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Connecting childhood wariness to adolescent social anxiety through the brain and peer experiences

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Abstract

Wariness in early childhood manifests as shy, inhibited behavior in novel social situations and is associated with increased risk for developing social anxiety. In youth with childhood wariness, exposure to a potent social stressor, such as peer victimization, may potentiate brain-based sensitivity to unpredictable social contexts, thereby increasing risk for developing social anxiety. To test brain-based associations between early childhood wariness, self-reported peer victimization, and current social anxiety symptoms, we quantified neural responses to different social contexts in low- and high-victimized pre-adolescents with varying levels of early childhood wariness. Measures of early childhood wariness were obtained annually from ages 2-to-7-years. At age 11, participants were characterized as having low ($N=20$) or high ($N=27$) peer victimization. To index their neural responses to peer evaluation, participants completed an fMRI-based Virtual School paradigm (Jarcho et al., 2013). In highly victimized, relative to low-victimized participants, wariness was differentially related to right amygdala responsivity based on the valence and predictability of peer evaluation. More specifically, in highly victimized participants, wariness was associated with greater right amygdala responsivity to unpredictably positive peer evaluation. Effects of wariness were not observed in participants who reported low levels of victimization. Moreover, in victimized participants, high wariness and right amygdala response to unpredictably positive peer evaluation was associated with more severe social anxiety symptoms. Results can be

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

interpreted using a diathesis-stress model, which suggests that neural response to unexpectedly positive social feedback is a mechanism by which exposure to peer victimization potentiates the risk for developing social anxiety in individuals exhibiting high levels of early childhood wariness.

Keywords

shyness; peer feedback; neuroimaging; anxiety; adolescence; bullying

In social contexts, children exhibit many forms of solitary behavior (Coplan, Rubin, Fox, Calkins, & Stewart, 1994; Rubin, Coplan, & Bowker, 2009). One expression of solitary behavior is wariness (Coplan et al., 1994; Rubin et al., 2009). Wariness may be expressed as the engagement in fearful, unoccupied, or passive behavior in social contexts (Degnan, Henderson, Fox, & Rubin, 2008). This behavior likely reflects conflicting drives to interact with others and to withdraw from social situations (for review see Rubin, Barstead, Smith, & Bower, 2018). Wariness often emerges in novel or uncertain social situations (Coplan et al., 1994; Rubin et al., 2009). Thus, for wary children, the inability to predict social situations when they involve a new context or an unpredictable outcome may be particularly distressing. The neurocognitive mechanisms implicated in wariness undoubtedly play a role in promoting withdrawn behavior in familiar peer-based settings. However, unfamiliar peers embody both novelty and uncertainty (i.e., their behavior may be unpredictable). While the neurocognitive mechanisms implicated in wariness have been assessed in the context of interacting with novel peers (see Jarcho & Guyer, 2018 for review), parsing neural response to unpredictable (uncertain) relative to predictable (certain) social interactions may shed light on mechanisms that increase risk for developing social anxiety in youth with heightened wariness in childhood (Rubin et al., 2009).

Although early childhood wariness is associated with heightened risk for developing social anxiety, not all wary children exhibit social anxiety symptoms later in life. Exposure to social stressors may increase this risk, reflecting interactions between inherent vulnerabilities and environmental stressors. Peer victimization (e.g., bullying, social aggression) is a particularly salient form of social stress that becomes more common during late childhood to mid-adolescence (Troop-Gordon, 2017). Peer victimization is associated with many negative outcomes, including loneliness, social dissatisfaction, risk for internalizing problems, and social anxiety (Hawker & Boulton, 2000; Sentse, Prinzie, & Salmivalli, 2017; Takizawa, Maughan, & Arseneault, 2014). Youth with high, relative to low, levels of wariness who express anxiously withdrawn behavior often expect, and experience, higher levels of peer victimization (see Rubin, Bukowski, & Bowker, 2015 for review). Inflated expectations of experiencing victimization in socially-withdrawn youth may increase the likelihood that negative social interactions are interpreted as intentional, rather than unintended (e.g., Burgess, Wojslawowicz, Rubin, Rose-Krasnor, & Booth-LaForce, 2006). Furthermore, instances of social aggression, even among familiar peers, may be unpredictable. For instance, a familiar peer may aggress towards a target during some, but not all, social encounters. Unpredictability of social interactions more broadly may cause victimized youth to experience greater anxiety during all, not just novel, social interactions. Thus, in wary youth, peer victimization may exacerbate pre-existing tendencies towards

fearful or withdrawn behaviors during social exchanges. Assessing engagement of brain regions attuned to detecting social novelty and unpredictable, relative to predictable, social interactions may elucidate mechanisms by which peer victimization impacts relations between early childhood wariness and the expression of social anxiety.

