)
Any mood disorder	8.2 (<i>n</i> = 10)	6.7 (<i>n</i> = 1)	8.4 (<i>n</i> = 9)	0.78 (0.09–6.61)
Any disruptive disorder	23.8 (<i>n</i> = 29)	33.3 (<i>n</i> = 5)	22.4 (<i>n</i> = 24)	1.72 (0.54–5.54)
Social anxiety disorder	12.3 (<i>n</i> = 15)	20.0 (<i>n</i> = 3)	11.2 (<i>n</i> = 12)	1.98 (0.49–8.03)

Note: Odds ratio refers to odds of diagnosis given membership in the high-BI class relative to the low-BI class. BI = behavioral inhibition; CI = confidence interval.

Schedule for Affective Disorders and Schizophrenia for School-Age Children

The percentage of participants with current and lifetime anxiety, mood, and disruptive behavior disorders are presented in Tables 1 and 2, respectively. Rates of disorder did not differ across sex (*p*'s > .10). In many cases, neither the adolescent nor the parent could pinpoint the exact age of onset; however, review of parent and adolescent interviews for adolescents with anxiety diagnoses confirmed that clinically significant anxiety was present after age 7 years, the last previous temperament assessment before adolescence in all but one case (for which the precise timing of remission was unclear). This establishes the prospective nature of the associations between early BI and social anxiety examined here.

Logistic regression analyses modeled the risk for current and lifetime diagnosis as a function of BI profile. Results are shown in Tables 1 and 2, respectively. Stable high BI predicted a fourfold significantly increased odds of a lifetime SAD diagnosis (*B* = 1.33, *p* < .05); the association with any lifetime anxiety disorder was marginally nonsignificant (*B* = 1.08, *p* = .055). No significant findings emerged for current diagnoses; however, for most classes of disorder (except mood), there was a greater percentage of cases in the stable high BI class.

Screen for Child Anxiety-Related Emotional Disorders–Revised

The adolescents in the stable high-BI class had significantly higher SCARED-R Social Phobia scores than the low-BI class, according to independent reports from both adolescents (*t*₁₁₁ = 2.09, *p* = .04; mean 5.54 [SD 4.12] versus mean 3.52 [SD 3.15]; *d* = 0.39) and parents (*t*₁₁₀ = 3.95, *p* = .00; mean 7.31 [SD 4.73] versus mean 3.29 [SD 3.26]; *d* = 0.75). The parents of the participants in the high-BI class also reported higher total SCARED-R scores relative to the parents in the low-BI group (*t*₁₁₀ = 2.56, *p* = .01; mean 17.00 [SD 12.42] versus mean 9.77 [SD 9.19]; *d* = 0.66).

DISCUSSION

The present study extends existing literature examining temperament as a predictor of adolescent psychopathology by using multiple assessments of temperament in infancy and early childhood and following participants into adolescence—the period of greatest risk for SAD onset, and the point at which data demonstrate robust relatively stable trajectories of anxiety disorders into adulthood.⁴⁹ Furthermore, this study uses semistructured diagnostic interviews conducted with both adolescents and their parents to determine the presence of current and lifetime psychiatric disorders,

TABLE 2

Percentage of Participants Within Each Latent Class That Met Criteria for Lifetime *DSM-IV* Disorders

<i>DSM-IV</i> Diagnosis	Total, % (<i>n</i> = 122)	“High” BI class, % (<i>n</i> = 15)	“Low” BI Class, % (<i>n</i> = 107)	Odds Ratio (95% CI)
Any disorder	54.1 (<i>n</i> = 66)	60.0 (<i>n</i> = 9)	53.3 (<i>n</i> = 57)	1.32 (0.44–3.96)
Any anxiety disorder	31.1 (<i>n</i> = 38)	53.3 (<i>n</i> = 8)	28.0 (<i>n</i> = 30)	2.93 (0.98–8.80)
Any mood disorder	14.8 (<i>n</i> = 18)	20.0 (<i>n</i> = 3)	14.0 (<i>n</i> = 15)	1.53 (0.39–6.08)
Any disruptive disorder	27.0 (<i>n</i> = 33)	33.3 (<i>n</i> = 5)	26.2 (<i>n</i> = 28)	1.41 (0.44–4.49)
Social anxiety disorder	18 (<i>n</i> = 22)	40.0 (<i>n</i> = 6)	15.0 (<i>n</i> = 16)	3.79 (1.18–12.12)

