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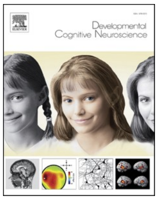

Social anxiety and age are associated with neural response to social evaluation during adolescence☆

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ABSTRACT

Adolescence is a sensitive period for the development of adaptive social behaviors and social anxiety, possibly due to aspects of brain development. However, research is needed to examine interactions among age, social anxiety, and social dynamics previously shown to influence neural responding. The current functional magnetic resonance imaging (fMRI) study examines brain function in 8–18 year-olds with varying levels of social anxiety. Interactions are examined among age, social anxiety, and two key task factors: valence and predictability of social interactions. Results demonstrate age, social anxiety severity, and each of the two key task-based factors interact to predict neural response in the caudate, middle and superior temporal gyri. In particular, among adolescents less-than 13 years of age, higher social anxiety predicted *greater* responding to unpredictable *negative* evaluations. However, in this same age group, the opposite pattern emerged during receipt of unpredictable *positive* evaluations, with *less* neural response in more anxious youth. Adolescents aged 13 and older overall showed less robust effects. We discuss these findings in terms of age- and anxiety-related differences in socio-emotional processing.

Among the many adolescent transitions, social changes are particularly notable. A marked shift occurs in peer relations (for reviews, see Blakemore and Mills, 2014; Crone and Dahl, 2012; Nelson, 2017), which coincides with age-related increases in social anxiety (Wittchen et al., 1999). While such anxiety can be normative, it also can predict risk for long-term problems (Pine et al., 1998; Walczak et al., 2018). Because adolescence is a critical window for socioemotional development (Blakemore and Mills, 2014; Nelson et al., 2016), social anxiety may constrain normative development and adversely affect functioning. Given the dramatic changes in brain function that occur across childhood and adolescence, it is important to map neural responses during peer interactions as a function of age and social anxiety during this period. Moreover, these relationships are likely to be complex, given adolescent brain response is influenced by features specific to the social interaction (e.g., Masten et al., 2009; Jarcho et al., 2015). Mapping neural responses during peer interactions may illuminate how brain mechanisms relate to adolescent social development. The present study used a peer-interaction task that manipulates key social factors, the predictability and valence of social evaluations, on a trial-by-trial basis. The study used this task to characterize brain responses among youth with varying levels of social anxiety spanning the adolescent age range.

During adolescence, social experiences engage multiple brain regions, including those involved in processing salient, affective social information (e.g., dorsal anterior cingulate, dACC; insula, striatum,

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amygdala) and cognitive aspects of social behavior (e.g., superior temporal gyrus, STG; temporoparietal junction, TPJ; for review see, Blakemore and Mills, 2014; Crone and Dahl, 2012). We broadly refer to these as socioemotional-processing regions. Heightened engagement of brain regions implicated in socioemotional processing in adolescents, relative to both children and adults, has been shown in response to both positive and negative social stimuli (e.g., Chein et al., 2011; Dreyfuss et al., 2014; Pfeifer et al., 2011; Smith et al., 2018a). However, fMRI-based (functional magnetic resonance imaging) studies often characterize adolescents as a homogenous group (e.g., Jarcho et al., 2012; Smith et al., 2015, 2018b;), or dichotomize youth based on discrete age groups (e.g., Gunther-Moor et al., 2012; Güroğlu et al., 2011; Padmanabhan et al., 2011). This approach fails to consider the numerous neural and psychosocial changes that occur during discrete phases of adolescence. For instance, the brain undergoes major reorganization during adolescence such that different regions implicated in social processing mature with distinct chronometry (e.g., Dosenbach et al., 2010; Giedd et al., 1996; for review see, Crone and Dahl, 2012). Further, regardless of biology, for many adolescents in Western settings, peer interactions in the elementary, middle, and high school years qualitatively differ (e.g., different levels of adult supervision and structured time, changes in emphasis on romantic relationships, peer group differentiation becoming more flexible and less hierarchical; Steinberg, 2019). Thus, treating age as a dimensional factor in the context of the broadly defined adolescent window may illuminate developmental inflection points when peer interactions begin to differentially engage particular brain regions implicated in socioemotional processing.

Finally, specific features of a social experience may shape neural response during adolescence. Some suggest that adolescence involves behavioral and neural hypersensitivity to all social stimuli (e.g., Foulkes and Blakemore, 2016). Indeed both positive and negative social stimuli elicit heightened brain response during adolescence (e.g., Chein et al., 2011; Dreyfuss et al., 2014; Pfeifer et al., 2011; Smith et al., 2018a). However, further work is needed to dissect nuances in these "sensitivity" effects. For instance, the predictability of social encounters may influence neural responses. In non-social contexts, unpredictable outcomes differentially elicit neural responses (e.g., Berns et al., 2001; Koppe et al., 2014) – particularly in adolescence (e.g., Cohen et al., 2010; Jarcho et al., 2015). Indeed, most social tasks used to probe brain responses utilize unpredictable events (e.g., Jarcho et al., 2013; Lau et al., 2012; Guyer, McClure-Tone, Shiffrin, Pine, & Nelson, 2009). However, few studies contrast the response to such events with the response to predictable outcomes, which is important given work suggesting that adolescents process unpredictable outcomes differently (e.g., Cohen et al., 2010; Jarcho et al., 2015; van den Bos, Cohen, Kahnt, & Crone, 2012).

The current study extends findings from typical social development to understanding atypical trajectories. This is important since social anxiety symptoms and onset of social anxiety disorder increase dramatically from 10 to 17 years of age (Knappe et al., 2015). Like other factors targeted in the current report, past research suggests that social anxiety also influences the effect of peer interactions on the adolescent brain (for review, see Caouette and Guyer, 2014). Indeed, past work suggests that heightened neural responses at particular ages may be further potentiated in groups with or at risk for anxiety (e.g., Bolling et al., 2011; Guyer et al., 2009, 2012; Lau et al., 2012; Jarcho et al., 2015, 2016; Masten et al., 2009; Will et al., 2016). As in typically developing youth, heightened brain response in anxious youth may also be shaped by predictability and/or valence of social encounters (for review, see Jarcho et al., 2013). While there is considerable overlap in brain regions implicated in socioemotional processing (e.g., dACC, insula, striatum, amygdala, STG, TPJ) and those implicated in both age- and anxiety-related responses during social information processing (e.g., Chansky and Kendall, 1997; Gunther-Moor, van Leijenhorst, Rombouts, Crone, & Van der Molen, 2010; Guyer et al., 2008; Guyer, McClure-Tone, Shiffrin, Pine, & Nelson, 2009; Guyer et al., 2014; Jarcho et al., 2015; Sebastian et al., 2011), surprisingly few pediatric brain-imaging studies consider the interactive effects of age and anxiety. The limited research suggests that anxious adolescents demonstrate differential engagement of socioemotional processing regions, compared to non-anxious adolescents, as well as anxious and non-anxious adults (e.g., Gunther-Moor et al., 2010; Jarcho et al., 2015; 2016; Swartz et al., 2014a, b). It remains unclear if there are specific points during adolescence when social experiences differentially engage brain regions as a function of social anxiety severity.