During late childhood and early adolescence increased focus on peer opinions and acceptance heightens behavioral and neural sensitivity to social evaluation (Nelson, Jarcho, & Guyer, 2016). Developmental neuroimaging studies find that the anticipation and receipt of peer acceptance and rejection elicits heightened neural engagement in brain regions implicated in detecting novelty, inconsistency, potential threat, social distress, reward, and salience processing (Guyer & Jarcho, 2018). These regions include the amygdala (Guyer et al., 2008; Spielberg et al., 2014), dorsal anterior cingulate (ACC) (Eisenberger, Lieberman, & Williams, 2003; Jarcho et al., 2016; Spielberg et al., 2014), striatum (Guyer et al., 2014; Guyer, McClure-Tone, Shiffrin, Pine, & Nelson, 2009; Jarcho et al., 2015), and insula (Guyer et al., 2009; Jarcho et al., 2015). Importantly, engagement of these regions is heightened during peer evaluation in adolescents with high, relative to low, childhood wariness (Jarcho & Guyer, 2018).

Environmental stressors may differentially influence how the brain responds to peer evaluation in youth with high versus low levels of wariness. For instance, harsh parenting style influences striatal response to peer rejection in adolescents with high, but not low, levels of wariness (Guyer et al., 2015). Given the importance of peer relationships during late childhood and early adolescence, victimization by one's peers may be another factor that influences relations between wariness and brain function. Indeed, peer victimization and chronic rejection is associated with altered engagement in ACC during social exclusion (Rudolph, Miernicki, Troop-Gordon, Davis, & Telzer, 2016; Schriber et al., 2018; Will, van Lier, Crone, & Guroglu, 2016) and moderates relations between brain function and internalizing symptoms (Rudolph et al., 2016). Yet, the potential interactive effects of peer victimization, early childhood wariness, and brain function on social anxiety are unknown.

We previously paired functional magnetic resonance imaging (fMRI) with a novel social interaction task (The Virtual School) to model brain function as pre-adolescents with or without a history of wariness engaged in ongoing, real-time interactions with predictable and unpredictable purported peers. High levels of social reticence, a construct closely related to wariness, were associated with greater ACC and insula engagement when participants anticipated evaluation from unpredictable compared to predictable peers. The predictability of social interactions also affected amygdala response during the receipt of social evaluations. Pre-adolescents with high social reticence exhibited less amygdala activity when they received negative evaluations from unpredictable, relative to predictable, peers. The opposite effect emerged in participants with low social reticence. This pattern of altered response to unpredictable feedback is consistent with studies of socially anxious youth, who show altered striatal response specifically to unexpected, relative to expected, social evaluation (Jarcho et al., 2015). This suggests that neural responses to unpredictable social interactions may contribute to the expression of social anxiety symptoms during adolescence. Further, because peer victimization is often inconsistent and conflicts with social norms, victimized youth may experience their social landscape as relatively

unpredictable. However, several questions remain. It is unclear whether: 1) pre-adolescents with high levels of childhood wariness who also experience peer victimization will exhibit heightened engagement in the amygdala, ACC, striatum, or insula during the anticipation or receipt of unpredictable relative to predictable peer feedback; and 2) this pattern of brain function will relate to concurrent social anxiety symptoms.

The current study uses fMRI to determine whether childhood wariness and exposure to peer victimization during pre-adolescence is associated with altered brain function during the anticipation and receipt of predictable and unpredictable evaluation from peers. Moreover, we predict that altered neural response to unpredictable social feedback is a mechanism by which exposure to peer victimization in pre-adolescence may potentiate pre-existing risk for the development of social anxiety conferred by early childhood wariness.

Method

Participants

All participants were enrolled in a larger longitudinal program of research that initially included 384 participants. These participants were randomly recruited at 2 years of age from the District of Columbia metro region (see Supplementary Materials for details about the difference between this cohort and two other cohorts our group has studied longitudinally). At the time of the scan all participants were 11 years of age.

At age 11, a subset of 70 participants were recruited to complete the current study (36 males; 60% Caucasian, 10% African American, 6% Hispanic, 20% Mixed/Other, 4% missing data; see Supplementary Materials for further details regarding sample selection). Data from 23 participants were excluded from analyses due to missing peer victimization ($N = 3$) or wariness ($N = 3$) data, low IQ ($N = 1$), excessive head motion during the fMRI scan ($N = 8$), failure to complete the fMRI scan ($N = 4$), technical failure ($N = 3$), and a structural brain abnormality ($N = 1$). This resulted in a final sample of 47. The 23 excluded participants did not differ from those included in the final sample based on age ($M = 10.91$, $SD = 0.38$; $t(68) = -1.96$, $p > .05$), wariness ($M = 0.11$, $SD = 0.63$; $t(64) = 1.14$, $p > .05$), or gender (Male $N = 14$, Female $N = 9$; $\chi^2(1) = .60$, $p > .05$). Data from this sample has been described previously in a report that relates social reticence to brain function (Jarcho et al., 2016); however, all analyses included here are new.

