

UC Davis

UC Davis Previously Published Works

Title

A Neurobehavioral Mechanism Linking Behaviorally Inhibited Temperament and Later Adolescent Social Anxiety

Permalink

<https://escholarship.org/uc/item/7w1594f1>

Journal

Journal of the American Academy of Child & Adolescent Psychiatry, 56(12)

ISSN

0890-8567

Authors

Buzzell, George A
Troller-Renfree, Sonya V
Barker, Tyson V
[et al.](#)

Publication Date

2017-12-01

DOI

10.1016/j.jaac.2017.10.007

Peer reviewed



HHS Public Access

Author manuscript

J Am Acad Child Adolesc Psychiatry. Author manuscript; available in PMC 2018 December 01.

Published in final edited form as:

J Am Acad Child Adolesc Psychiatry. 2017 December ; 56(12): 1097–1105. doi:10.1016/j.jaac.2017.10.007.

A Neurobehavioral Mechanism Linking Behaviorally Inhibited Temperament and Later Adolescent Social Anxiety

Dr. George A. Buzzell, PhD,
University of Maryland, College Park

Ms. Sonya V. Troller-Renfree, MS,
University of Maryland, College Park

Dr. Tyson V. Barker, PhD,
University of Maryland, College Park

Dr. Lindsay C. Bowman, PhD,
University of California, Davis

University of Waterloo, Waterloo, ON, Canada

Dr. Andrea Chronis-Tuscano, PhD,
University of Maryland, College Park

Heather A. Henderson, PhD, Dr. Jerome Kagan, PhD,
Harvard University, Cambridge, MA

Dr. Daniel S. Pine, MD, and
Emotion and Development Branch, Intramural Research Program, National Institute of Mental Health, Bethesda, MD

Dr. Nathan A. Fox, PhD
University of Maryland, College Park

Abstract

Objective—Behavioral inhibition (BI) is a temperament identified in early childhood that is a risk factor for later social anxiety. However, mechanisms underlying development of social anxiety

Correspondence to George A. Buzzell, PhD, Benjamin Building, 3942 Campus Dr. College Park, MD 20742; gbuzzell@umd.edu.
Disclosure: Dr. Fox has received additional funding from the following granting agencies: NIH (R01MH091363) The Effects of Early Psychosocial Deprivation on Mental Health in Adolescence; Harvard University (256458-509584) Assessing the Efficacy of Attention Bias Modification Training; NIMH (1R01MH107444) Prospective Determination of Neurobehavioral Risk for the Development of Emotion Disorders; NICHD (P01HD064653) Functions and Development of the Mirror Neuron System-Continuation; NSF (1625495) Collaborative Research: Action, Learning, and Social Cognition; NIH (1UG3OD023279-01) Environmental Influences on Child Health Outcomes in the Northern Plains Safe Passage Study Cohort. Drs. Buzzell, Barker, Bowman, Chronis-Tuscano, Henderson, Kagan, Pine and Ms. Troller-Renfree report no biomedical financial interests or potential conflicts of interest.

Supplemental material cited in this article is available online.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

remain unclear. To better understand the emergence of social anxiety, longitudinal studies investigating changes at both behavioral neural levels are needed.

Method—BI was assessed in the laboratory at ages 2 and 3 (N = 268). Children returned at age 12, and electroencephalography (EEG) was recorded while performing a flanker task under two conditions: once while believing they were being observed by peers, and once while not being observed. This methodology isolated changes in error monitoring (error-related negativity; ERN) and behavior (post-error reaction time [RT] slowing) as a function of social context. At age 12, current social anxiety symptoms and lifetime diagnoses of social anxiety were obtained.

Results—Childhood BI prospectively predicted social-specific ERN increases and social anxiety symptoms in adolescence; these symptoms directly related to clinical diagnoses. Serial mediation analysis revealed social ERN changes explained relations between BI and both social anxiety symptoms (n = 107) and diagnosis (n = 92), but only insofar as social context also led to increased post-error RT slowing (a measure of error preoccupation); this model was not significantly related to generalized anxiety.

Conclusion—Results extend prior work on socially-induced changes in error monitoring and error preoccupation. These measures may index a neurobehavioral mechanism linking behavioral inhibition to adolescent social anxiety symptoms and diagnosis. This mechanism may relate more strongly to social than generalized anxiety in the peri-adolescent period.

Keywords

Social anxiety; behavioral inhibition; temperament; ERN; post-error slowing

INTRODUCTION

Behavioral inhibition (BI) is an early-childhood temperament characterized by negative reactivity and avoidance of novelty,^{1,2} driven in part by enhanced activation of neural networks associated with salience detection.³ Over development, the stimuli that elicit distress in BI generally narrow to social contexts.⁴ Consistent with this pattern, BI is predictive of social reticence in childhood⁵ and remains one of the most robust predictors of later social anxiety.⁶ However, the exact reasons why early childhood BI is linked to later social anxiety remain unclear.

Children with a history of BI display enhanced error monitoring, indicated by an event-related potential (ERP) termed the error-related negativity (ERN).^{7,8} This measure of performance monitoring⁹ is sensitive to error salience,¹⁰ consistent with the notion that BI children display hypersensitivity toward errors. Risk for anxiety among children with BI is increased for those with a relatively large (more negative) ERN,^{7,8} possibly reflecting functioning in a salience network¹¹ encompassing the cingulate,¹² insula, and orbitofrontal cortex¹³—regions also associated with risk for anxiety.¹⁴ However, although the ERN elicited by standard laboratory tasks is useful for identifying BI children at heightened risk for anxiety, this moderation provides incomplete information on mechanisms underlying the link between BI and social anxiety. The ERN is related not just to social anxiety, but to many forms of anxiety and even other forms of psychopathology.¹⁵ Thus, understanding the link

between early BI and later social anxiety requires neurophysiological measures that consider social context.