Using a dynamic social paradigm, the current study maps interactive effects of social anxiety, age, and predictability on neural responses to positive and negative peer evaluations. Precise mapping may isolate nuances in "sensitivity" effects often ascribed to adolescent neural response to social experiences. To this end we utilize the Virtual School Paradigm (Clarkson et al., 2019; Jarcho et al., 2013, 2016), which quantifies participants' brain response while they anticipate and receive predictable or unpredictable social evaluations from purported peers. By varying the predictability and valence of the social evaluations, we parse responses during distinct social experiences. Further, studying more than 100 youth across a wide range of ages (8to 18 years-of-age) and social anxiety symptoms enables both age and anxiety to be treated dimensionally, allowing for greater precision and statistical power in isolating how these variables interact.

We predicted that age, severity of social anxiety, valence, and predictability of social interactions influence neural engagement during the anticipation and receipt of social evaluations. Given previous findings, we expected interactions in brain regions involved in socioemotional processing (e.g., dACC, insula, striatum, amygdala, STG, TPJ) during social interactions with peers who provide distinct types of evaluations (i.e., predictable or unpredictable, positive or negative). In particular, we hypothesized that unpredictable social experiences differentially engage these brain regions implicated in adolescents with higher levels of anxiety during both anticipation and receipt of social evaluations. We further predicted that this would be potentiated in younger adolescents due to their relatively limited experience with more complex adolescent social experiences that emerge over the course of adolescence (e.g., different levels of adult supervision and structured time, changes in emphasis on romantic relationships, peer group differentiation becoming more flexible and less hierarchical; Steinberg, 2019). Identifying specific age points where social anxiety severity differentially impacts brain responses during social experiences may inform age-specific prevention and intervention programs aimed at promoting adaptive, and/or reducing maladaptive, social behavior across this phase of life.

1. Method

1.1. Participants

Participants were aged 8–18 years (N = 128). We utilized a large age range to examine age-specific effects and to capture the broad range of ages during which anxiety symptoms increase (Knappe et al., 2015). Procedures were approved by the National Institute of Mental Health Institutional Review Board. Participants were recruited from the Greater Washington DC area. Parents and youth provided written consent and assent. Participants received up to $165 for their participation. Approximately half of the participants (N = 57; 17 males) met DSM-5 criteria for at least one anxiety disorder (assessed by KSADS, Kaufman et al., 1997). The rest were diagnosis free. Participants who met criteria for an anxiety disorder also received treatment as part of their participation. Exclusionary criteria included: any comorbid non-anxiety

Table 1
Demographic Information.

Variable	All Participants (N = 112)	Anxious (N = 57)	Healthy (N = 55)
Age			
M	12.81	12.22	13.43
SD	2.80	2.86	2.61
Tanner Stage (Pubertal Development Scale score)			
M	2.92	2.55	3.31
SD	1.45	1.40	1.40
Sex			
Female			
N (%)	75 (67)	40 (70.2)	35 (63.6)
Male			
N (%)	37 (33)	17 (29.8)	20 (36.4)
SES (Household Income)			
< $24,999	8 (7.1)	2 (3.5)	6 (10.9)
$25,000-$59,999	8 (7.1)	2 (3.5)	6 (10.9)
$60,000-$89,999	10 (8.9)	7 (12.3)	3 (5.5)
$90,000-$179,999	48 (42.9)	24 (42.1)	24 (43.6)
>$180,000	32 (28.6)	21 (36.8)	11 (20.0)
Unknown/ Missing	6 (5.4)ss	1 (1.8)	5 (9.1)
Race			
Caucasian			
N (%)	63 (56.3)	41 (71.9)	22 (40)
African American			
N (%)	26 (23.2)	5 (8.8)	21 (38.2)
Asian			
N (%)	4 (3.6)	1 (1.8)	3 (5.5)
Pacific Islander			
N (%)	2 (1.8)	1 (1.8)	1 (1.8)
Multiple Races			
N (%)	13 (11.6)	7 (12.3)	6 (10.9)
Unknown			
N (%)	4 (3.6)	2 (3.5)	2 (3.6)
Ethnicity			
Hispanic or Latino			
N (%)	14 (12.5)	7 (12.3)	7 (12.7)
Anxiety Diagnosis			
Generalized			
N (%)	—	47 (82.5)	—
Social			
N (%)	—	44 (77.2)	—
Separation			
N (%)	—	26 (45.6)	—
Specific Phobia			
N (%)	—	19 (33.3)	—

Note: 48 (84 %) of the anxious participants met criteria for more than one anxiety disorder.

psychiatric disorders, use of medications, or any fMRI contraindications, such as braces. Of those who completed the task, 16 participants were excluded due to: lack of deception regarding the social context manipulation ($N = 9$)[1], excessive head motion during the scanning session (> 20 % censoring rate; $N = 4$), and technical errors/issues ($N = 3$). The resulting sample consisted of 112 youth (37 males, age: $M = 12.8$, $SD = 2.8$). Full demographics are provided in Table 1.

1.2. Social anxiety composite

Given our interest in examining social anxiety dimensionally, we employed a confirmatory factor analysis using multiple self-report measures that quantify distinct symptoms of social anxiety. This allowed for a more robust and reliable characterization of a symptom complex not fully captured by a single indicator (Kim and Bentler, 2006), consistent with recent emphasis on a dimensional approach to psychiatric assessment (Insel et al., 2010). Specifically, total scores on the self-report Screen for Child Anxiety Related Disorders (SCARED) Social Anxiety subscale (Birmaher et al., 1997), the Fear of Negative Evaluation Scale (Watson and Friend, 1969), and the Social Anxiety Scale (La Greca and Lopez, 1998) were tested as three observed variables reflecting one common latent variable: social anxiety (Mplus; Muthén and Muthén, 2017). All three measures had high factor loadings (SCARED = .80, FNE = .80, SAS = .84, all $ps<.001$) on the latent social anxiety factor (See Fig. 1). A standardized factor score was extracted for each participant, with higher factor scores indicating more severe social anxiety. This factor score, the Social Anxiety Composite (SA), was used as a continuous variable in all behavioral and neuroimaging analyses. SA scores were not correlated with age ($r = .10$, p=ns), pubertal status ($r = .08$, p=ns), or IQ ($r = .00$, p=ns). Further, there were no sex differences in SA, $t(110) = 1.59$, p=ns.

1.3. Procedure

Participants attended two visits at the National Institute of Mental Health as part of the Virtual School Paradigm (Jarcho et al., 2013). During the first visit, participants were told that at the next visit, they would be the “new kid” at a virtual school and would be interacting with gender-matched “other students” who had all previously participated in the study. As part of being the new kid, they were asked to create a computer-based avatar and profile describing their interests. Participants were told these items would be shown to the other students before the next visit so that they could chat with them about the content of their profile. In reality, there were no other students; all communications were computer-generated.