Measures

Early childhood wariness.—A composite score was generated based on maternal report of their child's shyness and social fear obtained at 2, 3, 4, 5, and 7 years of age ($\alpha = .83$; see Supplemental Materials Table S1 for cross-year correlations). Wariness was measured using age-appropriate parent-report questionnaires, which included the Toddler Behavior Assessment Questionnaire (TBAQ; Goldsmith, 1996) social fear scale at 2 and 3 years, and the Child Behavior Questionnaire (CBQ; Rothbart, Ahadi, Hershey, & Fisher, 2001) shyness scale at 4, 5, and 7 years. Questions from the TBAQ social fear and CBQ shyness scales are highly overlapping and have equivalent construct validity (Goldsmith, Buss, & Lemery, 1997) that measure slow or inhibited approach and/or discomfort in social situations

involving novelty or uncertainty. The 10-item scale from the TBAQ (social fear) has parents rate the frequency of their child's fear response to familiar and unfamiliar individuals (e.g., When your child was approached by a stranger when you and s/he were out, how often did your child show distress or cry?). Items are rated on a 7-point scale (1=never to 4=about half the time to 7= always). The 6-item scale from the CBQ (shyness) has parents rate their children's shyness (e.g., Often prefers to watch rather than join other children playing) on a 7-point scale (1=extremely untrue of your child to 7= extremely true of your child).

Peer victimization.—At age 11, participants completed the Kids in My Class (KIMC) questionnaire (Eunice Kennedy Shriver National Institute of Child Health and Human Development Study of Early Child Care and Youth Development). This questionnaire is based on previously validated and reliable work on peer relations (Kochenderfer & Ladd, 1996; Ladd, Kochenderfer, & Coleman, 1996). The 4-item peer victimization subscale asks participants to rate how often people in their class at school: pick on them, say mean things to them, say bad things about them to other kids, or hit them on a 5-point scale (1= never, 2 = hardly ever, 3 = sometimes, 4 = most of the time, 5 = always). Peer victimization was quantified by the mean participant response on these four items. Scores were used to create a dichotomized indicator of victimization status: low victimized (score ≤ 1.25) or high victimized (score > 1.50).

Social anxiety.—Symptoms of social anxiety were assessed at age 11 using a subscale on the self-report Screen for Child Anxiety Related Emotional Disorders (SCARED; Birmaher et al., 1999; Birmaher et al., 1997). The 7-item social anxiety subscale asks participants to rate statements about general social anxiety (e.g., I am shy), and symptoms elicited by unfamiliar people in particular (e.g., I feel nervous with people I don't know well.) on a 3-point scale (0 = not true or hardly ever true, 1 = somewhat true or sometimes true, 2 = very true or often true). Summed responses created a score of current social anxiety symptoms. We focused on self-report given discrepancies between parent and self-report on the SCARED (Rappaport, Pagliaccio, Pine, Klein, & Jarcho, 2017), and our interest in the correspondence between participant's experience with peer victimization and their feelings about their symptoms of anxiety – both of which may be less well detected by parental observation during adolescence.

Loneliness and social dissatisfaction.—Peer victimization is associated with greater loneliness and social dissatisfaction (Hawker & Boulton, 2000). Given the relatively low level of peer victimization in this sample, it was important to confirm that the high victimization had a more negative general psychosocial experience than the low victimized group. Loneliness and social dissatisfaction were assessed at age 11 using the Children's Loneliness and Social Dissatisfaction Scale (Asher, Hymel, & Renshaw, 1984). This 16-item questionnaire assess feelings of loneliness (e.g., I'm lonely), social inadequacy (e.g., It's hard to get other kids to like me), and a subjective estimate of social status (e.g., I don't have any friends) on a 5-point scale (5 = always, 4 = usually, 3 = sometimes, 2 = rarely, 1 = never). Summed responses created a score of loneliness and social dissatisfaction.

Procedure

Institutional human subjects review boards at the National Institute of Mental Health (NIMH) and University of Maryland approved all procedures. The Virtual School Paradigm models brain function elicited by the anticipation and receipt of predictable and unpredictable social evaluation during real-time interactions (see Jarcho et al., 2016; Jarcho, Leibenluft, et al., 2013 for details). Participants completed two visits to the NIMH. At the first visit, participants were told that they were going to be the “New Kid” at our Virtual School. They generated a cartoon avatar and personal profile they believed would be shown to “Other Students” who were purportedly age and gender-matched peers, but were in actuality pre-programmed avatars.