Prior work finds social observation to influence the ERN,¹⁰ an effect linked to adult social anxiety.¹⁶ However, because both ERN and social anxiety change in the peri-adolescent period,¹¹ relations between ERN and anxiety may also change. Cognitive models suggest a framework for testing ideas relating neural, behavioral, and social effects in the peri-adolescent period, when peers become increasingly salient. For socially anxious individuals, these models suggest that social settings increase self-monitoring and error hypersensitivity, which further focus attention on performance.^{17,18} In the context of error commission, we refer to such focus on performance following errors as “error preoccupation.” We view error preoccupation as conceptually similar to rumination, but manifesting on a briefer time scale, over milliseconds as opposed to minutes. According to mechanistic models on capacity limits of attentional resources, error preoccupation may cause deficits in performance when error preoccupation competes for attentional resources devoted to flexibly deploying behavior in social contexts.^{17,18} Indeed, research demonstrates that sustained processing of errors or other salient events can predict subsequent distraction in terms of reduced attention, slower response times, and increased error rates.¹⁹⁻²³ Critically, distraction following error processing—as measured by post-error response time (PERT) slowing in the absence of post-error accuracy improvement—is extended for a longer period of time for individuals with anxiety.²⁰ These data support the use of PERT as an index of error preoccupation.

Social anxiety can be viewed as a complex disorder, with hypersensitivity to errors and error preoccupation as two specific constructs composing its etiology^{17,18}; ERN and PERT may reflect neural and behavioral markers of these constructs, respectively. Given prior associations between BI and the ERN,^{7,8} early BI may confer risk for later social anxiety specifically through associations with hypersensitivity to errors. In turn, in social situations, hypersensitivity to errors may relate to error preoccupation, as indexed by PERT. These two elements could inform understanding of mechanisms by which BI leads to social anxiety.

This current study reports prospective data on the associations between early BI and later, concurrent measures of error-related processes and social anxiety symptoms. A longitudinal cohort was assessed for BI temperament in early childhood; participants were seen again during early adolescence, when they performed a modified flanker task and were assessed for psychopathology. To isolate social influences on error monitoring and behavior, an adaptive flanker task²⁴ was performed in two contexts. In one context, participants performed the task alone, while in the other, they were led to believe that they were being evaluated by peers.^{25,26} The ERN assessed hypersensitivity to errors; PERT indexed error preoccupation. Based on prior work,⁶ we hypothesized that early BI predicts later social anxiety symptoms. We also hypothesized that early BI predicts a key feature of social anxiety: hypersensitivity toward errors while under social observation. Finally, we expected the association between early BI and later social anxiety to be explained by concurrent relations among hypersensitivity to errors, error preoccupation, and reported social anxiety symptoms.^{17,18} This final hypothesis was formalized in a serial mediation model, with the primary model using continuous social anxiety symptoms and a secondary model using binary diagnosis of social anxiety disorder.

METHOD

Participants

Participants were from a larger longitudinal study. Children were originally selected at 4 months of age ($N = 291$; 134 male) based on their behavior in the laboratory²⁷; 268 children returned to the laboratory at 2 and 3 years of age to assess BI.^{4,28} At approximately 12 years of age, 185 children returned to the laboratory, though the primary analyses focus on 107 children who had valid ERP and behavioral data, as well as parent and child reports of anxiety symptoms at age 12 and a prior BI assessment; see Supplement 1, available online, for attrition details. These 107 children ($M_{age} = 13.18$, $SD = .64$; 58 females; see Supplement 1, available online, for race/ethnicity) included in the primary analyses did not significantly differ from those not included in terms of gender or prior BI (both $p > .39$). Clinical diagnostic interviews were also available for 92 of these children at the 9-year visit ($M_{assessment\ age} = 10.3$, $SD = .05$), 12-year visit ($M_{assessment\ age} = 13$, $SD = .08$), or both; these children also did not differ in terms of gender or BI (both $p > .37$). All procedures were approved by the University of Maryland, College Park Institutional Review Board; all parents provided written informed consent, and children provided assent.

Procedure

Social Flanker Task—Participants completed a modified flanker task²⁴⁻²⁶ twice, once while believing they were being observed by peers, and once while not being observed (see Figure 1, Figure S1, and Supplement 1, available online, for full details); children completed the task in a counterbalanced order. Participants were led to believe that their performance was being monitored via webcam in the social condition and that other children would provide feedback after each block.^{25,26} During the non-social portion of the task, participants were told that no one would observe their performance, and instead, computer-generated feedback would follow each block of the experimental task. Prior work has established the validity of this paradigm.^{25,26}

EEG Acquisition—EEG data were acquired using a 128-channel HydroCel Geodesic Sensor Net and EGI software (Electrical Geodesic, Inc., Eugene, OR); EEG analysis was performed using the EEGLAB toolbox²⁹ and custom MATLAB scripts (The MathWorks, Natick, MA). See Supplement 1, available online, for details of EEG processing and analysis.

Measures

Behavioral Inhibition—At 2 and 3 years of age, children participated in laboratory-based structural observations, in which they interacted with unfamiliar adults and played with novel toys.^{4,28} Consistent with prior work, BI was coded based on the child's proximity to their caregiver and latency to approach throughout observations.⁴ Standardized BI scores were separately computed for the 2- and 3-year assessments; a composite BI measure was created by averaging BI scores at both assessments.³⁰ Use of purely behavioral measures of BI is advantageous, as it eliminates the issue of shared method variance when predicting outcome measures that rely partially on parental report. Mean BI for the 107 children analyzed here was .02 ($SD = .45$), with higher values reflecting greater inhibition; BI was

unrelated to gender ($t[1, 105] = 1.3, p = .197$) or age ($n = 107, r = .12, p = .22$) at the 12-year assessment. See Supplement 1, available online, for further details.

SCARED—At age 12, children and parents independently completed the Screen for Child Anxiety Related Disorders (SCARED),³¹ a reliable questionnaire assessment of symptoms linked to *DSM-IV* anxiety disorders.³¹ Based on prior work linking BI to social anxiety,^{6,7,32} we focused on the social phobia scale of the SCARED-R. Given the high comorbidity of social and generalized anxiety, the generalized anxiety subscale of the SCARED-R was also analyzed to determine the specificity of any neurobehavioral mechanism associated with social anxiety. Prior reliability estimates have identified good internal consistency for the social (parent $\alpha = .83$; child $\alpha = .74$) and generalized (parent $\alpha = .85$; child $\alpha = .84$) subscales of the SCARED-R.³¹ Parent and child reports of social anxiety were moderately correlated ($r = .498, p < .001$), with a modest correlation also present for generalized anxiety ($r = .211, p = .03$). Similar to prior work,⁷ scores for the subscales of the SCARED-R were averaged across reporter (parent/child) to create cross-informant indices for each of these symptom scales; however, see Supplement 1, available online, for additional analyses treating parent and child reports separately, which yield qualitatively similar results.

Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS)—Semi-structured diagnostic interviews were completed for children and parents at either 9 or 12 years of age, or both. Reliability for anxiety diagnoses was high ($k = .911$). The current report focused on lifetime presence of clinically significant social anxiety, defined by clinical diagnosis at either the age 9- or 12-year assessment. The 9-year assessments were included to increase sample size for diagnostic assessments. It should be noted that the primary outcome variable for this study was continuous measures of social anxiety symptoms at age 12 (SCARED), with lifetime clinical diagnosis of social anxiety disorder only serving as a confirmatory measure. See Supplement 1, available online, for further details.

Error-Monitoring ERPs—Mean amplitude of the ERN and CRN was calculated from a cluster of frontocentral electrodes surrounding FCz (EGI electrodes 12, 5, 6, 13, 112, 7, 106) for the first 100 ms following response.^{16,25,26} Only incongruent trials were analyzed to isolate error-specific effects. Hypersensitivity to errors in social settings was isolated by regressing the ERN in the nonsocial condition onto the ERN in the social condition and then saving the standardized residuals; this residualized social ERN is referred to as “social-effect ERN_{resid}” and is similar to prior work,^{16,25} with the addition of a regression-based approach that allows for isolating variance of interest³³; see supplementary material for analyses employing a more traditional difference-score approach, which yielded the same pattern of results. For ease of interpretability, social-effect ERN_{resid} was multiplied by -1 so that positive values for this measure would reflect hypersensitivity to errors. Social-effect ERN_{resid} was unrelated to age or gender (see Supplement 1, available online).

Flanker Task Behavior—For statistical analyses, all response time (RT) data was log-transformed³⁴; raw values are reported in table 1 for ease of interpretation. We extracted a behavioral measure of socially induced error preoccupation: correct RT on trials following

errors in the nonsocial condition were regressed onto similar trials in the social condition, and the standardized residuals were saved. This residualized PERT score, referred to as “social-effect $PERT_{resid}$,” reflects error preoccupation while under social observation (see Supplement 1, available online, for analyses using a difference-score approach). However, to confirm that social-effect $PERT_{resid}$ reflects performance inefficiency due to error preoccupation, we tested whether this residualized score correlated with a similar residualized measure of post-error accuracy. Critically, social-effect $PERT_{resid}$ was unrelated to changes in post-error accuracy ($n = 107$, $r = .072$, $p = .461$), confirming that slowing was unrelated to improved performance (control) after errors, and instead reflects performance inefficiencies³⁵ associated with error preoccupation.¹⁹⁻²³ Social-effect $PERT_{resid}$ was unrelated to age or gender (see Supplement 1, available online).

Analytic Plan

Preliminary analyses of the behavioral and ERP data were performed using analysis of variance (ANOVA) models. Next, we attempted to replicate prior work demonstrating that early childhood BI prospectively predicts social anxiety symptoms in adolescence. Critically, clinical relevance of these social anxiety symptoms was confirmed by testing their association with clinical diagnosis in the same children through logistic regression.

Having established that BI prospectively predicts social anxiety, neural and behavioral markers explaining this relation were explored. Adolescent brain function underlying hypersensitivity to errors in social settings was assessed using social-effect ERN_{resid} .^{16,25} We tested whether BI prospectively predicted adolescent neural activity within social settings by correlating BI (in early childhood) and social-effect ERN_{resid} (age 12).

We next tested whether hypersensitivity toward errors for children with high BI is associated with greater error preoccupation. Social-effect $PERT_{resid}$ was employed as a behavioral measure of socially induced error preoccupation. We tested whether hypersensitivity to errors when under social observation is associated with error preoccupation by correlating social-effect ERN_{resid} with social-effect $PERT_{resid}$. Moreover, we tested whether BI predicted increased error preoccupation (social-effect $PERT_{resid}$) with hypersensitivity to errors (social-effect ERN_{resid}) as an explanatory variable within a mediation framework. Finally, we tested whether error preoccupation in social settings is associated with social anxiety symptoms by correlating social-effect $PERT_{resid}$ (a measure of error preoccupation) with social anxiety symptoms. See Table S1 and Figures S2-S5, available online, for relations between variable of interest.

The relations described above suggest a set of neural and behavioral markers that can explain the link between early-childhood BI and adolescent social anxiety. Specifically, BI is believed to prospectively predict hypersensitivity to errors (social-effect ERN_{resid}). Moreover, social anxiety itself can be described as a set of interrelated constructs, including hypersensitivity to errors and error preoccupation in social settings. We therefore suggest that the link between BI and social anxiety is explained by additional connections between hypersensitivity to errors and error preoccupation. This neurobehavioral mechanism was formalized and tested as a serial mediation model, which allows for testing whether influence of a given predictor, BI, on another variable, social anxiety, can be explained by

connections between intermediate variables. Here, we suggest that BI leads to hypersensitivity toward errors while under social observation (social-effect ERN_{resid}); this hypersensitivity towards errors is further associated (concurrently) with error preoccupation (social-effect $PERT_{resid}$) within social settings; error preoccupation within social settings is ultimately associated with continuous social anxiety symptoms (SCARED-social). It should be noted that although a mediation framework was employed as a means to understand the prospective relations between BI and later social anxiety, full causal inference cannot be determined given concurrent assessment of social-effect ERN_{resid} , social-effect $PERT_{resid}$, and SCARED-social. Mediation analyses were conducted utilizing an ordinary least squares path analytical framework implemented in PROCESS³⁶; bias-corrected confidence intervals for indirect effects were calculated using 10,000 bootstrap samples. Given some prior work suggesting that gender may influence the BI-anxiety relation,³⁷ gender was controlled.

RESULTS

Preliminary Behavioral and ERP Results

Behavior—Analysis of RT data revealed a main effect of congruency, with participants responding slower to incongruent stimuli ($F[1, 106] = 1018.1, p < .001$). There was also a main effect of social context, with faster RT in the social condition ($F[1, 106] = 15.14, p < .001$), and no interaction between congruency and social context ($F[1, 106] = .37, p = .546$). Analysis of accuracy data revealed a main effect of congruency, with participants responding less accurately to incongruent stimuli ($F[1, 106] = 678.56, p < .001$). No main effect of social context was identified ($F[1, 106] = .11, p = .746$). However, a trend for an interaction between congruency and social context was identified ($F[1, 106] = 3.75, p = .056$).

