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Forgetting the best when predicting the worst: Preliminary observations on neural circuit function in adolescent social anxiety

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ABSTRACT

Social anxiety disorder typically begins in adolescence, a sensitive period for brain development, when increased complexity and salience of peer relationships requires novel forms of social learning. Disordered social learning in adolescence may explain how brain dysfunction promotes social anxiety. Socially anxious adolescents ($n = 15$) and adults ($n = 19$) and non-anxious adolescents ($n = 24$) and adults ($n = 32$) predicted, then received, social feedback from high and low-value peers while undergoing functional magnetic resonance imaging (fMRI). A surprise recall task assessed memory biases for feedback. Neural correlates of social evaluation prediction errors (PEs) were assessed by comparing engagement to expected and unexpected positive and negative feedback. For socially anxious adolescents, but not adults or healthy participants of either age group, PEs elicited heightened striatal activity and negative fronto-striatal functional connectivity. This occurred selectively to unexpected positive feedback from high-value peers and corresponded with impaired memory for social feedback. While impaired memory also occurred in socially-anxious adults, this impairment was unrelated to brain-based PE activity. Thus, social anxiety in adolescence may relate to altered neural correlates of PEs that contribute to impaired learning about social feedback. Small samples necessitate replication. Nevertheless, results suggest that the relationship between learning and fronto-striatal function may attenuate as development progresses.

1. Introduction

The drive for social acceptance can promote a corresponding fear of rejection that, if extreme, may manifest as social anxiety (Klapwijk et al., 2013). Since prediction error signaling supports learning, altered signaling may contribute to some of the hallmarks of social anxiety disorder. Specifically, altered prediction error signaling could lead to deficient recall of positive past social experiences, which in turn could promote the negative social expectation and interpretation biases that are common to patients with social anxiety (Clark and McManus, 2002; Rapee and Heimberg, 1997). Such deficits may be particularly detrimental during adolescence, a sensitive developmental period that is marked by heightened salience of social acceptance and rejection (Brown and Larson, 2009) and the establishment of complex, peer-focused patterns of behavior and learning (Blakemore, 2008; Crone and Dahl, 2012; Nelson et al., 2005; Steinberg and Morris, 2001). These shifts coincide with peak onset rates of social anxiety, and occur in conjunction with significant changes in brain function (Casey et al., 2000; Nelson et al., 2014; Ordaz et al., 2013; Pfeifer et al., 2013; Rubia et al., 2006; Satterthwaite et al., 2013). Adolescence begins with hormonal changes of puberty, followed by the physical expression of pubertal maturation over subsequent years (Grumbach, 2002); its conclusion is culturally constrained by the assumption of adult roles (Blakemore and Mills, 2014). This transition involves acquiring skills needed for peer-based relationships (Blakemore and Mills, 2014), which thereby promotes novel patterns of peer-focused behavior and learning (Blakemore, 2008; Crone and Dahl, 2012; Nelson et al., 2005; Steinberg and Morris, 2001). A Prediction Error (PE) model may explain how brain

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Table 1
Demographics.

	Adults				Adolescents			
	Anxious *n*		Non-anxious *n*		Anxious *n*		Non-anxious *n*	
Sample size	19		32		15		24	
Female/male	15/4		17/15		9/6		9/15	
% White non-Hispanic or Latino	52.63		44.75		66.67		83.33	
Current primary diagnosis								
SAD	5		–		7		–	
GAD	4		–		2		–	
SAD + GAD	10		–		6		–	
Current secondary diagnosis								
MDD	1		–		1		–	
ADHD	0		–		3		–	
	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*
Age (years)	27.86	*7.82*	26.17	*5.16*	12.79	*3.39*	13.68	*2.39*
Tanner Score	–		–		2.92	*1.16*	3.36	*1.36*
IQ	112.78	12.58	119.13	11.38	104.80	*12.45*	112.63	*11.69*
FNE	22.07	*8.07*	9.81	*4.92*	21.08	*8.27*	6.91	*4.97*
	Min	Max	Min	Max	Min	Max	Min	Max
Age range (years)	18.25	49.58	21.00	44.83	8.00	17.42	9.42	17.17

SAD, social anxiety disorder; GAD, generalized anxiety disorder; MDD, major depressive disorder; ADHD, attention deficit hyperactivity disorder; IQ, intelligence quotient; FNE, fear of negative evaluation.

dysfunction during adolescence, a sensitive period of brain development (Casey et al., 2000; Nelson et al., 2014; Ordaz et al., 2013; Pfeifer et al., 2013; Rubia et al., 2006; Satterthwaite et al., 2013), fosters maladaptive social responding. However, limited research uses PE models to assess adolescent psychopathology.

In general, PE models specify that predictions are elicited by cues that precede motivationally-salient outcomes; discrepancies between predicted and actual outcomes result in updated predictions (Pessiglione et al., 2006; Schonberg et al., 2007). PEs associated with unexpectedly positive and negative outcomes, respectively, heighten or diminish activity in the striatum (Schultz et al., 1997), a subcortical structure that guides reward-related behavior and learning (O'doherty, 2004; Yin et al., 2009). Functional connectivity between the striatum and medial prefrontal cortex (mPFC) is implicated in updating both predictions and the value ascribed to outcomes (Haber et al., 2006; O'doherty, 2004). However, such connectivity may reach functional maturity relatively late in development (Forbes and Dahl, 2012; Gogtay et al., 2004; Sowell et al., 2002). In fact, recent studies find PE-related developmental differences in the striatum (Cohen et al., 2010) and/or striatal-mPFC connectivity (van den Bos et al., 2012) as well as evidence of deficient mPFC-based connectivity in youths (Britton et al., 2013; Fitzgerald et al., 2011; Roy et al., 2013). Failure to establish normative striatal-MPFC connectivity during adolescence, when peer acceptance becomes a much more motivationally-salient outcome, may have a negative impact on PE-based social learning. This may be one mechanism that contributes to the particularly high onset rate of adolescent social anxiety disorders. However, the same mechanism may be less critical for maintaining symptoms among anxious adults, who have moved beyond a critical phase of development when behavior may be more easily shaped by social learning.

The neural correlates of PE are typically investigated using paradigms in which participants learn how arbitrary stimuli predict positive or negative outcomes. Such paradigms are well suited for examining general aspects of PE learning but may be less well suited for studying socially anxious adolescents, who have unimpaired performance on most such paradigms (Dickstein et al., 2010). The present study uses a paradigm known to elicit biased responding in socially anxious adolescents (Guyer et al., 2008) as a preliminary investigation of the relationship between age, social anxiety, and the neural correlates of PE in a social context. Relative to traditional PE paradigms, this novel approach may be better suited for capturing between-group differences in PE, but less well suited for examining general aspects of PE learning. Given past work, we hypothesized that striatal-mPFC engagement would be uniquely altered among socially anxious adolescents. To test this hypothesis, brain activity was assessed with functional magnetic resonance imaging (fMRI) as participants predicted, and then received, expected (accurately predicted) or unexpected (inaccurately predicted) positive and negative feedback from high and low-value peers. Brain activity was then related to performance on a surprise memory task in which participants were asked to recall feedback valence. Socially anxious and non-anxious adolescents and adults were studied to directly compare associations among these groups.