At a second visit, participants learned that two of these peers had a reputation for being ‘nice’, two for being ‘unpredictable’, and two for being ‘mean’ (Figure 1A). This information models real world contexts involving peers with distinct, known personalities (i.e., nice kids, unpredictable kids, bullies). Reputation comprehension was confirmed by participants rating the kind of person they thought each peer was on a 10-point Likert scale (Figure 1B). To eliminate confounds, peer reputations were randomly assigned to peer avatars across participants.

The Virtual School Paradigm was completed during fMRI across three runs (9-min per run), with two blocks per run. Each block began with random assignment to one of several classrooms (9-sec), populated by Other Student peers, who were randomly assigned to seats. Each run included 24 trials (See Figure 1 caption for trial details; N=72 trials total; N=24 trials per reputation type). Each trial included 3 events: (1) anticipation of social evaluation from each type of peer; (2) receipt of social evaluation, which was always positive or negative for nice or mean peers, respectively, and positive and negative half of the time for unpredictable peers; and (3) participant response to social evaluation (Figure 1C). Half of all social evaluative comments were generic (e.g. “We’d be friends in real life”, “I don’t like you”), and half were tailored to reference information obtained from each participant’s personal profile (e.g., “u r so cool - playing basketball is awesome!”, “only losers like Katy Perry”). After scanning, deception was assessed, and participants were debriefed. All participants were deceived by the task and no adverse events occurred. All participants were compensated monetarily for their participation.

fMRI Data Acquisition.—Data were acquired on a GE 750 3T-scanner (Waukesha, WI), at the NIH. Each functional run included, 231 image volumes, with 24 contiguous axial slices (in-plane resolution = 2.6×2.6 mm) obtained with a T2*-weighted echo-planar sequence (repetition time/echo time ([TR/TE]) = 2,300/25 ms, flip = 50° ; field of view (FOV) = 240 mm, matrix = 96×96). To facilitate anatomical localization and co-registration of functional data, a high-resolution structural scan was acquired (axial plane) with a T1-weighted magnetization- prepared spoiled gradient-recalled echo sequence (echo time/inversion time (TE/TI) = min full/425 ms, flip = 7° ; FOV = 220 mm, matrix = 256×256 , in-plane resolution, 1.2×1.2 mm).

Data Analyses

Validation Analyses.—All analyses were carried out in SPSS (Version 21, Armonk, NY: IBM Corp). An independent sample t-test was performed to confirm that high victimized peers reported a more negative psychosocial experience, as assessed by loneliness and social dissatisfaction, than low victimized peers. Measures of reputation comprehension were averaged across each pair of Other Student peers embodying each type of reputation (Nice, Mean, Unpredictable). To confirm that participants understood peer reputations and determine whether this comprehension was influenced by wariness and peer victimization, personality ratings for peers were analyzed using an analysis of co-variance (ANCOVA). This ANCOVA included peer reputation (nice, mean, unpredictable) as a within-subjects factor, and peer victimization (low, high) and wariness as between-subjects factors. Wariness was treated as a continuous covariate.

Response frequencies provided additional support that participants understood peer reputations and remain engaged in the task. Response frequency was averaged across each pair of Nice, Mean, and Unpredictable peers. To confirm the valence of social evaluation and the reputation of peers engendered distinct social experiences, and to determine if wariness and peer victimization interacted to bias frequency of participant response selection, we conducted an ANCOVA. This ANCOVA included type of social evaluation (predictably positive feedback from Nice peers, unpredictably positive feedback from Unpredictable peers, predictably negative feedback from Mean peers, unpredictably negative feedback from Mean peers) and participant response selection (You're nice, That's nice, That's mean, You're mean, *Thanks!!!*, ☹) as a within-subjects factor, and peer victimization (low, high) and wariness as between-subjects factors. Follow-up paired sample t-tests assessed differences in response frequency to: 1) positive feedback compared with negative feedback from all peer types; 2) positive feedback from Nice compared with Unpredictable peers; and 3) negative feedback from Mean compared with Unpredictable peers.

Preprocessing and Individual-level fMRI Analyses.—Preprocessing and individual-level fMRI analyses were conducted in AFNI (Cox, 1996). Standard preprocessing steps included slice-timing, coregistration, smoothing to 6-mm FWHM, spatial normalizing to standard Talairach space, and resampling, resulting in 2.5 mm³ voxels. Temporally adjacent TRs with a Euclidean Norm motion derivative >1.5 mm were censored.