Analysis of RT data, contingent on previous trial accuracy (post-error vs. post-correct) and social context revealed neither a main effect of previous trial accuracy ($F[1, 106] = 1.75, p = .189$) nor an interaction with social context ($F[1, 106] = .882, p = .35$). Instead, only a main effect of social context emerged ($F[1, 106] = 17.73, p < .001$). Thus, on average, RT for post-error and post-correct responses did not significantly differ. However, below, we report analyses demonstrating that individual differences in PERT, as a function of social context, relate to individual differences in social anxiety.

ERN—Analysis of the ERN and CRN revealed a main effect of trial accuracy, with the ERN being significantly more negative than the CRN ($F[1, 106] = 136.3, p < .001$). There was also a main effect of social context, such that the ERN and CRN were more negative in the social condition ($F[1, 106] = 5.51, p = .021$). Additionally, a trend for an interaction between social context and trial accuracy was present ($F[1, 106] = 3.22, p = .076$). See Figure 2 for a depiction of the ERP results.

Anxiety Measures

Mean reports of SCARED-R social anxiety were 4.27 (SD = 3.06), and mean generalized anxiety was 4.43 (SD = 2.82). For the 92 children with KSADS data, 10 cases (10.87%) of lifetime social anxiety diagnoses were identified.

Relations Between BI, Neurobehavioral Measures, and Social Anxiety

BI and Social Anxiety—Consistent with prior work, BI prospectively predicted social anxiety symptoms in adolescence ($n = 107$, $r = .213$, $p = .028$), whereas BI was unrelated to generalized anxiety ($n = 106$, $r = .125$, $p = .201$). Moreover, as expected, social anxiety symptoms also were associated with lifetime clinical diagnosis of social anxiety disorder ($n = 92$; 10 cases, odds ratio = 2.38, Wald $\chi^2 = 9.81$, $p = .002$).

BI and Error Salience—BI prospectively predicted increased hypersensitivity toward errors within a social setting. Specifically, BI positively correlated with an increased social-effect ERN_{resid} ($n = 107$, $r = .282$, $p = .003$); see Figure 3. Exploratory analyses (see Supplement 1, available online) suggest this relation between BI and increased social-effect ERN_{resid} was significant only for females ($n = 58$, $r = .347$, $p = .008$) and not males ($n = 49$, $r = .235$, $p = .103$), although caution is warranted when interpreting these supplementary analyses, given the reduced and unequal sample sizes.

BI, Error Preoccupation, and Social Anxiety—Hypersensitivity toward errors (social-effect ERN_{resid}) was positively correlated with increased error preoccupation (social-effect PERT_{resid}; $n = 107$, $r = .216$, $p = .026$). Moreover, BI prospectively predicted increased error preoccupation while under social observation (social-effect PERT_{resid}), as mediated by concurrent measurement of hypersensitivity toward errors (social-effect ERN_{resid}; $n = 107$, $\beta = .124$, 95% CI = .013 - .341). Finally, social increases in error preoccupation, measured by social-effect PERT_{resid}, positively correlated with social anxiety symptoms ($n = 107$, $r = .314$, $p = .001$).

Serial Mediation Model Linking BI and Social Anxiety

We fit a serial mediation model (Figure 4 and Table S2, available online), which explained links between BI and social anxiety through a series of explanatory neural and behavioral markers. Early BI predicted hypersensitivity towards errors within social settings, in the form of increased social-effect ERN_{resid}, which in turn was associated with concurrent behavioral signs of error preoccupation, in the form of social-effect PERT_{resid}, which ultimately was associated with social anxiety symptoms ($n = 107$, $\beta = .108$, 95% CI = .018 - .337); an alternative ordering of the serial mediation model was not significant (see Table S3, available online). When this series of links among BI, social-effect ERN_{resid}, and social-effect PERT_{resid} were included, the direct association between BI and social anxiety was no longer statistically significant ($n = 107$, $c' = 1.09$, $p = .138$). As a confirmatory analysis, this model was also significant in predicting social anxiety diagnoses when a 90% confidence interval was applied ($n = 92$, $\beta = .057$, 90% CI = .003 - .262), although the prediction of social anxiety diagnosis was also significant using a 95% CI when traditional difference scores, instead of residualized scores, were employed ($n = 92$; 10 cases, $\beta = .135$, 95% CI = .01 - .517; see Tables S4 and S5, available online). Of note, the serial mediation model was not significantly related to the generalized anxiety subdomain of the SCARED (see Supplement 1, available online).

DISCUSSION

The early childhood temperament of BI has long been of interest to psychologists and clinicians, given its association with later social anxiety.⁶ The current study informs mechanisms linking these two constructs. BI expressed 10 years earlier predicted hypersensitivity toward errors while adolescents were under social scrutiny. However, this effect alone did not explain the prospective relations between BI and social anxiety symptoms. Instead, BI-related risk for social anxiety was best explained by interrelations among hypersensitivity to errors and error preoccupation. Specifically, BI predicted later social anxiety symptoms, insofar as concurrently-assessed hypersensitivity toward errors (social-effect ERN_{resid}) was associated with greater error preoccupation (PERT); together, these neural and behavioral markers explain the link between early childhood BI and adolescent social anxiety.

The current study employed PERT as a measure of error preoccupation associated with social anxiety. Response time has long been regarded as a behavioral correlate of processing speed or efficiency,^{34,35} and more recent work suggests that PERT is associated with cortical inhibition³⁸ and distraction.¹⁹⁻²³ Similarly, a confirmatory analysis demonstrated that social changes in PERT were unrelated to social changes in accuracy within the current task. This analysis suggests that slowing after errors did not reflect the allocation of control, and is instead driven primarily by distraction caused by error preoccupation.

Existing models of social anxiety suggest that this disorder is associated with enhanced salience of social threat and as a result, preoccupation with errors, which impairs social performance.^{17,18} However, these cognitive models have been difficult to formally test within the laboratory in a neuroscience framework. The current findings provide support for these models and embed them within a developmental, neuroscience framework. Specifically, we demonstrate that early-life BI temperament predicts later hypersensitivity toward errors while under social scrutiny, particularly for females (see Figure S6, available online). Moreover, we found no direct relation between hypersensitivity toward errors and social anxiety in adolescence, which could reflect immaturity in the performance-monitoring system¹¹ as a direct relation has been found in adults.¹⁶ Finally, direct relations with adolescent social anxiety were found for error preoccupation, and the patterns in other portions of the data extended prior models of social anxiety and BI,^{17,18} with BI predicting error hypersensitivity, and in turn, error preoccupation correlating with concurrent social anxiety symptoms.