Note: Odds ratio refers to odds of diagnosis given membership in the high-BI class relative to the low-BI class. BI = behavioral inhibition; CI = confidence interval.

as well as a longitudinal data analysis that took into account temperament measurements obtained at four time points across infancy and childhood. Membership in the class reflecting early, stable high BI in early childhood (as reported by mothers) specifically predicted increased risk for lifetime SAD diagnoses evaluated during adolescence, as well as independent parent and adolescent reports of social anxiety on the SCARED-R.

A handful of previous studies yielded similar findings, relating childhood BI to specific risk for later SAD^{22,23}; however, none found the precise pattern revealed in the current work, where early, stable maternal-reported BI showed specific and consistent associations with SAD, based on independent ratings performed by parents, adolescents, and clinicians. Moreover, diagnoses were made only in the presence of clinically significant distress or impairment and were based on reports of both parents and adolescents, both fundamental features of assessing psychopathology in youths.^{24,25,50} As such, the results of this study provide clear evidence that trajectories reflecting stable BI, assessed via maternal report across infancy and early childhood, is associated with four times increased risk for clinically meaningful SAD diagnoses in adolescence.

Of note, two prospective longitudinal studies failed to find associations between early BI and later anxiety disorders. For instance, Caspi and colleagues²⁶ found that age-3 BI predicted depression, but not anxiety, in early adulthood. However, lifetime diagnoses were not assessed, leaving open the possibility that early BI may result in a diagnosis of anxiety that precedes a later-emerging diagnosis of depression. Second, Prior and colleagues¹² found that participants who met criteria for anxiety disorders in adolescence did not evidence extreme or stable BI in earlier assessments. However, this was a small sample and only current diagnoses were examined. Indeed, we too failed to find associations between stable early BI and current SAD in adolescence.

Despite the strength of these longitudinal associations, it is important to note that a sizable proportion of children exhibiting stable BI did not go on to develop anxiety disorders.³ In addition, our finding that early BI was associated with lifetime, but not current, SAD implies that social anxiety remits in many cases. Future studies, conducted with larger samples, should examine the manner in which other factors, including the child's environmental context (e.g., parenting), cognitive biases,

and underlying neural circuitry, moderate the relation between temperament and psychopathology, as well as the persistence of psychopathology. The modest association observed here, when considered in light of previous findings on biology and familial risk, might reflect the fact that temperament exhibits particularly strong associations with later psychopathology in some contexts but very weak associations in others. This suggests the importance of examining the manner in which physiological, environmental, and family-genetic factors moderate the temperament-by-disorder association over time.^{51,52} Consistent with this perspective, because the child, from a very early age, actively shapes his/her environment, moderation of the temperament-by-disorder association may reflect reciprocal influences between the child and his or her social environment.^{3,10}

It should also be noted that we took a multimethod approach to the assessment of temperament in this study, yet only maternal reports of early temperament were associated with later social anxiety. Although maternal reports of temperament provide valuable information about infant and child behavior that occurs across a wider sample of real-world contexts outside of the contrived research setting, these reports may also reflect disorder-relevant biases.^{53,54} On the other hand, maternal reports can be easily obtained at low cost and do not require extensive training or coding to administer or interpret, which enhances their use for screening purposes in nonresearch settings. Behavioral observations have been widely used in the study of early temperament^{13,22,26} and indeed provide rich objective data relatively free of such biases. However, behavioral observations are based on a very limited sample of behavior that may be influenced by the artificial context in which behavior is assessed.⁵⁵ Despite the limitations inherent in using maternal report, this type of data obtained during infancy and early childhood predicted both consensus diagnoses of SAD based on interviews conducted with the parents and adolescents, as well as independent adolescent and parent reports on the SCARED-R. Thus, biases in maternal report or shared method variance cannot fully account for the findings reported here.