2. Methods and materials

2.1. Participants

Participants included 90 medication-free, anxious and non-anxious adolescents and adults (see Table 1 for demographics and Supplemental Materials for recruitment methods and exclusionary criteria). All patients met DSM-IV criteria for clinical anxiety and all expressed clinically significant fear of social situations during diagnostic interviews and on the Fear of Negative Evaluation (FNE; Watson and Friend, 1969) scale, although only 82% of cases patients met full criteria for social anxiety disorder. However, consistent with dimensional perspectives (Insel et al., 2010), patients with generalized anxiety disorder and sub-threshold social anxiety were also studied. Non-patients were free of psychopathology; all participants were medication free (see Supplemental Materials for full exclusion criteria). Some parents withheld consent to administer the Tanner stage of pubertal development scale, thus developmental stage reflects data from a subset of adolescents (Anxious $n = 12$, Non-Anxious $n = 22$). Anxious and non-anxious participants in each age group did not differ on age, IQ, or self-reported Tanner stage; FNE scores were higher for anxious than non-anxious groups ($t = 8.99$, $p < .001$), but did not differ by age group. Sex was not explicitly used as a matching variable across

groups. Thus, the sample studied reflects the general tendency for a higher prevalence of anxiety disorders among females than males. Thus, there was an overall trend towards group differences in sex (χ^2 (3, 87) = 7.58; p = .06). This trend was driven by adults (χ^2 (1, 50) = 3.40; p = .07). No such trend was observed between anxious and non-anxious adolescents (χ^2 (1, 38) = 1.88; p > .10). Although the group of youths included those aged 8 to 17, over 90% of the sample reported a Tanner stage of ≥2. Moreover, even for the 10% not yet rated as having starting puberty, other markers of pubertal onset, such as changes in the hormonal regulation of the adrenal glands and gonads, often begin at 7-to-9 years of age, well before physical maturation is detected (Grumbach, 2002). Since the few participants without physical signs of puberty had likely already begun to express these or other pubertal changes in hormones, we have chosen to characterize this group as adolescents, despite the potential presence of a very small number of pre-pubertal individuals. Informed consent from adults, and assent with parental consent from adolescents, were obtained prior to participation in this Institutional-Review-Board approved study. During the consent process, participants were informed that the study involved deception.

All results are from deceived participants. An additional 33 participants were studied, but not deceived. Rates of deception are similar to prior studies that have used versions of this paradigm (Guyer et al., 2008; Guyer et al., 2009), and did not vary across groups (Chi-squared = 2.87, p > .05). Deceived anxious and non-anxious participants in each age group did not differ from non-deceived participants on age, IQ, Tanner stage of development, or FNE (Table S1). Additional participants were studied but excluded from analyses due to an insufficient distribution of event types (n = 2) or acquisition-related artifacts (n = 8).

2.2. Chatroom task

Participants completed the "Chatroom Task" (Fig. 1A–D; see Guyer et al., 2008, 2009, 2012, 2014a; Lau et al., 2011). As described below and depicted in Fig. 2, trials were categorized based on peer valuation, predicted social feedback, and whether this feedback was expected, as determined by the accuracy of participant predictions.

2.2.1. Peer valuation (Fig. 1A)

At their first visit, participants were led to believe they would chat online with a peer, and were asked to sort photographs of 60 peers into high-value (30 peers with whom they would like to chat) and low-value groups (30 peers with whom they would not like to chat) based on their preferences (see Supplementary Materials and Table S2). Participants were then photographed, and led to believe that their picture would undergo scrutiny by the 60 peers they had just evaluated, and that their valuations would be shown to purported peers prior to this scrutiny. Four sets of photographs depicted purported peers from four age categories (8–11, 12–14, 15–17, or 18+ years). Each participant was presented with the photograph set that matched his or her age.

2.2.2. Predict social feedback (Fig. 1B)

At their second visit (11.87 ± 7.42 days later), participants underwent an fMRI scan (see Supplementary materials for fMRI acquisition methods). During a first functional run, participants predicted the degree to which each peer would be interested in chatting with them, using a 0-to-100 (not at all-to-very interested in chatting with me) point scale. Negative predictions (i.e., this peer is *not* interested in chatting) and positive predictions (i.e., this peer is interested in chatting) were defined by ratings of ≤50 and >50, respectively.

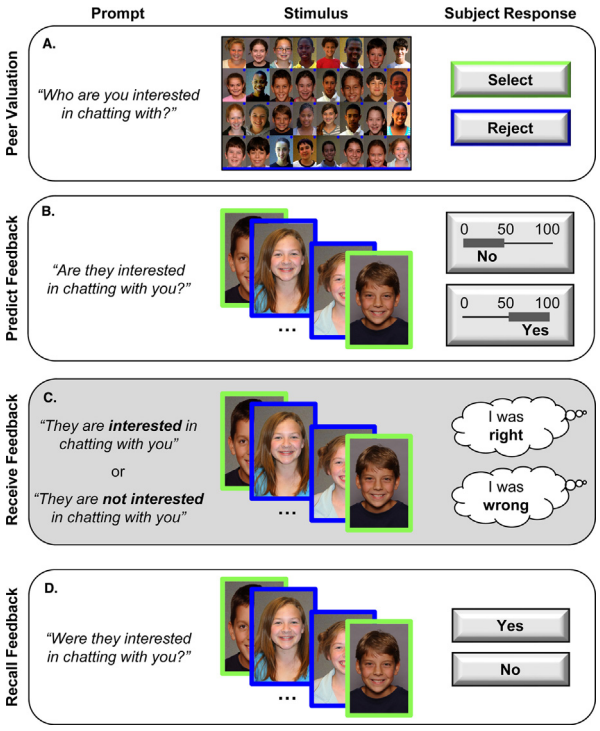

Fig. 1. Depiction of "Chatroom Task". (A) On the initial visit, participants selected peers they wanted to chat with (high-value) and rejected those they did not want to chat with (low-value). (B) On the second visit, participants underwent an fMRI scan. During the first run of fMRI data acquisition, participants predicted the social feedback they would receive from high- and low-value peers (ratings 0–50 = negative feedback predicted; ratings 51–100 = positive feedback predicted). (C) During the second run of fMRI data acquisition, participants received expected (accurately predicted) or unexpected (inaccurately predicted) social feedback from peers. Neuroimaging results were constrained to this functional run. (D) After scanning, participants were unexpectedly asked to recall the social feedback they received from each peer.