These novel findings extend prior work linking BI, social anxiety, and error monitoring in non-social situations.⁷ Specifically, without accounting for social context and behavior, prior findings were not exclusive to social anxiety and may instead reflect the relation between BI and anxiety risk more generally.^{8,32} In contrast, the current findings pertain specifically to adolescent social anxiety, which may represent a distinct form of anxiety that is heavily dependent on developmental stage and context.³⁹ A prominent theory of between-subject ERN variation suggests that the ERN reflects a more general endogenous threat response.^{15,40} Our data are consistent with this interpretation of the ERN, but suggest that it is also possible to isolate specific subtypes of threat or salience indexed by the ERN. Here, we

employed a social manipulation and calculated residualized scores to remove ERN variance due to a more general threat response (i.e. the non-social ERN), leaving only variance caused by the social manipulation.^{16,25,26} Critically, this social ERN variance alone did not mediate relations between BI and social anxiety symptoms; only by also indexing error preoccupation (social-effect $PERT_{resid}$) associated with such social ERN variation was a relation to social anxiety established. Here, it's worth noting related work by Moser et al.,⁴¹ which argues that preoccupation with worries unrelated to the task at hand is what causes a larger ERN for individuals with anxiety. In contrast, we outline here a model in which worries about the task itself (i.e. error preoccupation) are a result of a larger ERN while under social observation. Thus, the current findings provide an important extension of prior theory,⁴¹ at least in relation to adolescent social anxiety and for children with a temperamental bias toward increased social threat; these data suggest the importance of also considering task-relevant worry (error preoccupation) in the study of anxiety disorders and describe associations with early childhood temperament.

It should be noted that this paper treats BI as a temperament because the behaviors that define this concept are often correlated with a specific set of biological measures. Kagan and Snidman⁴² have suggested that BI behaviors can be the result of experience, without contribution of a specific temperamental bias. They prefer the hypothesis that high reactivity in 4-month-old infants is the temperament that biases children to display BI behaviors in the second year. For this reason, we also conducted a supplementary analysis in order to explore relations to infant reactivity. However, switching out BI for infant reactivity was not significant; this analysis suggests a degree of specificity in the mechanism linking early temperament with later anxiety.

Two limitations of the current study should be noted. First, although the reported mediation analyses improve understanding of the link between BI and later social anxiety, causal inference cannot be drawn from these data, given that some variables were measured concurrently. Second, relations between the variables studied were relatively moderate; future research is needed to replicate these findings using a larger sample size, allowing for investigations of other variables, such as the family context, that may also influence the mechanism described.

Findings of this report have implications for early prevention or later treatment of social anxiety. Prevention of social anxiety for those at risk might be improved by targeting factors that influence the link between early BI and later hypersensitivity toward errors; parenting is one promising factor that may influence this relation.^{43,44} Conversely, in adolescents already diagnosed with social anxiety or expressing symptoms, improved treatment might target error preoccupation, as opposed to hypersensitivity toward errors. Consistent with this notion, intervention studies have shown that treatment for anxiety disorders does not influence the ERN itself.^{45,46} In conclusion, future research should not only seek to replicate the mechanism described here, but also identify variables that selectively influence subcomponents of this neurobehavioral mechanism explaining the link between BI and social anxiety.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by grants from the National Institute of Mental Health (NIMH) U01MH093349 and U01MH093349-S to N.A.F., the National Science Foundation (NSF) DGE1322106 to S.V.T., the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) 5T32HD007542 (to Melanie Killen) supporting T.V.B., and the NIMH Intramural Research Program supporting D.S.P.

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. [PubMed: 15709935]
2. Kagan J, Reznick S, Snidman N. Biological Bases of Childhood Shyness. *Sci Wash.* 1988; 240(4849):167.
3. Henderson HA, Pine DS, Fox NA. Behavioral Inhibition and Developmental Risk: A Dual-Processing Perspective. *Neuropsychopharmacology.* 2015; 40:207–224. [PubMed: 25065499]
4. 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. [PubMed: 11280472]
5. Degnan KA, Almas AN, Henderson HA, Hane AA, Walker OL, Fox NA. Longitudinal Trajectories of Social Retiience with Unfamiliar Peers across Early Childhood. *Dev Psychol.* 2014; 50(10): 2311–2323. [PubMed: 25181648]
6. Clauss JA, Blackford JU. Behavioral Inhibition and Risk for Developing Social Anxiety Disorder: A Meta-Analytic Study. *J Am Acad Child Adolesc Psychiatry.* 2012; 51(10):1066–1075.e1. [PubMed: 23021481]
7. Lahat A, Lamm C, Chronis-Tuscano A, Pine DS, Henderson HA, Fox NA. Early behavioral inhibition and increased error monitoring predict later social phobia symptoms in childhood. *J Am Acad Child Adolesc Psychiatry.* 2014; 53:447–455. [PubMed: 24655654]
8. 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. [PubMed: 19108817]
9. Gehring, WJ., Liu, Y., Orr, JM., Carp, J. The error-related negativity (ERN/Ne). In: Luck, SJ., Kappenman, ES., editors. *Oxford Handbook of Event-Related Potential Components.* Oxford: Oxford University Press; 2012. p. 231-291.
10. Hajcak G, Moser JS, Yeung N, Simons RF. On the ERN and the significance of errors. *Psychophysiology.* 2005; 42(2):151–160. [PubMed: 15787852]
11. Buzzell GA, Richards JE, White LK, Barker TV, Pine DS, Fox NA. Development of the error-monitoring system from ages 9-35: unique insight provided by MRI-constrained source localization of EEG. *NeuroImage.* 2017; 157:13–26. [PubMed: 28549796]
12. Ullsperger M, Danielmeier C, Jocham G. Neurophysiology of Performance Monitoring and Adaptive Behavior. *Physiol Rev.* 2014; 94:35–79. [PubMed: 24382883]
13. Liu Y, Hanna GL, Carrasco M, Gehring WJ, Fitzgerald KD. Altered relationship between electrophysiological response to errors and gray matter volumes in an extended network for error-processing in pediatric obsessive-compulsive disorder: ERN and VBM in Pediatric OCD. *Hum Brain Mapp.* 2014; 35:1143–53. [PubMed: 23418104]
14. Seeley WW, Menon V, Schatzberg AF, et al. Dissociable Intrinsic Connectivity Networks for Salience Processing and Executive Control. *J Neurosci.* 2007; 27:2349–2356. [PubMed: 17329432]
15. Olvet DM, Hajcak G. The error-related negativity (ERN) and psychopathology: Toward an endophenotype. *Clin Psychol Rev.* 2008; 28:1343–1354. [PubMed: 18694617]