Another notable limitation is the absence of data on parental psychopathology. Previous studies found that the BI-SAD link may be particularly strong among offspring of parents with anxiety disorders.²² Without this information, it remains unknown whether BI

predicts social anxiety in the general population or chiefly among children with family history of anxiety disorders.

Finally, our sample consisted largely of white middle-class families. There are likely important differences in perceptions of and response to inhibited behavior across members of diverse cultural groups,⁵⁶ which may mitigate or exacerbate the influence of early temperamental profiles on the unfolding of pathological behavior. There may also be a resulting restricted range of sociocontextual stressors present in our sample. Future studies conducted with more diverse samples, both in terms of race/ethnicity and socioeconomic status, will allow a more comprehensive examination of these potential moderators.

Despite these limitations, this study provides clear evidence that maternal-reported stable BI across infancy and early childhood is associated with increased risk for clinically meaningful SAD diagnoses in adolescence—a finding which has important implications for the early identification and prevention of social anxiety.

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REFERENCES

1. Fox NA, Henderson HA, Marshall PJ, Nichols KE, Ghera MM. Behavioral inhibition: linking biology and behavior within a developmental framework. *Annu Rev Psychol.* 2005;56:235–262.
2. Kagan J. *Galen's Prophecy.* New York: Basic Books; 1994.
3. Degnan KA, Fox NA. Behavioral inhibition and anxiety disorders: multiple levels of a resilience process. *Dev Psychopathol.* 2007;19:729–746.
4. Schmidt LA, Fox NA, Schulkin J, Gold PW. Behavioral and psychophysiological correlates of self-presentation in temperamentally shy children. *Dev Psychobiol.* 1999;35:119–135.
5. Schmidt LA, Fox NA, Sternberg EM, Gold PW, Smith CC, Schulkin J. Adrenocortical reactivity and social competence in seven year-olds. *Pers Individ Dif.* 1999;26:977–985.
6. Schmidt LA, Fox NA. Fear-potentiated startle responses in temperamentally different human infants. *Dev Psychobiol.* 1998;32:113–120.
7. Perez-Edgar K, Fox NA. A behavioral and electrophysiological study of children's selective attention under neutral and affective conditions. *J Cogn Dev.* 2005;6:89–118.
8. Schwartz CE, Wright CI, Shin LM, Kagan J, Rauch SL. Inhibited and uninhibited infants "grown up": adult amygdalar response to novelty. *Science.* 2003;300:1952–1953.
9. Pérez-Edgar K, Roberson-Nay R, Hardin MG et al. Attention alters neural responses to evocative faces in behaviorally inhibited adolescents. *Neuroimage.* 2007;35:1538–1546.
10. Perez-Edgar K, Fox NA. Temperament and anxiety disorders. *Child Adolesc Psychiatr Clin N Am.* 2005;14:681–706.
11. Biederman J, Rosenbaum JF, Chaloff J, Kagan J. Behavioral inhibition as a risk factor for anxiety disorders. In: March JS, ed. *Anxiety Disorders in Children and Adolescents.* New York: Guilford Press; 1995:61–81.
12. Prior M, Smart D, Sanson A, Oberklaid F. Does shy-inhibited