2.2.3. Receive social feedback (Fig. 1C)

During a second run, participants viewed the same purported peers and received positive (i.e., the peer is interested in chatting) or negative feedback (i.e., the peer is not interested in chatting). Thus, procedures across run 1 and 2 generated eight event-types (Fig. 2), which reflect crossing of peer valuation (high/low), actual social feedback (positive/negative), and prediction error. Here, "prediction error" was defined as the discrepancy between the prediction of positive or negative feedback and actual social feedback (expected or accurately predicted/unexpected or inaccurately predicted social feedback). Because PEs manifest during receipt of social feedback, neuroimaging results were constrained to the second functional run, defined by a combination of peer valuation, prediction, and feedback.

2.2.4. Recall of social feedback (Fig. 1D)

Immediately after scanning, participants completed a self-paced surprise memory task. As each peer's photograph was displayed, participants were asked to recall if they received positive or negative social feedback from that peer.

2.3. Data analyses

2.3.1. Predicted social feedback

Analyses were performed to determine whether groups differed in the degree to which they predicted positive or negative feedback from high and low value peers. Group differences on the continuous measure of predicted social feedback were assessed with a repeated measure ANOVA that included two between-participants

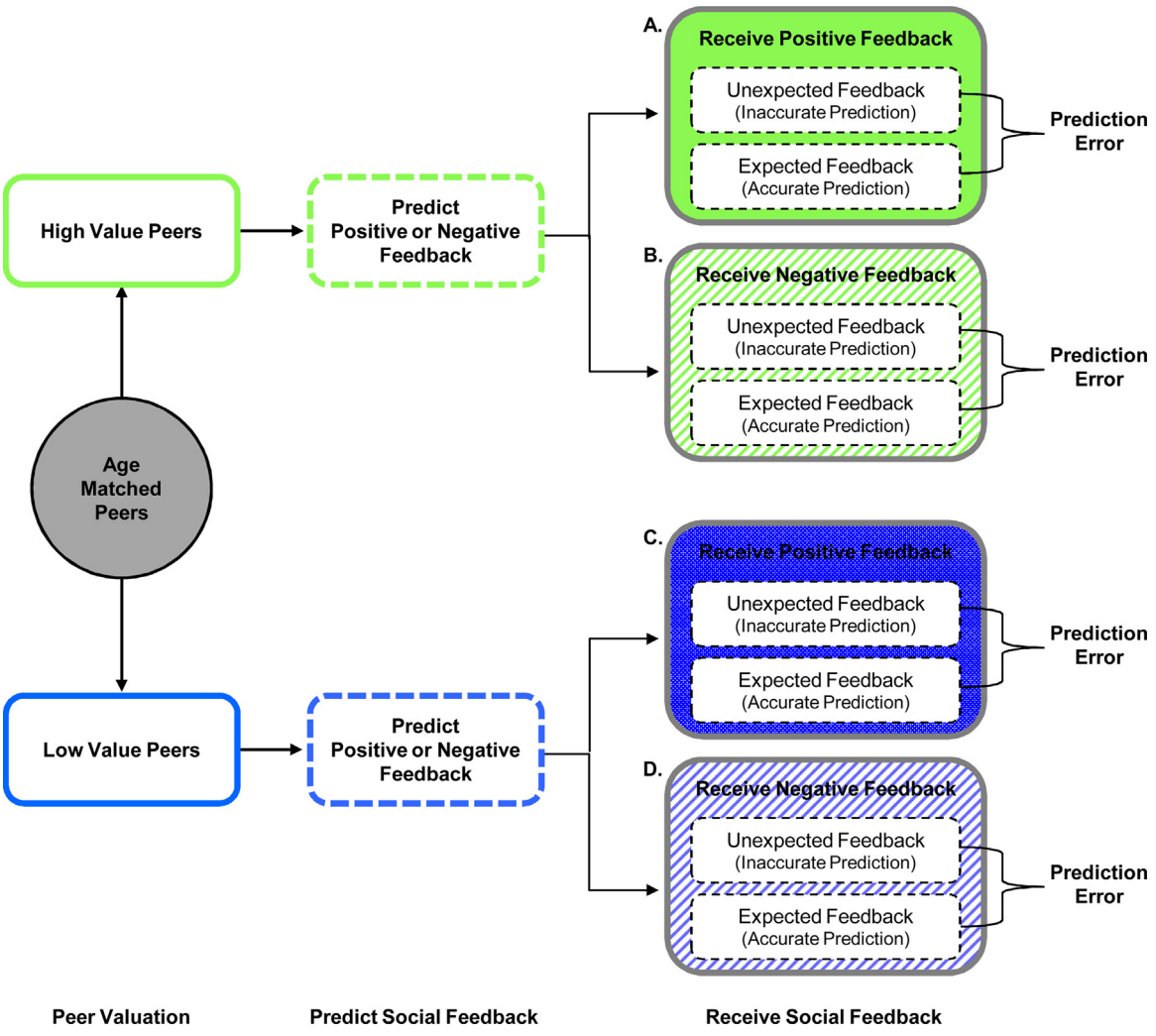

Fig. 2. Flow-chart depicting definition of events. Three within subject factors are depicted in columns across the bottom. *Peer valuation* (column 1): Participants selected age-matched peers they wanted to chat with (high-value) and rejected those they did not want to chat with (low-value) in a pre-scan visit. *Predict social feedback* (column 2): Participants predicted whether high- and low-value peers would provide them with positive or negative social feedback. *Receive social feedback* (column 3): Participants received unexpected (inaccurately predicted) or expected (accurately predicted) social feedback from peers. This column depicts the eight task-specific regressors that were modeled for individual level fMRI analyses. For example, a participant may have predicted negative feedback from a high value peer. If they received positive feedback, that event would be characterized as unexpected (inaccurately predicted). However, if the participant predicted positive feedback, and then received positive feedback, that event would be characterized as expected (accurately predicted). Brain activity associated with prediction error was calculated by subtracting expected from unexpected social feedback from high-value peers [(A) positive and (B) negative feedback] and from, low-value peers [(C) positive and (D) negative feedback].

factors [social anxiety group (anxious/non-anxious), age group (adult/adolescent)], and two within-subject factors [peer value (high/low), prediction valence (positive feedback/negative feedback)]. Chi-square analyses determined whether the number of negative (ratings ≤ 50) and positive (ratings > 50) prediction trials varied as a function of social anxiety and age group.

2.3.2. Individual-level fMRI analyses

Analyses and pre-processing were conducted in AFNI (Cox, 1996). Standard preprocessing steps included slice-timing, coregistration, and smoothing to 6 mm FWHM, spatial normalization to standard Talairach space, and resampling, resulting in 2.5 mm^3 voxels. Temporally adjacent TRs with a Euclidean Norm motion derivative >1 mm were censored ($2.05 \pm 4.04\%$ TRs per participant). Extent of censoring did not vary by group, experimental condition.

Separate regressors were created for social feedback events, classified by three criteria: (1) peer value (high/low); (2) actual feedback (positive/negative); and (3) prediction error (expected or accurately predicted/unexpected or inaccurately predicted positive or negative social feedback). Thus, eight task-specific regressors were modeled (Fig. 2). The number of trials per event type was partially determined by participant predictions and therefore varied across participants (Table S3). Data from two additional participants missing ≥ 3 event types were acquired but omitted from analyses. A small number of the 90 participants were missing one ($n = 13$) or two event types ($n = 6$); individual level analyses for these participants excluded the corresponding regressor for the missing event types.

Task-specific regressors were convolved with a γ-variate basis function approximating the blood oxygen level dependent (BOLD) response (Cohen, 1997). Additional regressors modeled motion residuals and baseline drift. This analysis produced a β-coefficient and associated t-statistic for each voxel and regressor. Percent signal-change maps were generated by dividing signal intensity at each voxel by the mean voxel intensity and multiplying by 100.

2.3.3. Group-level fMRI prediction error analyses

Primary analyses used 3dMVM-based (Chen et al., 2014) repeated measures ANOVA with two between-subject factors [social anxiety (anxious, non-anxious), age group (adult,

adolescent)], three within-participants factors [peer value (high/low), actual social feedback (positive/negative), prediction error (expected or accurately predicted/unexpected or inaccurately predicted social feedback], and one covariate of no-interest to control for scanner [scanner acquisition (scanner 1/scanner 2)]. Significance was set using an overall false detection probability based on 10,000 Monte Carlo simulations. The mean estimated spatial correlation used in these simulations was 8.97 mm × 8.89 mm × 7.92 mm FWHM. This value, which was derived by taking the average intrinsic smoothness of each participant's individual level data, was then entered into AlphaSim to determine cluster-size thresholds. Based on these data, simulations determined that a cluster size (*ke*) of 70 contiguous voxels was needed to achieve a threshold of $p < .005$, with an overall family-wise error rate of $\alpha < .05$. A whole brain analyses strategy was utilized to facilitate more extensive hypotheses testing in the context of future work. However, given our a priori hypothesis about the importance of striatum in PE, group differences that emerge in this region were further interrogated. Significant group differences outside this region are reported for completeness.

Significant striatal clusters were extracted, plotted, and tested in SPSS (IBM SPSS Statistics for Mac, Version 22.0. Armonk, NY: IBM Corp) to facilitate interpretation and explicate factors driving interactions. There are many ways to approach decomposing a 5-way interaction. The strategy used here reflects the balance between minimizing Type I error by using conservative thresholds for the initial higher-order tests of interactions, thereby minimizing the number of tests needed, and minimizing Type II errors, while attempting to successfully isolate the specific groups or conditions driving the complex 5-way interaction. As a first step in decomposing this interaction, a repeated-measure ANOVA was conducted for each participant group, using three within subject factors [peer value (high/low), actual social feedback (positive/negative), prediction error (expected or accurately predicted/unexpected or inaccurately predicted social feedback)]. Groups with significant three-way interactions were further interrogated. To minimize the number of within group tests, activity during expected feedback was subtracted from activity during unexpected feedback (Unexpected–Expected Feedback) to generate an index of prediction error. Paired *t*-tests were then used to determine whether this prediction error signal varied depending on whether positive or negative feedback was provided by high or low value peers. See Supplemental materials for secondary group-level analyses that are (1) restricted to females, and (2) match participants in adult and adolescent groups for sample size across social anxiety, gender, and pubertal development.

2.3.4. Functional connectivity analyses

A psychophysiological interaction (PPI) approach (Friston et al., 1997) tested condition-dependent covariation between a 'seed' and other regions. Definition of the seed and the conditions selected for the PPI analysis were derived from the 5-way interaction obtained in the primary ANOVA. Thus, the seed was defined as a 6 mm sphere, centered at the peak voxel (14, 14, 6) of striatal activation that emerged from the 5-way interaction. The PPI was designed to isolate social anxiety-by-age group differences in co-variation with the seed during expected and unexpected positive feedback from high-value peers. These specific conditions were selected because of the role they played in driving results that emerged from the primary analysis.

For each participant, mean-adjusted eigenvariate time-series data were extracted from the seed. Data in the time-series that occurred outside of the receipt of positive social feedback from high-value peers was coded as a zero. Data that corresponded with the receipt of inaccurately predicted (unexpected) positive feedback from high value peers was coded as +1. Data that corresponded with the receipt of accurately predicted (expected) positive feedback from high value peers was coded as −1. Time series data were then deconvolved with the hemodynamic response function. A PPI term was then generated for unexpected vs. expected positive social feedback from high-value peers. A random-effects model identified regions showing striatal coupling that differed for unexpected, compared with expected, positive social feedback from high-value peers. Negative values from such results indicate more negative coupling during unexpected vs. expected feedback, whereas positive values indicate more positive coupling during unexpected vs. expected feedback. As with the primary analysis, a whole brain strategy was utilized to facilitate more extensive hypothesis testing in the context of future work. However, given our a priori hypothesis about the importance of striatal-mPFC connectivity, group differences that emerge in this region were further interrogated. PPI analyses have relatively low sensitivity (e.g., Gitelman et al., 2003; O'Reilly et al., 2012). Thus, the less-conservative threshold was applied ($p < .005$; $ke > 20$).

2.3.5. Relationship between recall of peer feedback and strength of functional connectivity

Given the PPI analysis was constrained to testing expected and unexpected positive social feedback from high-value peers, analyses relating recall to functional connectivity were likewise limited to these conditions. Effects of social anxiety and age group were assessed with repeated measures ANOVA with two between-participants factors [social anxiety (anxious, non-anxious), age group (adult, adolescent)], and one within-subject factor [expected or accurately predicted/unexpected or inaccurately predicted positive social feedback from high value peers)]. Additionally, for each participant group, one-sample *t*-tests were performed to determine whether recall accuracy was greater than chance.

Correlation analyses assessed the relationship between recall and mPFC-striatal connectivity across participants. To do this, a recall score was calculated as follows: accuracy for recall of unexpected feedback–expected feedback from high value peers. Results from robust regression analyses (MATLAB 7.1, MathWorks, Inc. Natick Massachusetts, United States), which de-weight potential outliers, are also reported. Group differences were evaluated via two-tailed Fisher's *r*-to-*z* transformation.

3. Results

3.1. Predicted social feedback

Average participant predictions about social feedback, as measured by behavioral responding, are depicted in Fig. 3A and described in Table 2A. For the continuous measure of predicted social feedback, there was no overall social anxiety × age group × peer value interaction; however, effects of age and social anxiety emerged. Predictions varied by peer value, depending on age group ($F(1, 86) = 9.31$, $p < .005$; Fig. 3B). Adolescents and adults predicted a similarly high likelihood of receiving positive feedback high-value peers. Relative to adults, adolescents predicted significantly lower levels of positive feedback from low-value peers ($t = 3.59$, $p < .001$). There was also a trend towards a main effect of anxiety such that anxious, relative to non-anxious, participants predicted lower levels of positive feedback from peers ($F(1, 86) = 3.78$, $p = .055$; Fig. 3C). Number of negative (ratings ≤50) and positive (ratings ≥51) prediction trials did not vary as a function of social anxiety or age group (Table 2B and C).

3.2. fMRI prediction error analyses

As expected, the whole-brain repeated measures ANOVA revealed brain activity for PEs varied by social anxiety and age

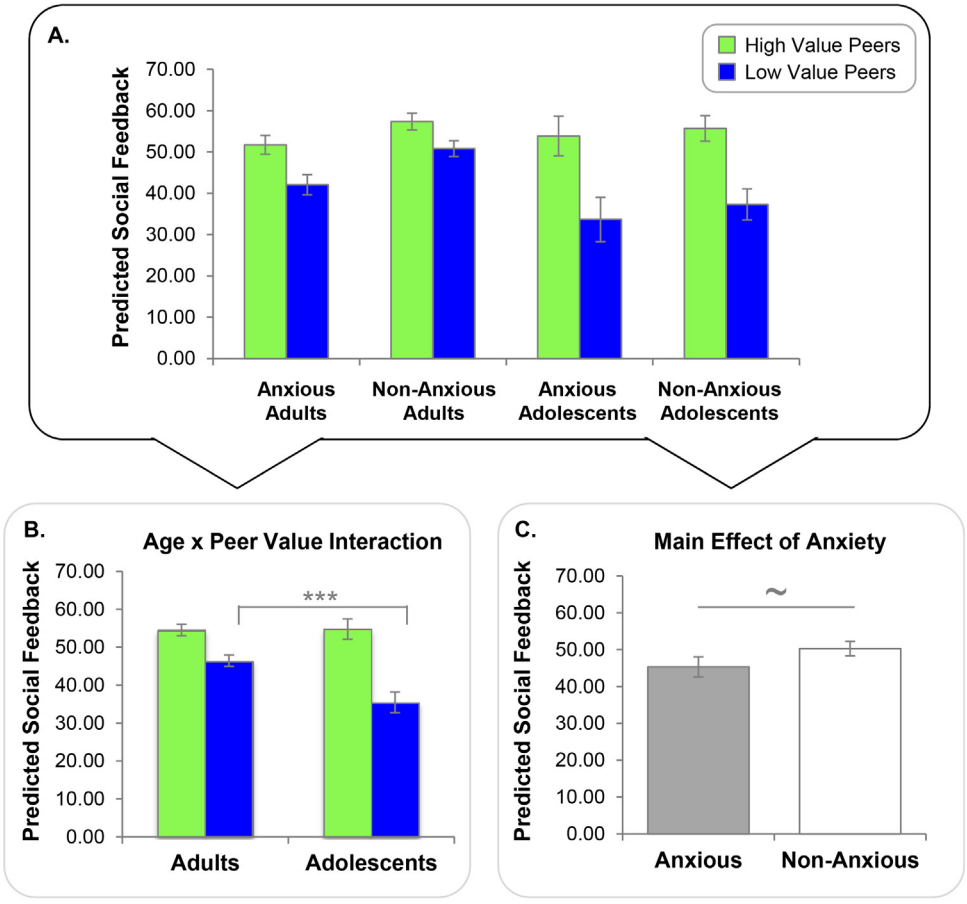

Fig. 3. Predicted social feedback measured by behavioral responding. (A) Average predicted social feedback for high- and low-value peers across all groups. (B) An age group × peer value interaction was driven by adolescents predicting lower levels of positive feedback from low-value peers than adults. (C) Anxious participants had a trend towards predicting lower levels of positive feedback from peers than non-anxious participants. ***$p < .005$; ~$p < .06$.

group, depending on peer value and feedback valence (i.e., 5-way interaction). Only two clusters of activation emerged: one, in striatum, as expected, the other, in cerebellum (Table 3A). The large cluster that encompassed bilateral striatum had multiple sub-peaks in right caudate (maximum peak), left caudate, putamen, and ventral striatum (Fig. 4A). To decompose this 5-way interaction, data were extracted from a 6 mm sphere centered at the peak activation voxel in the right caudate, and plotted in a bar graph (Fig. 4B); each bar reflects activity engaged by PE (i.e., the difference in brain response to unexpected vs. expected feedback). This decomposition revealed a significant three-way (peer value × actual social feedback × prediction error) interaction among socially anxious adolescents; no significant findings emerged in other groups. This interaction was driven by heightened reactivity to unexpected positive feedback from high-value peers, relative to each other event type ($p < .005$ for each comparison). These results remained significant when participants with <4 accurate and inaccurate prediction trials for positive feedback from high value peers error were eliminated from the analysis (see Supplementary materials).

Table 2
Predicted social feedback measured by behavioral responding.

	Adults				Adolescents			
	Anxious		Non-anxious		Anxious		Non-anxious	
	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*
High value peers								
A. Average predicted social feedback	51.70	*10.02*	57.34	*11.43*	53.85	*18.61*	55.69	*15.07*
Number of trials by prediction category:								
B. Positive feedback predictions	17.47	*5.12*	20.81	*5.49*	18.00	*8.23*	18.75	*5.71*
C. Negative feedback predictions	12.53	*5.12*	9.19	*5.49*	12.00	*8.23*	10.53	*5.70*
Low value peers								
A. Average predicted social feedback	42.06	*10.67*	50.80	*10.72*	33.67	*20.85*	37.28	*18.36*
Number of trials by prediction category:								
B. Positive feedback predictions	13.47	*6.12*	18.00	*5.29*	10.07	*8.37*	10.79	*7.53*
C. Negative feedback predictions	16.53	*6.12*	12.00	*5.29*	19.93	*8.37*	18.63	*8.07*

During a first run of fMRI data acquisition, participants used a 0 (not at all) to 100 (very much) scale to predict whether high and low value peers would want to chat with them. (A) Describes average prediction values. Trials were then parsed into a positive feedback prediction category (ratings of 51–100) or negative feedback prediction category (ratings of 0–50). The average number of trials for each prediction category is described by B and C.

Table 3
Significant group-level activation clusters for primary prediction error analyses.

	MNI coordinates			Cluster size	*F*	Partial η^2
	x	*y*	*z*	*voxels*		
A. Prediction error signaling						
Striatum	14	14	6	282	22.61	0.20
Caudate	−11	11	13			
	14	14	6			
Putamen	31	11	5			
Ventral striatum	14	4	−1			
Cerebellum	24	−66	−50	115	24.15	0.09
B. Functional connectivity with striatum						
Medial prefrontal cortex	−4	42	7	28	12.35	0.14
Lentiform nucleus	−21	−5	20	83	18.63	0.18
Thalamus	16	−15	11	66	21.02	0.16
Caudate	−4	11	2	48	16.48	0.17
Lateral prefrontal cortex	−49	42	9	45	14.04	0.14

(A) Activation clusters reflect social anxiety (anxious/non-anxious) × age group (adult/adolescent) × peer value (high/low) × actual social feedback (positive/negative) × prediction error (expected/unexpected feedback) interaction. Whole brain analysis, $p < .005$, cluster size >70. (B) Activation clusters reflect social anxiety (anxious/non-anxious) × age group (adult/adolescent) psychophysiological interactions for expected and unexpected positive social feedback from high value peers. Whole brain analysis, $p < .005$, cluster size > 20; Seed = 6 mm sphere (centered at 14, 14, 6). Suggested norms for effect size with partial η^2: small = .01; medium = .06; large = .14.

3.3. Functional connectivity analyses

PPI analyses using a striatal seed defined based on results in the 5-way interaction (thus limited to positive feedback from high-value peers) revealed that, as hypothesized, levels of striatal-mPFC functional connectivity varied as a function of prediction error, social anxiety, and age group. Specifically, connectivity during inaccurately predicted (unexpected) relative to accurately predicted (expected) positive feedback from high-value peers, varied by anxiety and age group (Fig. 5A; Table 3B). As depicted in Fig. 5B, socially anxious adolescents exhibited negative functional connectivity between striatum and mPFC during inaccurately predicted (unexpected) relative to accurately predicted (expected) feedback ($M = -0.06$, SD = .08) to a greater degree than anxious adults ($M = .01$, SD = .06), non-anxious adults ($M = -.02$, SD = .06), and non-anxious adolescents ($M = .02$, SD = .06; $p < .05$ for each comparison). Significant group differences outside of mPFC region are reported for completeness in Table 3B.

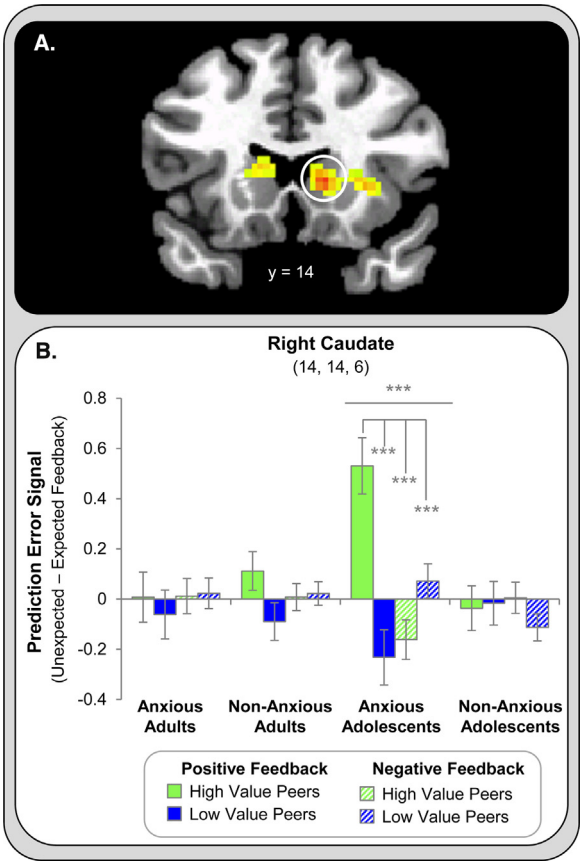

Fig. 4. Brain regions differentially engaged by prediction errors. (A) Bilateral striatal activity for prediction errors varied by age group and anxiety, depending on peer value and feedback. This reflects a significant 5-way interaction between social anxiety (anxious/non-anxious) × age group (adult/adolescent) × peer value (high/low) × actual social feedback (positive/negative) × prediction error (expected/unexpected peer feedback) interaction. (B) Activation from right caudate was extracted and plotted to facilitate interpretation. Brain activity associated with prediction error (reflected by each bar) was calculated by subtracting inaccurate predictions from accurate predictions. ***$p < .005$.

3.4. Relationship between recall and strength of functional connectivity

A repeated measures ANOVA demonstrated recall for expected and unexpected positive feedback from high-value peers varied by social anxiety and age group ($F(1,86) = 5.91$, $p < .02$; Fig. 5C; Table S4 shows data for all event types). Decomposing this interaction using paired samples t-tests within each group, revealed a significant difference for expected and unexpected feedback for socially anxious adolescents ($t(14) = 2.60$; $p < .02$), but no other group (Fig. 5C).

To further characterize these data, recall rates were compared with chance (.50 recall rate; dotted line in Fig. 5C). Socially anxious adolescents accurately recalled expected feedback ($t(14) = 3.52$; $p < .005$), but performed at chance level for unexpected feedback. Regardless of expectation, non-anxious adults ($t(31) = 4.53$, $p < .001$) and adolescents ($t(23) = 2.63$, $p < .03$) accurately recalled feedback, whereas anxious adults performed at chance levels. Results for non-anxious adolescents do not remain significant after using Bonferroni correction for multiple comparisons.

To determine the extent to which striatum-mPFC functional connectivity related to memory biases, recall was related to PPI values across groups. While there was no relationship in adults (standard and robust r's = −.004; p's > 0.10), among adolescents, negative mPFC-striatal functional connectivity was associated with worse recall for unexpected feedback (standard $r = .33$, $p < .05$; robust $r = .34$, $p = .09$; Fig. 2D). Anxious adolescents were driving this relationship. Specifically, there was a significantly positive relationship between functional connectivity and recall in anxious adolescents (standard $r = .53$, $p < .05$; robust $r = .55$, $p < .05$), but not healthy adolescents (standard $r = -.15$, $p > 10$; robust $r = 14$, $p > 10$).

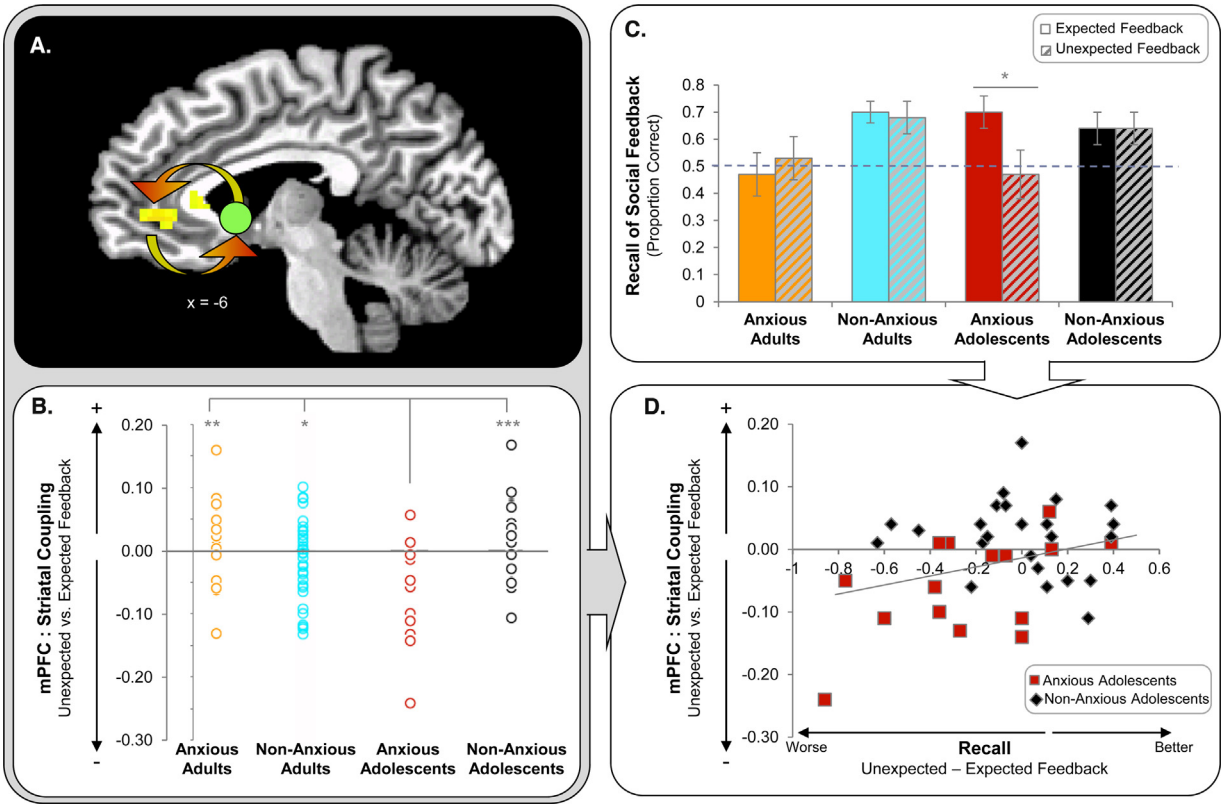

Fig. 5. Functional connectivity and recall for positive feedback from high-value peers. (A) Results from psychophysiological interaction analyses, using a 6 mm sphere in right caudate as a seed (centered at 14, 14, 6), demonstrate group differences in functional connectivity between the striatum and mPFC during unexpected, relative to expected, positive feedback. (B) Activity from right caudate was extracted for each participant and plotted to facilitate interpretation. On the *y*-axis: negative values reflect more negative mPFC-striatal functional connectivity during unexpected (inaccurately predicted) relative to expected (accurately predicted) feedback, positive values reflect more positive mPFC-striatal functional connectivity during unexpected (inaccurately predicted) relative to expected (accurately predicted) feedback. (C) Recall of social feedback. Dotted line represents chance (probability of recall = .50). (D) Among adolescents, but not adults, negative mPFC-striatal functional connectivity was associated with worse recall for unexpected feedback, relative to expected positive feedback. On the *x*-axis: negative values indicate worse recall for unexpected than expected positive feedback; positive values indicate better recall for unexpected than expected positive feedback; 0 values indicate equal recall for expected and unexpected positive feedback. $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .005$.

Fisher's *r*-to-*z* transformation confirmed that the association was stronger for anxious adolescents relative to healthy adolescents ($z = 2.10$, $p < .05$), and stronger for anxious adolescents relative to all adults ($z = 2.35$, $p < .05$).

4. Discussion

This study assessed brain activity as participants predicted, and then received, social feedback. Whole brain analyses revealed that bilateral striatal activity for PEs varied as a function of social anxiety and age group, depending on peer value and feedback valence. The pleasant surprise of unexpected positive feedback from highly-valued peers was related to striatal hyperactivity and weaker striatal-mPFC functional connectivity in anxious compared to non-anxious adolescents. Thus, unique brain-behavior relationships manifest for social PEs in socially anxious adolescents.

This study replicates prior behavioral findings in adolescents (Guyer et al., 2008) and extends them to adults. We demonstrate that predicted feedback from peers is related to their initial value. Both adults and adolescents expected more positive feedback from high-, relative to low-value peers. However, we also found age-based differences such that adolescents predicted significantly lower levels of positive feedback from low-value peers.

Unique fMRI findings also emerged. Socially-anxious adolescents were the only group to show patterns typical of PE processing: striatal engagement during unexpected, relative to expected, positive outcomes (Schultz et al., 1997). This finding may reflect unique reward-related behavior and learning (O'doherty, 2004; Yin et al., 2009) in response to unexpected positive social feedback. Alternatively, since striatal engagement has also been linked to various forms of arousal (e.g., Izuma et al., 2008; Miller et al., 2014; Schiller and Delgado, 2010), findings may reflect more complex influences, including a mixture of fear and excitement specific to anxious adolescents. Likewise, the positive social feedback provided in the context of the chatroom task may not have been sufficiently potent to engender the experience of reward among anxious adults, and healthy participants. This paradigm includes one-time social feedback, purportedly generated at a distinct time period, from unknown peers with whom they are unlikely to interact with in the future. Thus, it is possible that striatal engagement during unexpected, relative to expected positive outcomes was observed among anxious adolescents because they were the only ones who experienced the outcomes as salient. Future work that matches the salience of social outcomes across adults and adolescents is needed to tease apart this relationship.

PE-based learning, which occurs when predictions are updated (Schultz et al., 1997), has been linked to striatal-mPFC connectivity (Haber et al., 2006; O'doherty, 2004). Here, we found that socially anxious adolescents were unique in exhibiting more *negative* striatal-mPFC functional connectivity for unexpected, relative to expected, positive feedback from high-value peers. Thus in adolescence, an important contributor to social anxiety may relate to dysfunctional communication between the striatum and mPFC in response to unexpected positive social feedback. Specifically, dysregulated striatal-mPFC functional connectivity may have a

deleterious effect on the ability to learn from a pleasantly surprising social interaction. Support for this hypothesis comes from results in the current study linking striatal-mPFC functional connectivity to deficits in recall for social feedback among socially anxious adolescents. Group differences in striatal connectivity were also found in ventrolateral PFC. This brain region is not typically implicated in PE processing, and did not relate to PE-based learning. Thus, differential striatal-vlPFC connectivity may relate to other aspects of cognition engaged during the task. One shortcoming of our use of traditional, as opposed to generalized PPI (gPPI) methods is that functional connectivity can only be interpreted for one condition (i.e., unexpected positive feedback from high value peers), relative to another condition (i.e., expected positive feedback from high value peers). gPPI analyses, which can accommodate more than two conditions within a single model, allows for more flexibility in statistical analyses, and provides greater insight into directionality of results by contrasting connectivity in each condition of interest relative to an implicit or explicit baseline (McLaren et al., 2012). Such techniques could be very beneficial to future work in this area.

Replicating prior studies, we found that non-anxious individuals are capable of learning from positive outcomes, regardless of age (Moutsiana et al., 2013). However, this ability was impaired in both anxious adolescents and adults. Although anxious adolescents recalled expected positive feedback from high-value peers, they were unable to recall unexpected positive feedback, and thus could not draw on the 'pleasant surprise' of being proven wrong to update subsequent predictions. While memory impairments were relatively specific among anxious adolescents, there were more general or pervasive among anxious adults, who failed to recall both expected and unexpected positive outcomes from high-value peers. This finding may indicate that memory for social feedback is impaired in anxious adults regardless of its valence.

Our focus on positive PEs reflects the fact that neural response during positive PE processing varied as a function of social anxiety and age group; no such effects were observed during negative PE processing, when participants expected positive, but received negative, feedback. Given that models of reinforcement learning emphasize the importance of both positive and negative PEs for learning, the specificity of our findings are somewhat surprising. Despite an emphasis on similarities in the neural mechanisms mediating positive and negative PEs, the two types of events can generate somewhat different neural responses (Redish, 2013). In fact, some evidence suggests positive and negative PEs differentially influence learning in social contexts similar to those in the current study. For instance, recent work demonstrated that healthy youths and adults effectively learned from positive, but not negative, PEs generated by social feedback (Jones et al., 2014). Thus, the present findings could reflect the fact that positive and negative PEs differentially influence social learning, and that the neural circuits engaged by negative social PEs fail to vary as a function of social anxiety and age group. Although null results must be interpreted with caution, these findings suggest that it is the dysregulated response to positive, but not negative, social PEs that may contribute to social anxiety in adolescents.

One major limitation in the current study is the relatively small number of trials for some event types in our primary analyses. As the complexity of questions posed in fMRI research grows, task complexity has also increased. Our primary analysis parsed social experiences based on peer value, expectations, and feedback. This precisely mirrored the task structure, but came at a cost: some event types had relatively few trials. Although other well-established paradigms utilize similarly sparsely-populated events (e.g., Lebron-Milad et al., 2012; Milad et al., 2007, 2009, 2013; Visser et al., 2013; Wheelock et al., 2014), the small number of trials raises concerns about the stability of results. Research aimed at extending these findings should consider increasing the sample size, and/or implementing novel paradigms that include more trials for each event type while maintaining task complexity needed to retain external validity (Jarcho et al., 2013).

A second limitation was our categorical approach to studying age and social anxiety. This facilitated the interpretation of complex higher-order interactions, which would have been difficult to interpret in the context of continuous, rather than categorical, analyses. A shortcoming of this approach is that we were unable to test whether unique patterns of brain response occurred during specific developmental phases (Blakemore and Mills, 2014; Forbes and Dahl, 2010, 2012; Spielberg et al., 2014a,b; van den Bos et al., 2012). Although we hypothesize that the greatest difference in brain function emerges during adolescence, puberty was not assessed via exam or hormonal assay. Thus, developmental phase could not be characterized with appropriate specificity (Blakemore et al., 2010). Moreover, since adolescents were not stratified by age according to puberty, we were unable to differentiate the effects of age and puberty on brain or behavioral outcomes (Blakemore et al., 2010). A categorical approach also precluded analyses based on severity of social anxiety symptoms. Although a dimensional approach to the study of psychopathology is critical, treatment is most commonly delivered to individuals who meet specific diagnostic criteria. Thus, treating social anxiety as a categorical variable was more closely in line with the overarching goal of our research, which seeks to inform potential treatment strategies.

A third limitation is that participant characteristics including sex, stage of pubertal development, and race were only minimally considered. Beyond the comparison of adults and adolescents, we did not have a sufficiently large number of participants to isolate influences of these and other potentially important variables on the anxiety-brain function relationship. Mounting evidence suggests sex (Guyer et al., 2009, 2012, 2014b; Lee et al., 2014) and pubertal stage (Jankowski et al., 2014; Klapwijk et al., 2013) based differences in brain and behavioral responses to social stimuli. We had insufficient power to test for interactions among sex, pubertal development, social anxiety, and age group. However, we did conduct two secondary analyses (see Supplementary Material), one restricted to female participants, and another that closely matched adult and adolescent groups based on sex, age, and pubertal development. For both of these analyses, results showed similar patterns as in the primary analyses, despite their markedly smaller sample size. This suggests that while sex and pubertal development play some role in influencing brain response in the current study, our results for social anxiety and age group remain when controlling for these factors. Finally, brain responses engaged by social exclusion (Masten et al., 2011), emotion processing (Lieberman et al., 2005), and trust-based evaluations (Stanley et al., 2012) also vary depending on the congruency of race with participants. These differences are influenced by early life exposure people of other races (Telzer et al., 2013a), and vary based on development (Telzer et al., 2013b). Given that the majority of participants in this study were White, non-Hispanic or Latino, we were unable to test the effects of race on brain function. Future studies should be designed specifically to disentangle the effects of sex, race, pubertal phase, and severity of anxiety symptoms on brain function during social processing.

A fourth limitation is that peers selected and rejected for a potential chat may have been categorized based on factors other than social value. For instance, peers may have been selected or rejected because of their perceived similarity or mismatch with the participant. However, positive characteristics were considered more frequently when making the decision to select, rather than reject, peers (Table S2). This is consistent with our definition of selected peers as having high social value, and rejected peers as having low social value. Yet, the conceptualization of peer value may vary across groups. For example, anxious adolescents may generally

value peers more highly than non-anxious adolescents or adults. Thus peers categorized as low value by anxious adolescents may still be of higher value than those similarly categorized by other groups. Such differences in peer value could, in turn, differentially influence the emotional impact of accurately or inaccurately predicted positive or negative peer feedback. Future studies that utilize the Chatroom task may be able to address this issue by explicitly assessing the value participants ascribe to selected and rejected peers, as well as the extent to which they think peers are similar or dissimilar to themselves, and the subsequent effect of positive and negative feedback on their affective state in the presence or absence of a PE. Additionally, introducing more levels of positive and negative, as well as neutral feedback, may further clarify the role of value in the findings reported here. For example, this might allow parametric analyses to model associations among graded levels of valenced feedback, development, and individual differences in anxiety.

5. Conclusion

Despite these limitations, the present findings support the idea that unique neural mechanisms mediate social anxiety during adolescence and adulthood. During adolescence, peers are highly salient, as complex social learning operates in the service of establishing new behavior patterns. Dysregulated social PE-based fronto-striatal engagement during this sensitive period may set the stage for abnormal development of emotional and cognitive processes that contribute to long-term expression of social anxiety. Although longitudinal research is needed to explicitly test this relationship, the current data suggest that interventions aimed at modulating fronto-striatal connectivity that support PE-based social learning in adolescents may be particularly promising.

Conflict of interest

No authors have any conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dcn.2015.03.002

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