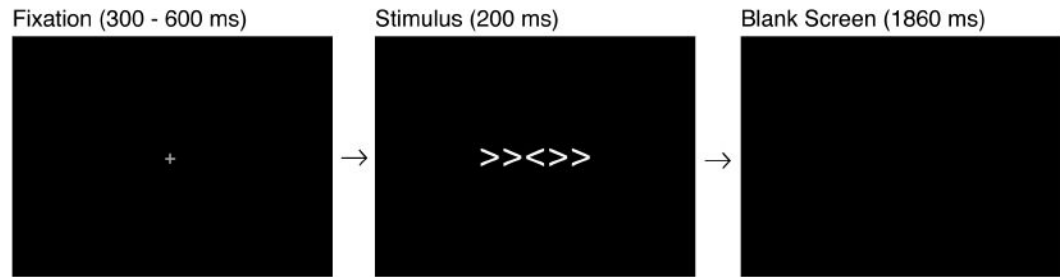
16. Barker TV, Troller-Renfree S, Pine DS, Fox NA. Individual differences in social anxiety affect the salience of errors in social contexts. *Cogn Affect Behav Neurosci*. 2015; 15:723–735. [PubMed: 25967929]
17. Rapee RM, Heimberg RG. A cognitive-behavioral model of anxiety in social phobia. *Behav Res Ther*. 1997; 35(8):741–756. [PubMed: 9256517]
18. Clark DM, Wells A. A cognitive model of social phobia. *Soc Phobia Diagn Assess Treat*. 1995; 41(68):22–3.
19. Danielmeier C, Ullsperger M. Post-error adjustments. *Front Psychol*. 2011; 2:233. [PubMed: 21954390]
20. Van der Borgh L, Braem S, Stevens M, Notebaert W. Keep calm and be patient: The influence of anxiety and time on post-error adaptations. *Acta Psychol (Amst)*. 2016; 164:34–38. [PubMed: 26720098]
21. Buzzell GA, Beatty PJ, Paquette NA, Roberts DM, McDonald CG. Error-Induced Blindness: Error Detection Leads to Impaired Sensory Processing and Lower Accuracy at Short Response-Stimulus Intervals. *J Neurosci*. 2017; 37:2895–2903. [PubMed: 28193697]
22. Jentzsch I, Dudschig C. Why do we slow down after an error? Mechanisms underlying the effects of posterror slowing. *Q J Exp Psychol*. 2009; 62:209–218.
23. Notebaert W, Houtman F, Van Opstal F, Gevers W, Fias W, Verguts T. Post-error slowing: an orienting account. *Cognition*. 2009; 111(2):275–279. [PubMed: 19285310]
24. Eriksen BA, Eriksen CW. Effects of noise letters upon the identification of a target letter in a nonsearch task. *Percept Psychophys*. 1974; 16(1):143–149.
25. Barker, TV. [October 6, 2017] Social influences of error monitoring. Digital Repository at the University of Maryland. 2016. <https://drum.lib.umd.edu/handle/1903/18271>
26. Barker TV, Troller-Renfree S, Bowman LC, Pine DS, Fox NA. Social Influences of Error Monitoring in Adolescence. Under Review.
27. Hane AA, Fox NA, Henderson HA, Marshall PJ. Behavioral reactivity and approach/withdrawal bias in infancy. *Dev Psychol*. 2008; 44:1491. [PubMed: 18793079]
28. Kagan J, Snidman N. Infant predictors of inhibited and uninhibited profiles. *Psychol Sci*. 1991; 2:40–44.
29. Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods*. 2004; 134:9–21. [PubMed: 15102499]
30. Pérez-Edgar K, Reeb-Sutherland BC, McDermott JM, et al. Attention biases to threat link behavioral inhibition to social withdrawal over time in very young children. *J Abnorm Child Psychol*. 2011; 39:885–895. [PubMed: 21318555]
31. Muris P, Dreessen L, Bögels 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. [PubMed: 15056312]
32. Chronis-Tuscano A, Degnan KA, Pine DS, et al. Stable early maternal report of behavioral inhibition predicts lifetime social anxiety disorder in adolescence. *J Am Acad Child Adolesc Psychiatry*. 2009; 48:928–935. [PubMed: 19625982]
33. Meyer A, Lerner MD, De Los Reyes A, Laird RD, Hajcak G. Considering ERP difference scores as individual difference measures: Issues with subtraction and alternative approaches. *Psychophysiology*. 2017; 54(1):114–122. [PubMed: 28000251]
34. Luce, RD. *Response Times: Their Role in Inferring Elementary Mental Organization*. New York: Oxford University Press; 1986.
35. Eysenck MW, Derakshan N, Santos R, Calvo MG. Anxiety and cognitive performance: attentional control theory. *Emotion*. 2007; 7:336. [PubMed: 17516812]
36. Hayes, AF. *Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach*. New York, NY: Guilford Press; 2013.
37. 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. [PubMed: 10434493]