- temperament in childhood lead to anxiety problems in adolescence? *J Am Acad Child Adolesc Psychiatry.* 2000;39:461–468.
13. Biederman J, Hirshfeld-Becker DR, Rosenbaum JF et al. Further evidence of association between behavioral inhibition and social anxiety in children. *Am J Psychiatry.* 2001;158:1673–1679.
14. Gladstone GL, Parker GB, Mitchell PB, Wilhelm KA, Malhi GS. Relationship between self-reported childhood behavioral inhibition and lifetime anxiety disorders in a clinical sample. *Depress Anxiety.* 2005;22:103–113.
15. Hayward C, Killen J, Kraemer K, Taylor C. Linking self-reported childhood behavioral inhibition to adolescent social phobia. *J Am Acad Child Adolesc Psychiatry.* 1998;37:1308–1316.
16. Mick MA, Telch MJ. Social anxiety and history of behavioral inhibition in young adults. *J Anxiety Disord.* 1998;12:1–20.
17. Kagan J, Snidman N. Early childhood predictors of adult anxiety disorders. *Soc Biol Psychiatry.* 1999;46:1536–1541.
18. Caspi A, Harrington H, Milne B, Amell JW, Theodore RF, Moffitt TE. Children's behavioral styles at age 3 are linked to their adult personality traits at age 26. *J Pers.* 2003;71:495–513.
19. Kagan J, Snidman N. Infant predictors of inhibited and uninhibited profiles. *Psychol Sci.* 1991;2:40–44.
20. Biederman J, Rosenbaum JF, Hirshfeld DR et al. Psychiatric correlated of behavioral inhibition in young children of parents with and without psychiatric disorders. *Arch Gen Psychiatry.* 1990;47:21–26.
21. Biederman J, Rosenbaum JF, Bolduc-Murphy EA et al. A 3-year follow-up of children with and without behavioral inhibition. *J Am Acad Child Adolesc Psychiatry.* 1993;32:814–821.
22. Hirshfeld-Becker DR, Biederman J, Henin A et al. Behavioral inhibition in preschool children at risk is a specific predictor of middle childhood social anxiety: a five-year follow-up. *J Dev Behav Pediatr.* 2007;28:225–233.
23. Schwartz CE, Snidman N, Kagan J. Adolescent social anxiety as an outcome of inhibited temperament in childhood. *J Am Acad Child Adolesc Psychiatry.* 1999;38:1008–1015.
24. The Research Unit on Pediatric Psychopharmacology Anxiety Study Group. Fluvoxamine for the treatment of anxiety disorders in children and adolescents. *N Engl J Med.* 2001;344:1279–1285.
25. Pine DS. Research review: a neuroscience framework for pediatric anxiety disorders. *J Child Psychol Psychiatry.* 2007;48:631–648.
26. Caspi A, Moffitt T, Newman D, Silva P. Behavioural observations at age 3 years predict adult psychiatric disorders. *Arch Gen Psychiatry.* 1996;51:1033–1039.
27. Prior M, Smart D, Sanson A, Oberklaid F. Relationships between learning difficulties and psychological problems in preadolescent children from a longitudinal sample. *J Am Acad Child Adolesc Psychiatry.* 1999;38:429–436.
28. Prior M, Smart D, Sanson A, Oberklaid F. Longitudinal predictors of behavioural adjustment in pre-adolescent children. *Aust N Z J Psychiatry.* 2001;35:297–307.
29. Hirshfeld DR, Rosenbaum JF, Biederman J et al. Stable behavioral inhibition and its association with anxiety disorder. *J Am Acad Child Adolesc Psychiatry.* 1992;31:103–111.
30. Fox NA, Henderson HA, Rubin KH, Calkins SD, Schmidt LA. Continuity and discontinuity of behavioral inhibition and exuberance: psychophysiological and behavioral influences across the first four years of life. *Child Dev.* 2001;72:1–21.
31. Calkins SD, Fox NA, Marshall TR. Behavioral and physiological antecedents of inhibited and uninhibited behavior. *Child Dev.* 1996;67:523–540.
32. Goldsmith HH. Studying temperament via construction of the Toddler Behavior Assessment Questionnaire. *Child Dev.* 1996;67:218–235.
33. Rowe DC, Plomin R. Temperament in early childhood. *J Pers Assess.* 1977;41:150–156.
34. Buss AH, Plomin R. *Temperament: Early Developing Personality Traits.* Hillsdale, NJ: Erlbaum; 1984.
35. Kaufman J, Birmaher B, Brent D, Rao U. Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry.* 1997;36:980–988.