Separate regressors were created for three groups of events: (1) anticipated social evaluation included three regressors for Nice, Mean, and Unpredictable peer reputations; (2) receipt of social evaluation based on peer reputation included four regressors consisting of positive evaluation from Nice peers, positive evaluation from Unpredictable peers, negative evaluation from Mean peers, and negative evaluation from Unpredictable peers; and (3) one regressor for participant response to evaluation, which was collapsed across response type and not further analyzed due to insufficient power. The classroom selection process that occurred at the beginning of each block was treated as a regressor of no interest.

Task-specific events were convolved with a duration-modulated boxcar regressor, spanning the duration of each event. Additional regressors modeled motion residuals and baseline

drift. This analysis produced a β -coefficient and t -statistic for each voxel and regressor, corresponding to percent signal-change maps.

Group-level fMRI analyses

Anatomically-defined regions of interest (ROI) from the Talairach and Tournoux and Eickhoff-Zilles atlases were used for all group-level analyses. ROIs were defined a priori based on studies of brain function (in samples distinct from the present participants) associated with wariness and the related construct of behaviorally inhibited temperament in youth (Bar-Haim et al., 2009; Fu, Taber-Thomas, & Perez-Edgar, 2017; Guyer et al., 2014; Guyer et al., 2015; Perez-Edgar et al., 2007) peer victimization (Rudolph et al., 2016; Schriber et al., 2018), and informed by the literature on unpredictability, threat, salience, and distress processing during social evaluation (see Guyer & Jarcho, 2018 for review). ROIs were bilateral striatum (caudate, nucleus accumbens, and putamen), amygdala (Talairach & Tournoux, 1988), dorsal ACC, and insula (Eickhoff et al., 2007). Average percent signal change for each ROI was extracted from individual level data and input into SPSS for statistical testing.

A series of ANCOVAs on ROIs were performed to determine whether relations between wariness and neural response during specific types of peer interactions varied depending on whether adolescents were low or high victimized. To test for 3-way interactions on brain function during anticipated peer evaluation, each ROI was subjected to a peer reputation (nice, mean, unpredictable) x peer victimization (low, high) x wariness ANCOVA. Thus, eight ANCOVAs were performed, one for each of the four ROIs in the left and right hemisphere of the brain. To test for 3-way interactions on brain function during the receipt of peer evaluation, each ROI was subjected to an evaluation type (predictably positive, unpredictably positive, predictably negative, unpredictably negative) x peer victimization (low, high) x wariness ANCOVA. Gender was included as a covariate of no interest in both analyses. To correct for the eight comparisons made during the anticipation and receipt of peer evaluation, ANCOVAs were required to achieve a Bonferroni corrected significance level of $p < .003$. Significant 3-way interactions were decomposed to isolate which reputation (anticipation) or evaluation type (receipt of evaluation) was driving effects, and whether these relations differed in low and high victimized youth.

Decomposition analyses therefore isolated specific reputations or evaluation types for which the brain response varied depending on early childhood wariness and exposure to current peer victimization. We then tested whether expression of social anxiety symptoms in low and high victimized youth varied depending on level of wariness and brain function within these previously isolated social contexts. Specifically, for each relevant social context, separate ANCOVAs tested wariness x brain function interactions on social anxiety symptoms in low and high victimized youth.

Results

Preliminary Analyses

Low ($N = 20$; 10 female) and high ($N = 27$; 13 female) victimized groups did not differ on mean levels of age ($M \pm SD$; low $11.15 \pm .42$; high $11.05 \pm .52$ years), wariness (low: 3.88 ± 1.01 ; high: 3.34 ± 1.00), pubertal status (low: $1.36 \pm .30$; high: $1.49 \pm .44$), or gender $\chi^2(1, N = 47) = 3.60, p > .05$. High relative to low victimized youth described themselves as having more social anxiety (low: 3.76 ± 3.27 ; high: 6.29 ± 4.06 ; $t(45) = 2.36, p < .05$).

Validation Analyses

High relative to low victimized youth described themselves as having more loneliness and social dissatisfaction (low: 26.40 ± 7.65 ; high: 34.95 ± 13.16 ; $t(45) = 2.73, p < .01$). This confirmed that victimization was associated with a more negative psychosocial experience.

Consistent with earlier reports (Jarcho et al., 2016; Jarcho, Fox, et al., 2013), there was a main effect of peer reputation on participants' initial ratings of peers $F(2,45) = 17.92, p < .001$. Nice peers ($M = 8.82, SD = 1.35$) were rated as "nicer" than Unpredictable peers ($M = 4.64, SD = 1.30$), who were in turn rated as "nicer" than Mean peers ($M = 2.54, SD = 1.32$). Contrasts were significant (p 's $< .001$) for each pair-wise comparison, thus confirming learned associations of peer reputations. No effects of peer victimization or wariness were observed (see Supplemental Table S2 for means separated by peer victimization group).

Also consistent with earlier reports, there was a robust effect of social evaluation on frequency of response type utilized $F(15,32) = 4.28, p < .001$. Positive evaluations yielded more positive than negative responses, and vice versa (all t 's $> 8.50, p$'s < 0.001). There were also effects of reputation. Compared with Unpredictable peers, positive evaluation from Nice peers elicited less frequent Avoidant, $t(46) = -2.83, p = 0.007$, and "That's nice" responses, $t(46) = -7.94, p < .001$, and more frequent "You're nice" responses, $t(46) = 10.93, p < .001$. Compared with Unpredictable peers, negative evaluation from Mean peers elicited less frequent "That's mean" responses, $t(46) = -2.93, p = .005$, and more frequent "You're mean" responses, $t(46) = 4.74, p < .001$. Frequency of avoidant and sarcastic responses did not vary. No effects of peer victimization or wariness were observed (see Supplemental Table S3 for means separated by peer victimization group).

fMRI analyses

Anticipated social evaluation.—No significant interactive effects of reputation, peer victimization, and wariness on brain function were observed.

Receipt of social evaluation.—There were interactive effects of peer evaluation, peer victimization, and wariness on right amygdala activation $F(3,44) = 5.32, p = .002$. This was primarily driven by a peer victimization $\times$ wariness interaction on brain function in response to positive social evaluation from unpredictable peers $F(1,46) = 6.64, p = 0.01$. Specifically, among high victimized youth, greater wariness was associated with greater amygdala activity. No relation was observed among the low victimized youth (see Figure 2). Interactions were not observed in the other peer evaluation conditions. Although main and

interaction effects in other ROIs failed to survive Bonferroni correction, similar 3-way peer evaluation x peer victimization x wariness interactions emerged in bilateral striatum and left insula (all F 's > 3.00 , p 's < 0.05).

We then tested whether expression of social anxiety symptoms in low and high victimized youth varied depending on level of wariness and right amygdala response to positive social evaluation from unpredictable peers. Significant interaction effects emerged for high $F(1,26)=6.67$, $p < .05$, but not low victimized youth $F(1,19)=3.31$, $p > .05$. Specifically, among high victimized youth, greater wariness and amygdala activity were associated with more severe symptoms of social anxiety (see Figure 3).

Discussion

This study generated two main findings. First, early childhood wariness differentially related to pre-adolescents' neural response to peer evaluation, depending on concurrent exposure to peer victimization. Specifically, among highly victimized youth, greater wariness was associated with higher levels of engagement in the right amygdala during the receipt of positive evaluation from unpredictable, compared to predictable, peers. Second, in participants who experienced peer victimization, the relation between early childhood wariness and expression of social anxiety symptoms were dependent on right amygdala engagement during peer evaluations. Thus, the brain-based relation between early childhood wariness and subsequent expression of social anxiety symptom expression was linked to exposure to peer victimization. These results support a diathesis–stress model (Steinberg & Avenevoli, 2000) for the development of social anxiety. Such a model predicts that wariness is a vulnerability that interacts with exposure to the social stress of peer victimization, to influence brain function. Brain function, in turn, may serve as a potential mechanism that supports the expression of social anxiety symptoms.

A growing number of fMRI studies suggest that wariness and associated temperamental traits in early childhood underlie altered patterns of neural response in adolescence (e.g., Fu et al., 2017; Guyer et al., 2014; Guyer et al., 2015) that persist into adulthood (e.g., Jarcho, Fox, et al., 2013; Jarcho et al., 2014; Schwartz et al., 2012). Although most studies suggest that these alterations are associated with the development of social anxiety disorder, few specifically test relations between brain function and the expression of social anxiety symptoms (Fu et al., 2017). Our results suggest wariness may serve as a behavioral marker of brain-based vulnerability to social stress, such as peer victimization. It is plausible that this vulnerability may be particularly detrimental early in adolescence. During this sensitive developmental phase, stress reactivity is heightened (Spear, 2009) and social evaluation is highly salient (Brown & Larson, 2009) as youth learn to implement complex, peer-based patterns of behavior that provide the foundation for social behavior in adulthood (Nelson et al., 2016). In this way, disruption in neural response to peer evaluation may have a lasting impact on social cognition and behavior. Thus, early childhood wariness, when combined with exposure to social stressors, was associated with neural responses to peer evaluation, which may increase risk for psychopathology in pre-adolescents.

The interactive effects of early childhood wariness and pre-adolescent peer victimization on amygdala activity were specific to the receipt of social evaluation. These effects were driven by a differential response to unpredictably positive social evaluation. Relative to low victimized youth, high victimized pre-adolescents with higher levels of wariness exhibited greater amygdala response to unpredictable, compared to predictable, positive social evaluation. Our prior work in this subsample showed that social reticence was associated with heightened engagement of the dorsal ACC and insula during anticipated social evaluation, and amygdala activity during the receipt of unpredictably negative social evaluation (Jarcho et al., 2016). Thus, it is somewhat surprising that interactive effects of wariness and peer victimization were not observed during anticipated social evaluation, and those that emerged during the receipt of feedback occurred during unexpected positive, rather than negative, social evaluation. This is particularly puzzling given that being bullied victimized may map more closely onto the experience of receiving unexpected negative social evaluation. Three factors may have contributed to this difference. First, due to missing data from six individuals, only a subset of participants from our prior work were included in analyses for this paper. Second, wariness was operationalized in a more focused way by using a composite score derived from maternal report. In our prior work, we focused on social reticence, which was operationalized as a composite score derived from a combination of maternal report and observational data. Finally, from a conceptual perspective, this discrepancy highlights the importance of using a multifactorial approach when testing relations between brain function and risk for psychopathology. Exposure to stressors, such as peer victimization, may not simply potentiate or dampen brain function typically associated with a primary risk factor. Instead, the effect of this exposure may cause a shift in the neurocognitive mechanisms youth engage during social interactions. For example, the direction of effects observed during receipt of unexpected positive social evaluation may be partially explained by novelty effects specific to victimized youth. Prior studies have shown that wariness and associated temperamental traits in early childhood predict heightened amygdala response to novelty, particularly in the social domain (e.g., Blackford, Avery, Shelton, & Zald, 2009; Schwartz et al., 2012). For high, relative to low, victimized youth with childhood wariness, the receipt of unpredictable positive social evaluation may be more unexpected and perceived as less common. This is consistent with prior work demonstrating that socially anxious youth had a heightened striatal response specifically to the receipt of unexpected, relative to expected, positive social evaluation (Jarcho et al., 2015). Altered reactivity was, in turn, associated with impaired recall of unexpected positive evaluations. While the striatum is often implicated in reward learning, the amygdala is also implicated in coding for salience of positive and negative prediction error outcomes (Belova, Paton, Morrison, & Salzman, 2007; Metereau & Dreher, 2013), and is necessary for successful reinforcement learning in unpredictable contexts (Janak & Tye, 2015). In the present study, neural mechanisms implicated in learning were not directly assessed. Indeed, participants learned the reputation of each peer prior to undergoing scanning. This may help explain why striatal response commonly associated with prediction error-based learning failed to emerge. However, reinforcement learning may have still been possible in this context. Although further studies are needed to directly test these relations, it is possible that heightened amygdala response may reflect perturbed reinforcement processing in victimized adolescents with higher levels of wariness. This is consistent with studies that demonstrate

youth exposed to other forms of physical and psychological stressors have deficits in reinforcement-based learning (Hanson et al., 2017; Harms, Shannon Bowen, Hanson, & Pollak, 2017). Failure to learn from unexpectedly positive outcomes may contribute to social avoidance and bias expectations that novel and unpredictable social encounters will go poorly. These hallmark symptoms of social anxiety may be promoted and sustained through elevated amygdala responding. In this context, it is also worth noting that individuals with low wariness displayed a blunted response to positive peer feedback from unpredictable peers. This may reflect a relative disengagement indicative of differential social learning in response to peers whose behavior is inconsistent.

The present work builds on prior studies that support the idea that early childhood wariness and related temperamental traits make youth more vulnerable to contextual risk factors. For example, authoritarian, relative to authoritative parenting styles have a negative impact on social development (Steinberg, 2001), and the effects are stronger in children with high relative to low early childhood wariness (Degnan, Almas, & Fox, 2010; Rubin, Burgess, Dwyer, & Hastings, 2003). Moreover, authoritarian parenting in those with high early childhood wariness is associated with altered neural response to social evaluation in adolescence (Guyer et al., 2015). This suggests wariness may increase the likelihood that an environmental stressor will cause perturbations in brain function during social interactions. A similar relation was found here with peer victimization. This underscores the importance of considering contextual risk factors when testing neural mechanisms implicated in social cognition (Schriber & Guyer, 2016). Using a multivariate approach that simultaneously considers traits and social contexts may provide a more nuanced understanding of how individual differences influence the brain's response to the social world.

Although self-reported levels of victimization were relatively low in this sample, high relative to low victimized participants reported greater loneliness and relationship dissatisfaction. This, coupled with the brain-based results, suggest that even mild victimization is associated with broader social distress and alterations in neurophysiological functioning. This is particularly troubling given the high prevalence rate of peer victimization, and the increased risk for long-term negative psychosocial outcomes for adults who experience peer victimization during childhood and adolescence (e. g., Copeland, Wolke, Angold, & Costello, 2013; Takizawa et al., 2014). Yet, there are marked individual differences in long term outcomes in those who are exposed to peer victimization. Our data suggest such individual differences may relate to effects of temperamental risk factors, such as early childhood wariness, on neural function. Thus, in the context of targeting victimized youth for interventions, it may be important to obtain information about psychosocial history, including wariness, to best evaluate the potential consequences of even minor exposure to peer victimization.

Despite its strengths, this study has several limitations. First the relatively small sample size requires results to be replicated. Our primary analyses controlled for gender, but we were unable to perform other gender-based analyses due to sample size. It is critical that replication studies have sufficient power to test gender differences given that socially withdrawn versus non-withdrawn males experience more peer victimization (Gazelle, Peter, & Karkavandi, 2014; Rubin & Barstead, 2014), and there are gender-based differences in the

brain's response to social evaluation (e.g., Distefano et al., 2018; Guyer et al., 2009; Vrtka et al., 2014). Although many participants reported experiencing bullying, its severity was relatively mild. This, coupled with a relatively small sample size and task differences, may help explain the inconsistency between this and prior studies in which ACC activity was associated with exposure to peer victimization (Rudolph et al., 2016; Schriber et al., 2018; Will et al., 2016). Because of the sample characteristics, our measure of bullying was used as a dichotomous indicator of peer victimization. While this approach was warranted given the skewed distribution and preponderance of responses at an extreme end of the distribution (i.e., none), this strategy results in a loss of information about variation among the victimized youth. With a larger sample that is better stratified and normally distributed, peer victimization could be treated as a continuous variable. This would allow for inferences about potential dose response relations between peer victimization, early childhood wariness, brain functioning, and social anxiety.

Another limitation is that only concurrent peer victimization was considered. Given the small sample size, it was impossible to test for differences related to peer victimization in childhood, relative to current peer victimization. Larger samples and repeated prospective assessments are needed to determine whether continuity or discontinuity in exposure to peer victimization across development differentially influences brain function and expression of social anxiety. Prospective work that includes the acquisition of fMRI data at multiple points is also needed to determine if alterations in brain function are a cause or consequence of wariness, peer victimization, and/or social anxiety. Despite the longitudinal nature of the present study, such relations cannot be determined without longitudinal acquisition of neuroimaging data.

In conclusion, pre-adolescents exposed to peer victimization exhibit atypical amygdala engagement during the receipt of social evaluation, depending on their level of wariness in social contexts early in childhood. These relations, in turn, relate to expression of pre-adolescent social anxiety symptoms. Results can be interpreted using a diathesis-stress model that suggests brain function is a mechanism by which exposure to peer victimization in adolescence may potentiate the risk for development of social anxiety conferred by wariness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig 1. The Virtual School paradigm.

(A) Participants learn the reputation of 6 gender-matched “Other Students” by viewing their avatars, chat names, comments and ratings purportedly provided by “prior subjects.” (B) Reputation comprehension is assessed. (C) **1:** Each trial is preceded with an inter-trial interval (0–8 sec; M=4 sec). **2:** Participants are cued to anticipate social evaluation when the word “Typing...” appears above one of the Other Students (2–4 sec; M=3 sec). **3:** An evaluative comment is provided (2–10 sec; M=6 sec). Nice and Mean peers provide 100% positive or negative evaluations, respectively. Unpredictable peers provide 50% positive and negative evaluations. **4:** Participants then use a button box to respond (4-sec). **5:** This response is purportedly delivered to the Other Students when it is on the screen (2-sec). Responses are positive (You’re nice, That’s nice), negative (That’s mean, You’re mean), sarcastic (*Thanks!!!*), or avoidant (☹).

Fig 2. Associations between wariness, peer victimization, and right amygdala activity during receipt of social evaluation.

Graphs depict correlations between early childhood wariness and brain function for each type of social evaluation to illustrate factors contributing to the reputation x wariness x peer victimization interaction.

Fig 3. Associations between social anxiety, wariness, and right amygdala activity during unpredictably positive social evaluation in high and low victimized participants.

Graphs depict predicted right amygdala activation to illustrate wariness x right amygdala brain function interactions within low and high peer victimized groups. Wariness was used as a continuous variable in analyses, but for illustrative purposes, selected wariness levels are plotted. High and low wariness are depicted at ± 2 SD from the mean, respectively.