38. Wessel JR, Aron AR. On the Globality of Motor Suppression: Unexpected Events and Their Influence on Behavior and Cognition. *Neuron*. 2017; 93:259–280. [PubMed: 28103476]
39. Spence SH, Rapee RM. The etiology of social anxiety disorder: An evidence-based model. *Behav Res Ther*. 2016; 86:50–67. [PubMed: 27406470]
40. Weinberg A, Meyer A, Hale-Rude E, et al. Error-related negativity (ERN) and sustained threat: Conceptual framework and empirical evaluation in an adolescent sample. *Psychophysiology*. 2016; 53:372. [PubMed: 26877129]
41. Moser JS, Moran TP, Schroder HS, Donnellan MB, Yeung N. On the relationship between anxiety and error monitoring: a meta-analysis and conceptual framework. *Frontiers in Human Neuroscience*. 2013; 7:466. [PubMed: 23966928]
42. Kagan, J., Snidman, N. *The Long Shadow of Temperament*. Cambridge, MA: Harvard University Press; 2004.
43. Meyer A, Proudfit GH, Bufferd SJ, et al. Self-reported and observed punitive parenting prospectively predicts increased error-related brain activity in six-year-old children. *J Abnorm Child Psychol*. 2015; 43:821–829. [PubMed: 25092483]
44. Chronis-Tuscano A, Rubin KH, O'Brien KA, et al. Preliminary evaluation of a multimodal early intervention program for behaviorally inhibited preschoolers. *J Consult Clin Psychol*. 2015; 83:534–540. [PubMed: 25798728]
45. Hajcak G, Franklin ME, Foa EB, Simons RF. Increased Error-Related Brain Activity in Pediatric Obsessive-Compulsive Disorder Before and After Treatment. *Am J Psychiatry*. 2008; 165:116–123. [PubMed: 17986681]
46. Kujawa A, Weinberg A, Bunford N, et al. Error-related brain activity in youth and young adults before and after treatment for generalized or social anxiety disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2016; 71:162–168. [PubMed: 27495356]

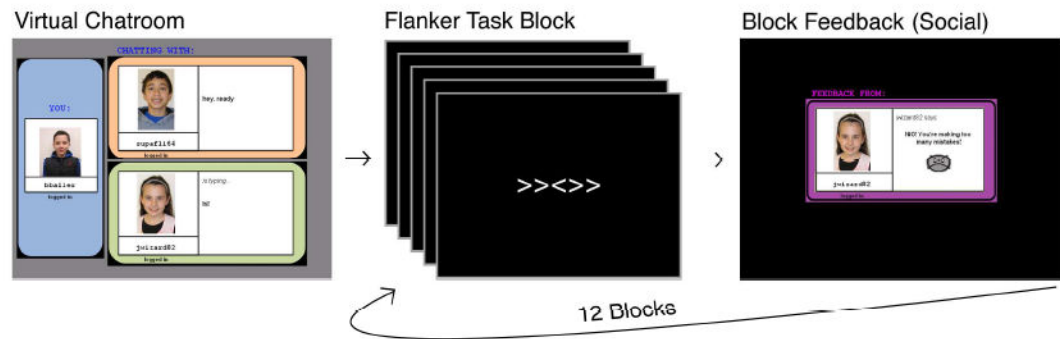
Clinical Guidance

- Individuals with social anxiety focus on their perceived mistakes and performance particularly in social contexts.
- The degree to which mistakes capture attention and cause strong emotional responses is called “hypersensitivity to errors,” and its neural correlates can be measured using EEG.
- The degree to which an individual continues to focus on an error, called “error preoccupation,” compromises their ability to pay attention to other aspects of the (social) environment.
- Data from a longitudinal study of infant temperament suggests that behavioral inhibition (BI) is related to social anxiety. BI predisposes a child to have stronger neural responses to mistakes (hypersensitivity to errors) while in social settings, which is in turn associated with continued focus on the mistake and distraction (error preoccupation).
- This research may have implications for intervention in that future research may examine the utility of including exposure to making errors within the social context for patients with social anxiety.

A. Flanker Task Trial Sequence



B. Social Condition



C. Non-social Condition

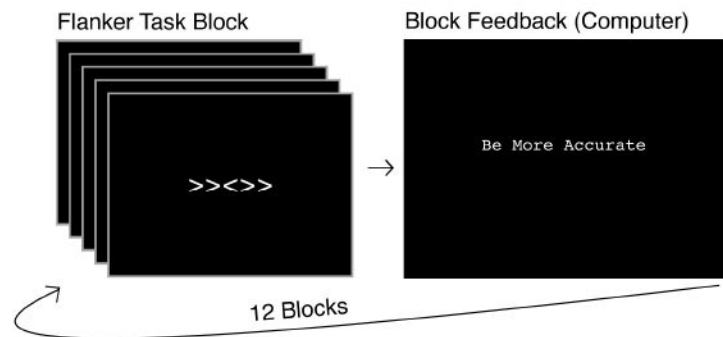


Figure 1. Experimental paradigm. Note: A) Trial sequence for the flanker task. B) Depiction of the social condition: participants were told that other children would monitor their performance during the flanker task. Before completing the flanker task, participants chatted with these children. Following each block of the flanker task, children believed that feedback was provided by one of the other children. C) Depiction of the non-social condition: children were told that their performance would not be monitored and that computer-generated feedback would follow each block.

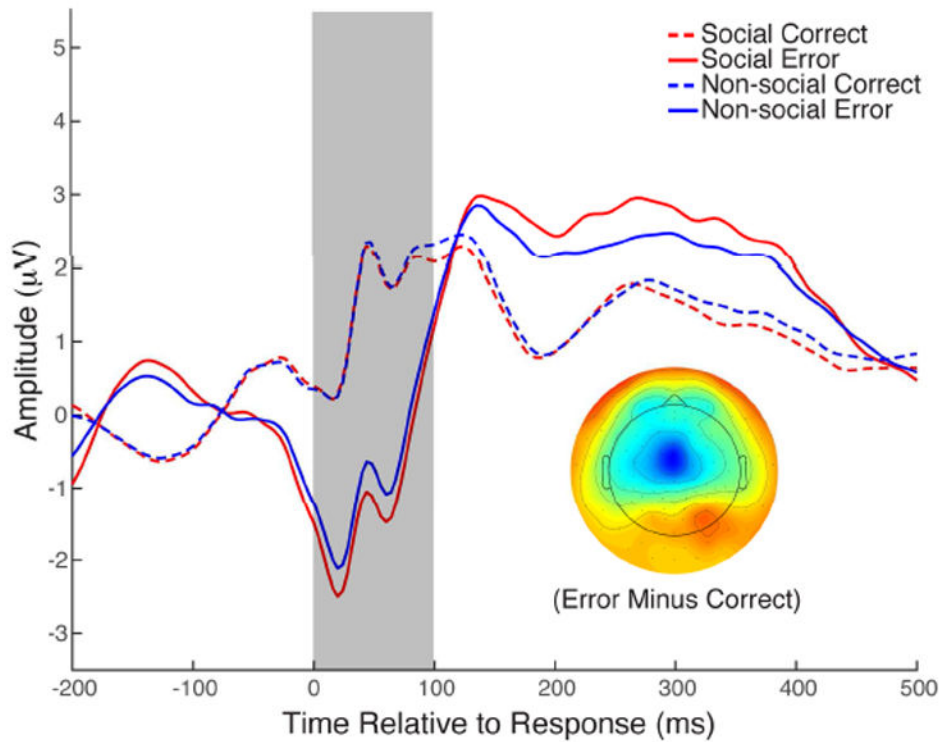


Figure 2. Event-related potential (ERP) results as a function of accuracy and social context. Note: Correct trials are plotted with dashed lines, error trials are plotted with solid lines; the social condition is plotted in red, and the non-social condition is plotted in blue. Topographic plot reflects error minus correct mean amplitude during the shaded time window (0 – 100 ms); this time window was used for statistical analyses.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