36. Orvaschel H, Puig-Antich J. *Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Epidemiologic 5th Version*. Ft. Lauderdale, FL: Nova University; 1995.
37. Silverman WK, Albano AM. *The Anxiety Disorders Interview Schedule for Children for DSM-IV, Child and Parent Versions*. San Antonio, TX: Psychological Corporation; 1996.
38. Muris P, Dressen L, Bogels S, Weckx M, van Melick M. A questionnaire for screening a broad range of DSM-defined anxiety disorder symptoms in clinically referred children and adolescents. *J Child Psychol Psychiatry*. 2004;45:813–820.
39. Muthén L, Muthén B. *Mplus 4.1 User's Guide*. Los Angeles: Author; 2006.
40. *Mplus* [computer program]. Version 4.1. Los Angeles: Muthén & Muthén; 2006.
41. Schafer JL, Graham JW. Missing data: our view of the state of the art. *Psychol Methods*. 2002;7:147–177.
42. Everitt B, Hand DJ. *Finite Mixture Distributions*. New York: Chapman & Hall; 1981.
43. Muthén B. Latent variable analysis: growth mixture modeling and related techniques for longitudinal data. In: Kaplan D, ed. *Handbook of Quantitative Methodology for the Social Sciences*. Newbury Park, CA: Sage Publications; 2004:345–368.
44. Dayton CM. Latent class scaling analysis. *Quantitative Applications in the Social Sciences, Series No. 126*. Thousand Oaks, CA: Sage Publications; 1998.
45. McCutcheon AL. Latent class analysis. *Quantitative Applications in the Social Sciences, Series No. 07-064*. Newbury Park, CA: Sage Publications; 1987.
46. Gibson WA. Three multivariate models: factor analysis, latent structure analysis and latent profile analysis. *Psychometrika*. 1959;24:229–252.
47. D'Unger A, Land K, McCall P, Nagin D. How many latent classes of delinquent/criminal careers? Results from mixed Poisson regression analyses of the London, Philadelphia, and Racine cohort studies. *AJS*. 1998;103:1593–1630.
48. Lo Y, Mendell NR, Rubin DB. Testing the number of components in a normal mixture. *Biometrika*. 2001;88:767–778.
49. Pine DS, Cohen P, Gurley D, Brook J, Ma Y. The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. *Arch Gen Psychiatry*. 1998;55:56–64.
50. APA. *Diagnostic and Statistical Manual of Mental Disorders (4th-TR)*. Washington, DC: American Psychiatric Association; 2000.
51. McDermott JM, Perez-Edgar K, Henderson HA, Chronis-Tuscano A, Pine DS, Fox NA. A history of childhood behavioral inhibition and enhanced response monitoring in adolescence are linked to clinical anxiety. *Biol Psychiatry*. 2009;65:445–448.
52. Reeb-Sutherland BC, Helfinstein SM, Degnan KA et al. Startle response in behaviorally inhibited adolescents with a lifetime occurrence of anxiety disorders. *J Am Acad Child Adolesc Psychiatry*. 2009;48:610–617.
53. Kagan J, Snidman N, McManis M, Woodward S, Hardway C. One measure, one meaning: multiple measures, clearer meaning. *Dev Psychopathol*. 2002;14:463–475.
54. Kagan J, Fox NA. Biology, culture, and temperamental biases. In: Eisenberg N, Damon W, Lerner RM, eds. *Handbook of Child Psychology: Vol. 3, Social, Emotional, and Personality Development*. 6th ed. Hoboken, NJ: John Wiley & Sons; 2006:167–225.
55. Gardner F. Observational methods for recording parent-child interaction: how generalisable are the findings? *Child Psychol Psychiatr Rev*. 1997;2:70–74.
56. Cheah CSL, Rubin KH. European American and Mainland Chinese mothers' responses to aggression and social withdrawal in preschoolers. *Int J Behav Dev*. 2004;28:83–94.