During the second visit, participants were introduced to each of the six students with whom they believed they would communicate. Descriptions of each student, purportedly provided by other new kids, enabled participants to learn student reputations prior to their interaction. This was intended to minimize between-subject variability in learning rates and mimic real-world social situations where the reputation of peers is often known prior to any social interaction. Participants learned that two students had positive reviews (“Predictably Nice”), two had negative reviews (“Predictably Mean ”), and two had mixed reviews (“Unpredictable ”). During the task, the students interacted with the participant in a manner consistent with their reviews. Specifically, Predictably Nice students provided 100 % positive feedback, Predictably Mean students provided 100 % negative feedback, and Unpredictable students provided 50 % positive and 50 % negative feedback. The “other students” avatars were randomly assigned to a reputation for each participant (see Fig. 2a). Participants were then asked to provide ratings for each student on a 10-point Likert scale (1=*mean*, 10=*nice*). There was a middle anchor of 5 (*can’t tell*) in the event that participants were unsure.

Participants then underwent fMRI scanning while completing three,

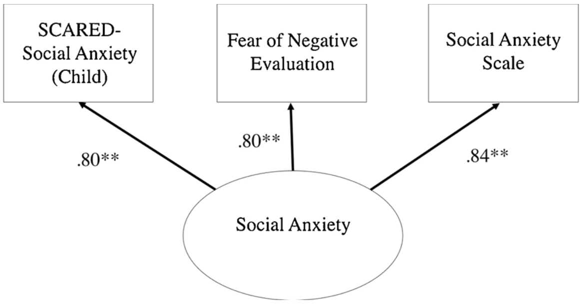

Fig. 1. Latent Factor Model. Results indicated that each variable was significantly associated with the latent factor (social anxiety). **$p<.001$.

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[1] Participants were not included if they reported not believing that they were interacting with other adolescents during the debriefing. Deception was assessed by a research assistant prior to any data analysis.

nine-minute runs of the Virtual School task. Each trial of the task included three phases: 1) an anticipatory phase in which participants waited to receive feedback from other students, 2) a feedback phase in which they received the evaluative feedback, and 3) a response phase in which they could respond to the feedback by selecting one of six response options (“That’s Nice,” “You’re Nice,” “That’s Mean,” “You’re Mean,” “∅” allowing the participant to avoid responding, and “Thanks… NOT!!” representing a sarcastic response). Each response was followed by an inter-trial interval (0–8 seconds, *M* = 4 s) before the next trial began (see Fig. 2b).

We collected three, nine-minute functional runs (47, 3-mm axial slices, 0-mm gap, TE = 25, TR = 2.3 s, flip = 50, 24 FOV, 96 × 96 in-plane matrix). Each run included 2 blocks that began with a change in classroom and other students being randomly assigned to a new seating position. Runs consisted of 24 trials (8 per student reputation).

1.4. *Data analyses*

1.4.1. *Pre-scan peer ratings*

Participant Likert ratings for peers were analyzed with a repeated-measures generalized linear model (GLM). SA and Age were entered as continuous between-subject variables, while Predictability (Predictable, Unpredictable) and Valence (Negative, Positive) were entered as repeated, within-subject variables.

1.4.2. *Behavioral responses during the virtual school paradigm*

Participants’ responses to feedback were analyzed with a repeated-measures GLM. Frequency of responding (i.e., the percentage of time a response was used) was used as the dependent variable in all behavioral analyses. SA and Age were entered as continuous between-subject variables, while Predictability (Predictable, Unpredictable), Valence (Negative, Positive), and response option were entered as repeated, within-subject variables.

1.4.3. *fMRI analyses*

All imaging analyses were conducted using AFNI (Cox, 1996). Standard preprocessing procedures were used (afni.proc.py) including: despiking, slice-time correction, coregistration, spatial smoothing with a 6-mm smoothing kernel (FWHM) and warping to standardized Talaraich space. TRs with greater than 1-mm of movement were censored. All participants included in the analyses had more than 80 % of TRs in each run following censoring (average percentage of censored TRs: *M* = 4.82, *SD* = 4.89). Individual-subject GLMs included 10 regressors: a) anticipation of each type of student (Predictably Positive, Predictably

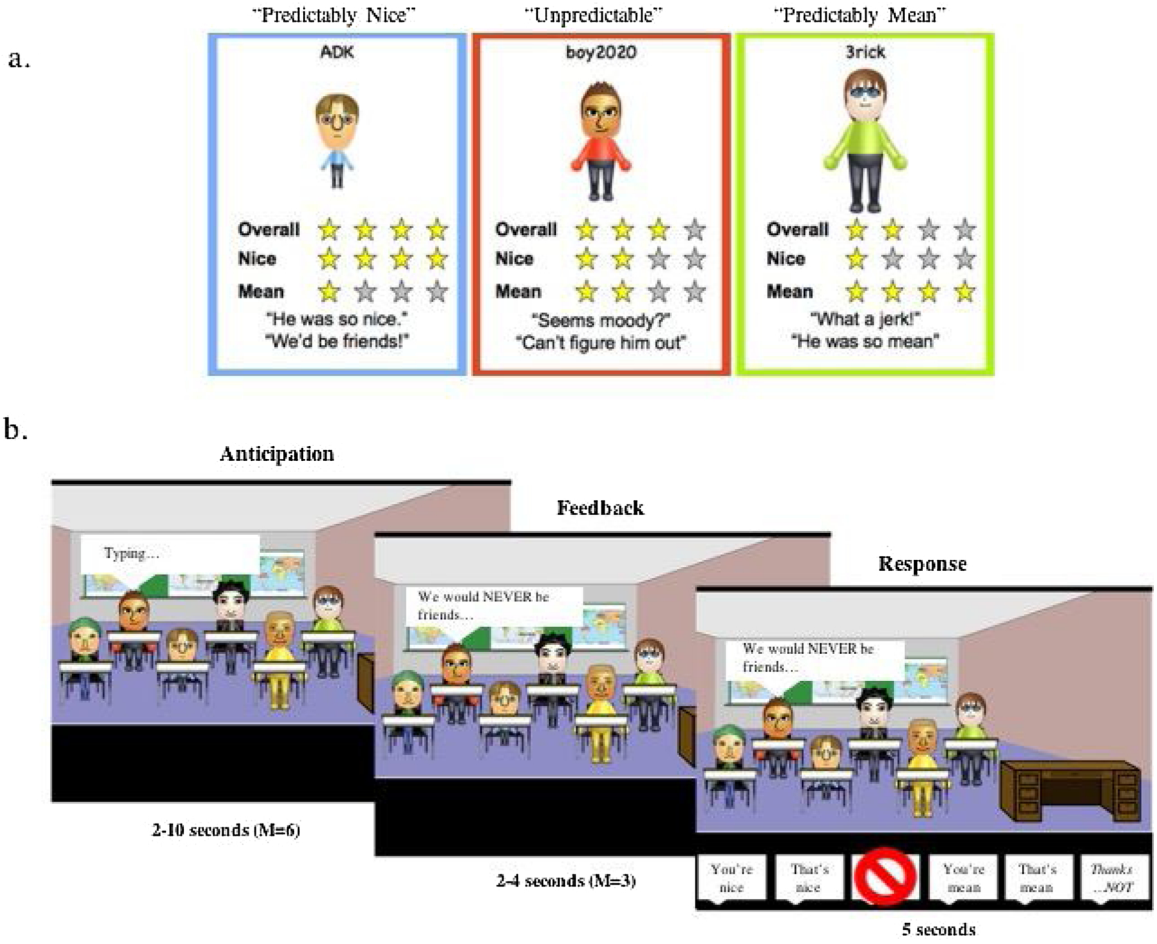

Fig. 2. Virtual School Paradigm. a). Prior to beginning the task participants learned the reputations of 6 “other students” who either received positive (“Predictably Nice”), negative (“Predictably Mean”), or mixed (“Unpredictable) reviews from other participants. b). In the Virtual School each trail began with an anticipatory phase (2–10 seconds, M = 6 s). Participants saw a comment bubble appear above one of the other student’s avatar. The word “Typing…” flashed on and off as they awaited a comment from that student. The feedback phase (2–4 seconds, M = 3 s) began when the peer’s comment appeared. Comments were preprogrammed into the task and randomly selected for each avatar (based on reputation). Participants then had the opportunity to choose from one of 6 response options (5 s). These responses were positive (“You’re nice,” “That’s nice”), negative (“You’re mean,” “That’s mean”), and sarcastic (“Thanks…NOT”). There was an additional “Avoidant” response (Æ) where participants could choose not to respond to the student’s comment. Participants were told that the response that they chose would be shown to the other students in the classroom (2 s). Each response was followed by an inter-trial interval (0–8 seconds, M = 4 s) before the next trial began.

Negative, Unpredictable), b) receipt of feedback from students (Predictably Positive, Predictably Negative, Unpredictably Positive, Unpredictably Negative), and c) regressors of non-interest: classroom choice (i.e., time between blocks), response period, and motion parameters. Regressors were time-locked to the onset of each phase and convolved based on the duration of that event.

Group-level analysis for the anticipation phase was analyzed using mixed-effects models (3dMVM in AFNI). In this model, SA and Age were entered as continuous between-subject variables and student reputation was entered as a repeated, within-subject variable (Predictable Nice, Predictable Mean, Unpredictable).

Group-level analysis for the feedback phase was analyzed using mixed-effects models (3dMVM in AFNI). In this model, SA and Age were entered as continuous between-subject variables and Predictability (Predictable, Unpredictable) and Valence (Negative, Positive) were entered as repeated, within-subject variables.

Output maps were masked to include grey matter and voxels where at least 90 % of the participants had signal to avoid Type I errors in regions where signal dropout occurred. Significance was determined based on AFNI's 3dClustSim program. The spatial autocorrelation function (2-sided thresholding) was utilized to obtain accurate estimates of spatial smoothing across the brain (Cox et al., 2017). To achieve a voxel-wise probability threshold of $p < .005$ and family-wise error rate of $\alpha = 0.05$, cluster contiguity was set to 101 voxels.

2. Results

2.1. Pre-scan peer ratings

All participants accurately identified the student reputations (see Supplement Materials for details). While there was no relation between these ratings and SA, a significant Age X Reputation interaction emerged ($F(2, 216) = 9.40$, $p < .001$, $\eta_p^2 = .08$). Correlations between Age and rating for each Reputation type were performed to decompose this interaction. Younger participants provided more "extreme" ratings for Predictably Mean (i.e., peers were rated as meaner; r=-.32, $p < .001$) and Predictably Nice peers (i.e., peers were rated as nicer; $r = .25$, $p = .007^2$; See Supplementary Fig. 1).

2.2. Behavioral responses during the virtual school paradigm

In line with prior reports (Jarcho et al., 2013, 2016), a significant Valence X Response interaction emerged ($F(5, 540) = 16.68$, $p < .001$, $\eta_p^2 = .13$). When decomposed, we confirmed participants' utilization of appropriate response options (see Fig. S1). In particular, participants used "Nice" responses ("That's Nice" and "You're Nice") more often for positive feedback ($t(111) = 50.25$, $p < .001$) and negative responses ("That's Mean," "You're Mean") more often for negative feedback. Sarcastic ($t(111) = 11.50$, $p < .001$) and "Avoidant" ($t(111) = 9.15$, $p < .001$) responses were also used more often for negative, compared to positive, feedback. There was also a significant main effect of Response ($F(5, 540) = 3.27$, $p = .006$, $\eta_p^2 = .03$), such that participants used "That's Nice" and "You're Nice" more often than other responses, suggesting that there is less variability in responding to positive, compared to negative, feedback.

There were several age-related effects (see Supplemental Table S1). Post-hoc analysis demonstrated that all age effects were driven by older participants using the Sarcastic response option more often during negative feedback (regardless of predictability) compared to younger participants. There were no main or interactive effects of SA on task behavior.

2.3. Whole brain analysis: anticipation

During the anticipation phase, no regions survived whole brain cluster correction for any interactions (Table S2). However, a main effect of SA emerged in the precuneus. More severe social anxiety symptoms were associated with diminished engagement of the precuneus (r=-.33, $p < .001$, 95 % CI: 0.15, 0.49) regardless of valence or predictability of the stimulus. There were also main effects of age in the bilateral insula and dACC (See Fig. 3). For each region, younger participants exhibited greater activation than older participants (right insula: r=-.40, $p < .001$, 95 % CI: .23, .55; left insula: r=-0.42, $p < .001$, 95 % CI: .26, .56; dACC: r=-0.42, $p < .001$, 95 % CI: .26, .56) across all event types during anticipation.

2.4. Whole brain analysis: feedback

During the feedback phase, significant Age X SA X Predictability X Valence interactions emerged in the striatum (peaking in the caudate and extending into the ventral portion of the striatum) and both the middle temporal gyrus (MTG) and STG (Fig. 4). All other significant lower-level interactions and main effects are presented in Table 2. Further, observed power of the 4-way interaction was estimated using NeuroPowerTools (Durnez et al., 2016; preprint) at 0.67 Bonferroni-corrected. Full details are provided in the Supplemental Materials.

Of note, a significant SA X Age X Valence interaction revealed a significant cluster in the frontal pole. In addition, main effects of predictability and valence elicited activation in several key socioemotional processing regions (e.g., dACC, insula, caudate) as well as several prefrontal regions (e.g., superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus). Follow-up tests showed that regions were more engaged during negative compared to positive evaluations (main effect of valence) and during unpredictable compared to predictable evaluations (main effect of predictability).

To help interpret these complex 4-way interactions we extracted signal from each region and implemented the data-driven, Johnson-Neyman technique with the PROCESS macro for SPSS (Hayes, 2017; Hayes and Matthes, 2009). The Johnson-Neyman method determines the specific value of predictor 1 (X) at which the relationship between predictor 2 (Y) and the dependent variable (Z) changes (i.e., where the relationship shifts from significant to non-significant and/or significant in the opposite direction). This technique provides a data-driven approach to decomposing the complex interactions that emerged from the whole-brain imaging analysis. This technique and all follow-up tests were only used to decompose the 4-way interaction for descriptive and illustrative purposes. All statistics provided are posthoc and are meant to aid in interpretation of the interaction.

For the current findings, we used this technique to determine the age (X) window at which the relationship between social anxiety (Y) and predictability-based brain response (e.g., caudate response during unpredictable – predictable social evaluations) changed from significant to non-significant and/or vice versa. Due to the large number of variables included in the interaction, the technique was run separately for brain response to positive and negative social feedback. Separate follow-up analyses were run for each brain region that emerged from the whole brain analysis.

Results from the Johnson-Neyman analysis of each region are provided in the Supplemental Materials (Table S3). However, results across regions were nearly identical. To simplify interpretation of results, age groupings were kept consistent across regions. Thus, the age groupings derived from the analysis of the largest cluster that emerged (caudate) in response to positive feedback was applied to all brain regions. Two distinct age groups were identified —an early adolescent group: age range = 8.12–12.81, $M = 10.53$, $SD = 1.19$ ($n = 60$); and a mid-to-late adolescent group: age range = 12.90–18.02, $M = 15.46$, $SD = 1.44$ ($n = 52$), and used in all post-hoc follow-up tests and illustrations. Groups did not differ in terms of SA, $t(110) = 1.02$, $p = 0.31$ (see Supplemental Materials for group-based demographic information).

To interpret the complex interactions isolated in the whole brain analysis, separate repeated-measures ANOVAs were performed for each

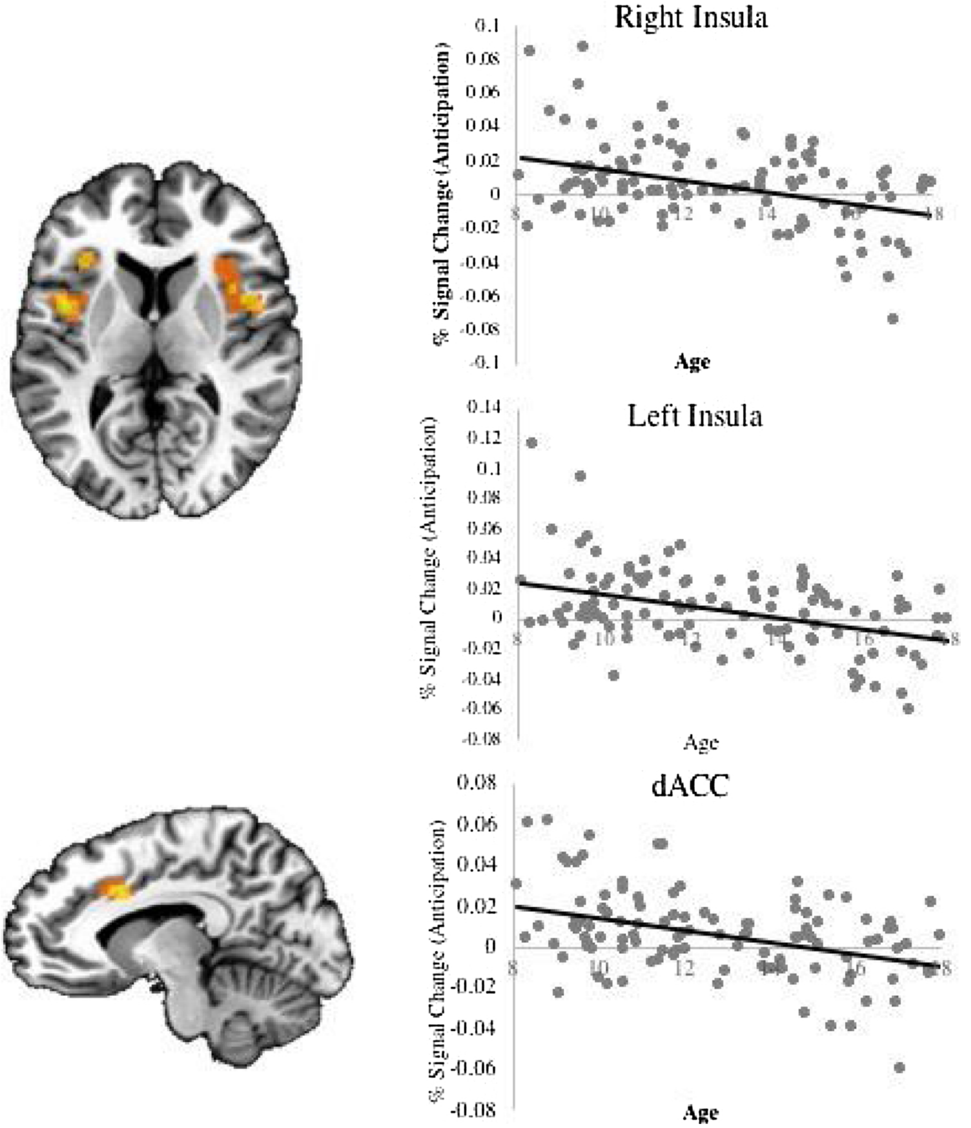

Fig. 3. Main Effects of Age during Anticipation. For each region, older participants showed less engagement than younger participants (right insula: r=-.40, $p < .001$; left insula: r=-.42, $p < .001$; dACC: r=-.42, $p < .001$).

significant cluster (Age X SA X Predictability X Valence). However, age was treated as a binary factor (using the Johnson-Neyman-derived grouping: early, mid-to-late) rather than a continuous variable[3]. This revealed that in the early adolescent group, neural response varied based on valence and predictability of evaluations as a function of SA. More severe SA was associated with greater neural response to negative evaluations that were unpredictable [correlations between brain activation following negative evaluations and level of SA: caudate: $r = .36$, $p = .005$, 95 % CI: .12, .56; MTG: $r = .32$, $p = .02$, 95 % CI: .07, .53; STG: $r = .34$, $p = .008$, 95 % CI: .10, .55]. The opposite pattern emerged for positive evaluations. Specifically, more severe symptoms were associated with greater neural response to predictable, positive evaluations [correlations between brain activation following positive evaluations and level of SA: caudate: r= -0.39, $p = .002$, 95 % CI: .15, .59; MTG: r= -0.28, $p = .03$, 95 % CI: .03, .50; STG: r= -0.18, $p = .17$, 95 % CI: -.01, .41].

Within the mid-to-late adolescent group, the only significant association between SA and social outcomes emerged in the caudate during negative social evaluations. In this age group, greater SA was associated with attenuated neural response to unpredictable, compared to predictable, negative outcomes (correlation between caudate activation and SA, r= -0.27, $p = .05$, 95 % CI: -.003, .51). No other patterns were significant in the mid-to-late adolescent group (correlation between brain activation and SA; positive evaluations: caudate: $r = .20$, $p = .16$, 95 % CI: -.08, .45; MTG: $r = .17$, $p = .23$, 95 % CI: -.12, .42; STG: $r = .20$, $p = .16$, 95 % CI: -.08, .45; negative evaluations: MTG: r= -0.22, $p = .12$, 95 % CI: -.06, .46; STG: r= -0.22, $p = .12$, 95 % CI: -.06, .46) meaning that brain response did not vary as a function of valence, predictability, and SA.

SA X Age X Valence. In line with our approach to decomposing the complex 4-way interaction, a repeated-measures ANOVA was performed for the significant cluster that emerged from the 3-way SA X Age X Valence interaction. Like the prior analysis, age was treated as a binary factor (using the Johnson-Neyman-derived groupings described above: early, mid-to-late) rather than a continuous variable. This revealed that in the early adolescent group, neural response varied based on the valence of evaluations as a function of SA. More severe SA was associated with greater neural response to positive evaluations regardless of predictability [correlations between brain activation following positive evaluations and level of SA: $r = .26$, $p = .05$, 95 % CI: .003, .48]. The mid-to-late adolescent group showed the opposite effect. While the correlation between brain activation and SA did not reach significance

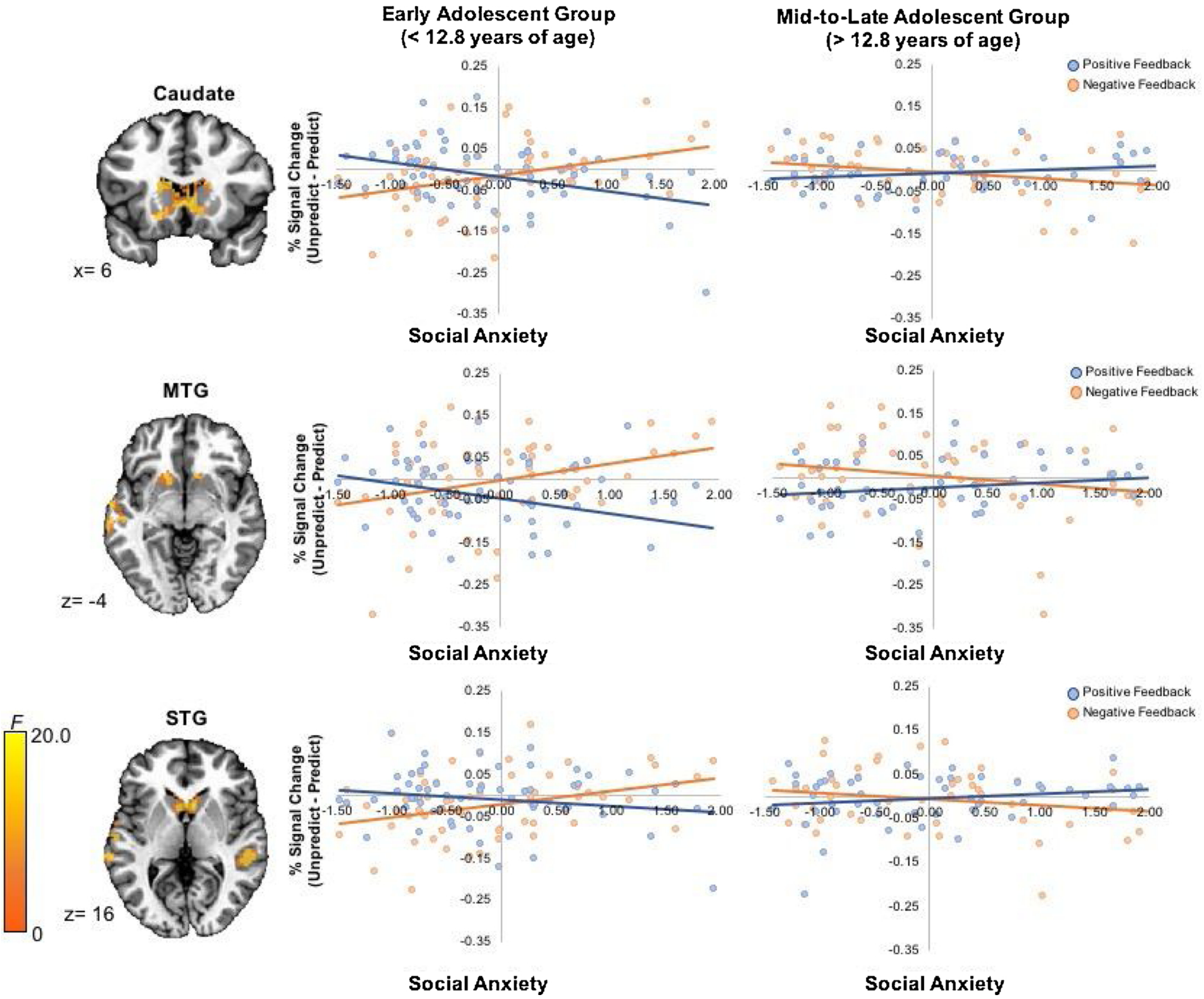

Fig. 4. Receipt of Evaluative Feedback. Significant Age X SA X Predictability X Valence interactions emerged in the caudate, medial temporal gyrus, and superior temporal gyrus.

in the mid-to-late adolescent group [*r*= -0.23, *p* = .09, 95 % CI: -.47, .05], the patterns for each age group were significantly different from one another (Fisher r-to-z, *Z* = 2.56, *p* = 0.01).

There were no significant associations between negative evaluations and brain response in either age group [correlations between brain activation following negative evaluations and level of SA: *r* = .26, *p* = .05, 95 % CI: .003, .48]. See Fig. 5.

3. Discussion

The present study revealed relations among age, social anxiety severity, and neural response during distinct types of social experiences. First, we demonstrate that earlier relative to later in adolescence, the brain is more responsive to anticipating social outcomes, regardless of the nuances associated with forthcoming interactions. This suggests that task-specific features of predictability and valence are not associated with unique brain responses when anticipating upcoming social interaction, lending support for a general neural sensitivity theory (Foulkes and Blakemore, 2016). However, while processing social evaluations these neural responses show unique patterns based on features of the interaction (valence, predictability) and factors inherent to the individual (SA, age). Thus, brain patterns vary at critical developmental inflection points as a function of contextual characteristics and individual differences in social anxiety. In particular, early, compared to late, adolescents show more dynamic brain responses: varying response patterns based on social anxiety severity, as well as the predictability and valence of the social evaluations. These associations were largely absent after mid-adolescence (> 12.8 years of age). Neural patterns may reflect age differences in the salience, or importance, of social evaluations and/or social learning processes. Taken together the current findings both support and extend the idea that adolescence is a general period of neural hypersensitivity to social stimuli.

3.1. Anticipating social evaluation

Regardless of peer reputation, during anticipation of social evaluation, younger participants exhibit greater activity than older participants in the dACC and bilateral insula. Given that the dACC and insula are implicated in processing salient events (Craig, 2002, 2009; Shenhav et al., 2013), age-related differences in engagement could reflect greater salience of anticipated social interactions among younger participants. This interpretation is partially supported by the fact that younger adolescents rate predictably nice and mean peers as more "extreme" (mean students as more mean and nice students as nicer) than older participants during pre-task ratings, suggesting that broad sensitivity to social interactions may be particularly evident in the early part of adolescence. Inconsistent with prior work (e.g., Guyer et al., 2012), including a recent study using the Virtual School task (Jarcho et al., 2016), anxiety-related differences in brain function while anticipating social evaluation and peer ratings were not observed in the current manuscript. This inconsistency may partially stem from the fact that prior participants studied with this task were all ~11 years of age, and while they were at risk for

Table 2
fMRI Whole Brain Results: SA X Age X Predictability X Valence.

	Cluster Size	TT coordinates		
Region	k	x	y	z
SA X Age X Predictability X Valence				
Caudate	415	6	14	4
Middle temporal gyrus	158	−61	−9	−4
Superior temporal gyrus	127	56	−34	16
SA X Age X Predictability				
No suprathreshold activations				
SA X Age X Valence				
Frontal pole	144	14	66	19
SA X Predictability X Valence				
No suprathreshold activations				
SA X Age				
No suprathreshold activations				
SA X Predictability				
No suprathreshold activations				
SA X Valence				
No suprathreshold activations				
Age X Predictability X Valence				
No suprathreshold activations				
Age X Predictability				
No suprathreshold activations				
Age X Valence				
No suprathreshold activations				
Predictability X Valence				
Precuneus	1251	6	−56	31
Superior medial gyrus	1173	6	64	9
Postcentral gyrus	1146	39	−26	44
Lingual gyrus	1077	−14	−76	−6
Angular gyrus	878	−39	−56	26
Angular gyrus	616	44	−59	24
Superior frontal gyrus	549	19	24	44
Superior temporal gyrus	371	44	−24	19
Middle frontal gyrus	365	−34	9	54
Lingual gyrus	243	11	−74	−1
Middle temporal gyrus	195	56	−11	−14
Middle temporal gyrus	184	−51	−11	−9
Insula	117	−26	16	−4
Supplementary motor area	115	6	−16	51
Main Effect of SA				
Postcentral gyrus	110	−54	−9	36
Main Effect of Age				
Inferior parietal lobule	4856	−29	−54	44
Fusiform gyrus	2837	24	−84	−11
Precentral gyrus	261	61	9	19
Cingulate cortex	248	−4	−26	29
Thalamus	154	11	−19	1
Thalamus	143	−14	−19	6
Main Effect of Valence				
Lingual gyrus	192	11	−76	−4
Intraparietal lobule	166	41	−56	36
Insula	156	−31	14	1
Superior frontal gyrus	121	21	49	21
Main Effect of Predictability				
Cingulate cortex	4048	6	−1	36
Insula	1330	−29	1	14
Orbitofrontal cortex	778	−11	44	1
Lingual gyrus	534	11	−76	6
Inferior frontal gyrus	407	−34	34	19
Inferior temporal gyrus	259	−49	−49	−4
Thalamus	147	−11	−26	24
Caudate	145	−6	14	−4
Inferior occipital gyrus	132	44	−71	−16
Middle frontal gyrus	124	44	14	41
Precuneus	118	−11	−49	11
Inferior parietal lobule	116	−24	−56	46
Lingual gyrus	112	−6	−69	−4
Angular gyrus	105	49	−64	39

Note: $p = .005$, $k = 101$.

developing social anxiety, very few had clinically significant symptoms (Jarcho et al., 2016). As such, the lack of differentiation between potentially positive and negative social outcomes in the present sample may represent some degree of neural hypersensitivity early in adolescence that does not vary as a function of anxiety levels.

3.2. *Receiving social evaluations*

Among early adolescents (< 12.8 years of age), hypothesized socioemotional-processing regions (striatum, STG) were differentially engaged by discrete forms of social evaluation depending on social anxiety severity. In addition, the MTG, a region believed to underlie speech processing (e.g., Hickock, 2009; Whitney et al., 2011) and not previously hypothesized, also emerged from this interaction. Post hoc analyses demonstrated that when early adolescents received negative social evaluations, SA was positively correlated with brain activation following unpredictable, compared to predictable, feedback. The opposite effect was seen during positive feedback—early adolescents with higher SA exhibited more activation during predictable, compared to unpredictable, positive social feedback. These findings underscore the importance of considering factors specific to the social interaction, such as valence and predictability, and person-specific factors, such as SA, when studying the neural correlates of social information processing. Such nuances may be particularly important early in adolescence, a developmental window when symptoms of anxiety most commonly emerge. Critically, these patterns suggest that the adolescent brain is not simply hypersensitive to receipt of all social evaluations. Instead, engagement of socioemotional-processing regions depends on specific features of the social evaluations and individual differences intrinsic to the adolescent.

There are several potential explanations for this response pattern. Differential engagement of striatal and temporal brain regions could reflect heightened affective response (i.e., salience) for specific social stimuli in younger, more anxious youth. In the current study, the enhanced responses of younger, highly SA participants to unpredictable negative social evaluation resembles response patterns in socially anxious adults during the processing of embarrassing social norm violations (Bas-Hoogendam et al., 2019) and during unexpected social exclusion (Kawamoto et al., 2012). Although the present study did not measure embarrassment or surprise, it is plausible that unexpected negative feedback is particularly emotional in younger and more severely anxious youth. This interpretation is also consistent with prior research showing that younger adolescents report more distress and negative affect following rejection- and evaluation-related social experiences (Gunther-Moor et al., 2010; Sebastian et al., 2011). However, the specific age at which social stress begins to decrease during adolescence varies within the literature (for review, see Somerville, 2013). On the other hand, regions, such as the insula and dACC, that are commonly engaged during salient events did not emerge from the 4-way interaction. The insula did emerge in the main effects of predictability and valence as well as during the anticipation phase of the task. The fact that commonly identified salience regions were not sensitive to person-specific factors (age, SA) it is possible that these activations are not indicative of increased affective responses. Additionally, other hypothesized socioemotional processing regions, the amygdala and TPJ, did not emerge in current analysis. Taken together, it is possible that patterns of response in the striatum, STG, and MTG could be interpreted in terms of increased salience response.

However, younger participants with higher SA also exhibited enhanced neural responses to predictably *positive* social feedback. This finding is in line with evidence demonstrating that early-to-mid adolescence is a period of heightened engagement of the reward system and regions implicated in socioemotional processing (e.g., dACC, insula, striatum, amygdala, STG, TPJ; for review, see Crone and Dahl, 2012). While previously demonstrated age-effects in socioemotional processing support this interpretation, findings from the pediatric anxiety literature demonstrate different patterns – greater response to negative stimuli (see Shechner, et al., 2012) or *unpredictable* positive stimuli (Jarcho et al., 2015). For instance, a recent study from our group (Jarcho et al., 2015) demonstrated greater striatal activation in anxious adolescents during *unpredictable* positive feedback from peers. Overall, if these brain responses reflect increased affective arousal, then the current

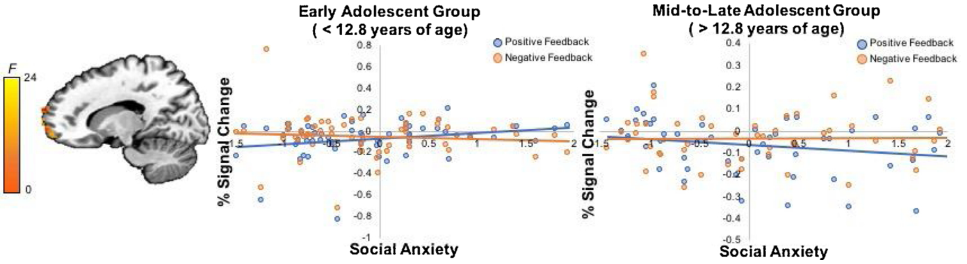

Fig. 5. Receipt of social evaluations. A significant cluster in the frontal pole emerged from the SA X Age X Valence interaction.

findings suggest that unpredictable negative and predictable positive social evaluations are the most salient in younger adolescents with higher social anxiety.

Another, closely related, potential explanation for dynamic response patterns among younger adolescents is engagement of social learning processes (i.e., updating expectancies and contingencies). Younger adolescents with more severe SA, as compared to other youth, may engage more social learning processes following unpredictable (compared to predictable) negative evaluations. Current social-cognition models link social learning to functioning within superior and middle portions of the temporal lobes function in concert with salience-related regions such as amygdala, striatum, and dACC (e.g., Liu et al., 2016; Rushworth et al., 2013; Yang et al., 2015). In adults, heightened caudate engagement has been shown in early stages of learning, where associations between stimuli and outcomes are still unknown, and decreases as these associations become learned (Seger and Cincotta, 2005, 2006). This may reflect limited social experiences among our early adolescent group however additional studies are needed to test this theory.

To date, age effects in reinforcement learning paradigms yield mixed results- some showing heightened learning rates in adolescents, compared to children and adults (Cohen et al., 2010), others showing a linear decrease with age (negative learning rate; van den Bos et al., 2012). More recently, another social task revealed an inverse U-shaped pattern of learning rates in the caudate following positive feedback (Jones et al., 2014). While each study demonstrates adolescent-specific effects, it is unclear how specific aspects of social experiences impact such patterns. Further, no study has examined the impact of SA on reinforcement learning rates during adolescence. Because the task in the current study does not manipulate learning, only tentative comparisons can be made between these past data and the current findings.

While either explanation is feasible, further research is needed to more directly link brain and behavior to test inferences made about the current findings. For instance, engagement of socioemotional-processing regions could be probed by self-report ratings of affect and/or physiological engagement following distinct social evaluations. A modified version of the task that manipulates whether participants learn about their peers prior to their social encounters versus through the social encounters alone is needed to directly test effects of learning on brain function. On the other hand, recording participant predictions regarding upcoming feedback from peers may help isolate effects linked to surprise or norm violation. Once isolated, specific cognitive mechanisms could then be targeted to promote adaptive social behaviors during this critical developmental phase.

Finally, the only significant association between SA and predictability among mid-to-late adolescents was observed in the striatum during negative social evaluations. Older adolescents with higher SA demonstrated less caudate engagement during unpredictable, negative feedback. These differences may suggest that role of the striatum in socioemotional processing changes as a function of SA severity across adolescence. Affective responses may shift from a greater response during unpredictable negative evaluations to predictable negative feedback across this period. However, a longitudinal study is needed to fully test this theory. For mid-to-late adolescents, no significant relations emerged among SA, predictability, and valence in the MTG or STG. Given that friend groups become more stable and social rejection is less distressing later in adolescence (Gunther-Moor et al., 2010; Sebastian et al., 2011), the social evaluations in the current task may not be as impactful to older adolescents (Masten et al., 2009).

3.3. Limitations

Despite its strengths, the current study is not without limitations. First, a lack of significant anxiety- or age-related differences in task behavior makes it difficult to draw conclusions regarding the influence of brain response on behavior during social evaluation. Task behavior was measured by participants' responses to social feedback. Although we gave participants the opportunity to avoid (i.e., not respond), in future studies we hope to make the task behavior more ecologically valid by allowing the participant to choose whether or not to interact with particular students. This would also allow us to link brain response from previous interactions with future decision-making. Moreover, responses were collected via sliding scale where participants were required to navigate to the option they wanted to select. Thus, response time could not be used as a behavioral measure as it was confounded with the spatial location of the response. Further, while pubertal hormones have important effects on social processes (for reviews, see Forbes and Dahl, 2010; Schulz and Sisk, 2006), these data were not collected. While age is often used as a proxy for pubertal status it is possible that varying levels of pubertal hormones would differentially impact brain response during social evaluations. Finally, an additional challenge inherent to understanding complex processes in specialized populations is having adequate power to find complex interactions. Despite our large sample size it is possible that our complex, 4-way interaction is underpowered and that post hoc statistics are inflated (Yarkoni et al., 2009). This may be particularly relevant given the disordinal pattern of the interaction (Chavez and Wagner, 2017; preprint). Observed power was estimated at 0.67 (Bonferroni). These findings should be interpreted with caution while they await replication. In addition, decomposing and interpreting complex interactions, such as the one presented in this manuscript, is also a challenge.

4. Conclusions

In sum, these findings begin to disentangle the complex interplay of age, SA, and social processing during adolescence, and extend the idea that adolescence is a period of neural hypersensitivity to social stimuli. In particular, in early adolescence anticipating social encounters may be associated with a broader neural responsivity, not dependent on interaction-specific factors, while neural responses to social outcomes are more nuanced. Notably, individual differences in SA severity may play a particularly important role in the processing of social outcomes during early adolescence. Neural correlates of social experiences may depend on development, social anxiety severity, and the valence and predictability of the social interaction itself. Future work needs to directly connect these neural patterns to adolescents' adaptive and maladaptive behaviors in social interactions, as these relations likely play a critical role in forming strategies for navigating peer relations. By understanding the mechanisms through which youth navigate their social world, we may be able to inform prevention and treatment programs at various stages of development.

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Disclosures

None of the authors have any declarations of interest to disclose.

Declaration of Competing Interest

None

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dcn.2020.100768.

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