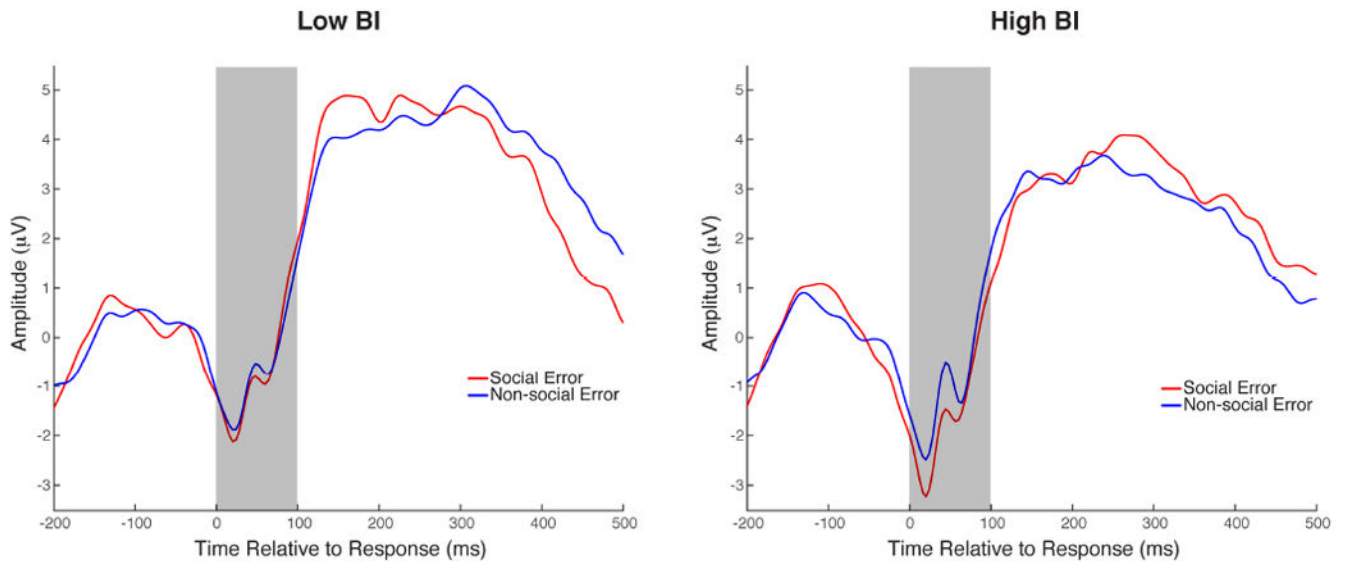


Figure 3. Event-related potential (ERP) results as a function of social context and behavioral inhibition (BI). Note: Error trials from the social condition are plotted in red; error trials from the non-social condition are plotted in blue. For plotting purposes only, children with a BI score 1 SD above/below the mean were plotted separately; children low in BI are plotted on the left, and children high in BI are plotted on the right. Shaded region reflects the time window for statistical analyses (0 – 100 ms).

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

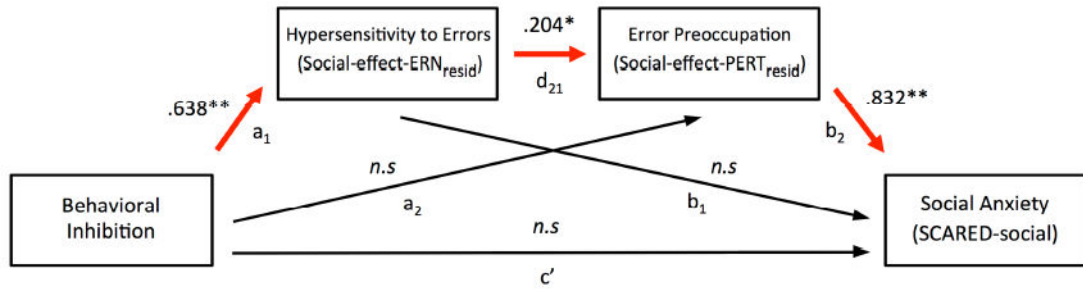


Figure 4. Serial mediation model linking behavioral inhibition (BI) and social anxiety. Note: Red lines trace the significant indirect serial mediation effect. Social-effect ERN_{resid} reflects the error-related negativity (ERN) within the social condition after removing variance predicted by the ERN in the non-social condition and multiplying by -1; positive values reflect a larger (more negative) ERN in the social condition. Social-effect-post-error response time (PERT)_{resid} reflects response time on correct trials following errors in the social condition after removing variance predicted by similar response times in the non-social condition. Individual path significance: * $p < .05$, ** $p < .01$.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Behavior and Event-Related Potential (ERP) Results

Condition	Accuracy	
	Congruent	Incongruent
Non-Social	94.7% (3.89)	73.75% (9.39)
Social	95.56% (3.64)	73.26% (8.19)
Condition	Response Time	
	Congruent	Incongruent
Non-Social	381.38 ms (4.4)	454.23 ms (5.76)
Social	369.02 ms (4.05)	441.11 ms (5.53)
Condition	ERPs	
	CRN	ERN
Non-Social	1.48 μ V (.15)	-0.6 μ V (.21)
Social	1.45 μ V (.16)	-.95 μ V (.2)
Condition	PERT	
	Post-correct	Post-error
Non-Social	413.3 ms (4.88)	412.94 ms (5.37)
Social	401.62 ms (4.75)	397.61 ms (4.43)

Note: Parentheses reflect standard error of the mean. CRN = correct-related negativity; ERN = error-related negativity; PERT = post-error response time.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript