Fearfulness moderates the link between childhood social withdrawal and adolescent reward response

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Withdrawal from peers during childhood may reflect disruptions in reward functioning that heighten vulnerability to affective disorders during adolescence. The association between socially withdrawn behavior and reward functioning may depend on traits that influence this withdrawal, such as fearfulness or unsociability. In a study of 129 boys, we evaluated how boys' fearfulness and sociability at age 5 and social withdrawal at school at ages 6 to 10 and during a summer camp at age 9/10 were associated with their neural response to reward at age 20. Greater social withdrawal during childhood was associated with heightened striatal and mPFC activation when anticipating rewards at age 20. Fearfulness moderated this effect to indicate that social withdrawal was associated with heightened reward-related response in the striatum for boys high on fearfulness. Altered striatal response associated with social withdrawal and fearfulness predicted greater likelihood to have a lifetime history of depression and social phobia at age 20. These findings add greater specificity to previous findings that children high in traits related to fear of novelty show altered reward responses, by identifying fearfulness (but not low levels of sociability) as a potential underlying mechanism that contributes to reward alterations in withdrawn children.

Keywords: reward; social withdrawal; fearfulness

Some children show high levels of withdrawn behavior in social situations (Coplan and Armer, 2007), and behavioral social withdrawal has been associated with various maladaptive outcomes such as clinical levels of social anxiety and depression in children and adolescents (Rubin *et al.*, 2009). Indeed, social withdrawal may be associated with regulatory processes in two specific ways. First, withdrawn behavior may reduce the amount of positive social interactions children have with their peers. Second, these limited experiences may make negative social interactions more salient, increasing children's sensitivity to reward and rejection (Masten *et al.*, 2012) and contributing to over-regulation in response to negative feedback in potentially rewarding events. As a result, socially withdrawn children—especially those who are socially fearful or sensitive to negative social experiences—may have altered reward processing, including altered function in neural reward circuitry. Possibly, this altered reward processing may have developed in response to social withdrawal, as prior animal work indicates that social environments can directly influence reward circuitry (Matthews and Robbins, 2003).

Both conceptual models and empirical evidence indicate that behavioral withdrawal in social contexts may be a heterogeneous category, with some children withdrawing because of social reticence and/or fear of novelty (i.e. fearfulness) and others withdrawing due to preferred solitude and low sociability (Rubin *et al.*, 2009). Research focusing on behavioral inhibition, an early, stable temperamental trait characterized by social reticence and that manifests behaviorally as social withdrawal (Kagan *et al.*, 1987), has indicated that inhibited children show hypersensitive responses to rewarding stimuli (Guyer *et al.*, 2006b) and are likely to develop social anxiety (Chronis-Tuscano *et al.*, 2009). While these findings indicate altered neural response to reward in children who exhibit social withdrawal, presumably as a result of fearfulness and social anxiety, little is known about neural response to

reward in children who withdraw due to low levels of sociability. These children's social withdrawal might reflect an enjoyment of solitary activities coupled with typical reward function.

Atypical functioning in reward circuitry has been linked to the pathophysiology of various clinical disorders, including both depression and anxiety (Guyer *et al.*, 2012; Zhang *et al.*, 2013), for which socially withdrawn and behaviorally inhibited children are at risk (Rubin *et al.*, 2009). The striatum, a region associated with subjective experience of pleasure and positive affect (Haber and Knutson, 2010), and the mPFC, a region associated with self-processing and abstract planning and pursuit of rewards, are two important reward regions implicated in these clinical disorders (Davey *et al.*, 2008; Price and Drevets, 2010). Reward alterations differ depending on clinical diagnosis, with depressed adolescents and adults showing low striatal and high mPFC response to reward (Zhang *et al.*, 2013) and clinically anxious adolescents showing high reward responses in both regions (Guyer *et al.*, 2012). These reward alterations could serve as a mechanism through which some socially withdrawn adolescents develop depression and others develop anxiety.

Similar brain regions are activated in response to non-social and social rewards (i.e. striatum and mPFC; Izuma *et al.*, 2008). Monetary reward paradigms are an established method of evaluating reward function and have been linked to various social influences, such as child maltreatment (Guyer *et al.*, 2006a). Given this study's focus on evaluating how social behaviors and temperament traits may combine to influence reward functioning, testing this question using non-social reward stimuli may be important, as it may clarify how these social variables can influence non-social forms of reward processing.

These prior findings suggest that different reasons for social withdrawal (fearfulness *vs* low sociability) may be associated both with different neural reward responses and the development of two distinct affective disorders (i.e. anxiety, depression). In particular, socially withdrawn children may show altered reward function either because they have greater anxiety over the receipt of rewards (i.e. worrying about not receiving rewards or hyping up the importance of rewards) or because they find rewards less inherently pleasurable. Temperamental traits (i.e. fearfulness or unsociability) may explain these neural differences and may distinguish risk for anxiety *vs* depression. Fearful children may be

triggered by the pursuit of rewards, and this heightened response may contribute to avoidance and higher levels of anxiety. Less sociable children who prefer solitude may care less about rewards or find them less pleasurable, and this blunted reward responding may lead to anhedonia and increased risk for clinical levels of depression during adolescence, when neural and social changes can combine to increase vulnerability to depression (Davey et al., 2008). Recent work has shown that fearful children both show heightened reward sensitivity (Bar-Haim et al., 2009) and are at increased risk for developing social phobia (Chronis-Tuscano et al., 2009). Less sociable youth are at risk for developing depression (Morgan et al., 2013) and show heightened positive connectivity between the ventral striatum and the mPFC during late adolescence (Healey et al., 2014).

The current study focused on how withdrawn behavior in childhood is associated with reward-related brain function during late adolescence in a sample of boys at high socio-demographic risk for behavioral and emotional problems. We viewed social withdrawal as a set of behaviors (e.g. playing alone) that could be due to preferred solitude or social fearfulness. We evaluated how the association between social withdrawal and reward response may differ depending on these two dimensions of temperament: fearfulness and sociability. We assessed fearfulness and sociability and socially withdrawn behaviors in childhood, as these dimensions become more stable during childhood (Rubin et al., 2009). We measured reward function during late adolescence (age 20), as this is a developmental period when affective disorders associated with reward functioning have likely onset and stabilized (Costello et al., 2002). As research linking withdrawn/inhibited behavior with reward response is comparatively understudied relative to research linking it to threat response, we focus on neural response to reward. Given growing evidence that altered reward functioning is associated with various clinical disorders (e.g. anxiety, substance dependence, depression; Koob and LeMoal, 2008; Guyer et al., 2012; Zhang et al., 2013), we believe our focus on reward functioning is warranted. Because evidence suggest that social withdrawal has greater costs, such as loneliness, for boys than girls (Coplan et al., 2007), evaluating these research questions in a sample of boys is needed.

We tested whether alterations in reward function associated with social withdrawal were associated with lifetime history of depression or social phobia. We chose to focus on social phobia vs. other anxiety disorders based on previous evidence that heightened striatal response to reward is particularly evident in socially anxious adolescents relative to adolescents with other forms of anxiety (Guyer et al., 2012). We tested the following hypotheses.

Hypothesis 1

Higher levels of social withdrawal would be associated with higher levels of striatal and mPFC activation to reward.

Hypothesis 2

We predicted significant interactions between child social withdrawal and child fearfulness and between social withdrawal and sociability on reward response in the striatum, such that social withdrawal would be associated with higher levels of striatal response to reward in the context of higher levels of fearfulness and higher levels of sociability.

Hypothesis 3

Heightened striatal response in regions associated with social withdrawal and fearfulness or sociability would be associated with a greater likelihood of lifetime history of social phobia. Low levels of striatal response in regions associated with social withdrawal and fearfulness or sociability would be associated with a greater likelihood of lifetime history of depression.

METHOD

Participants were 129 boys from a longitudinal project on vulnerability and resilience in boys from low-income families (Shaw et al., 2012). Families were recruited to the study when boys were between the ages of 7 and 17 months of age from the Women, Infants, and Children (WIC) Nutritional Supplement centers in the greater Pittsburgh area. All participants were boys due to the longitudinal project's focus on antisocial behavior. The sample was 54% European-American, 36% African-American and 9% were of other races/ethnicities (e.g. biracial, Hispanic). At the 18-month assessment, average family income was $1068.55 per month and the mean SES score was 23.4 using the Hollingshead Index, indicating working-class status (Hollingshead, 1975, unpublished data). Average number of years mothers completed in school was 12.6 years at the 18 month time-point.

Parents reported on boys' fearfulness and sociability when boys were 5.5 years old. Teachers reported on boys' withdrawn behavior in the classroom between ages 6 and 10. When boys were 9 to 10 years old, they were invited to participate in a summer camp to evaluate peer-context social behavior in a naturalistic setting. Peers nominated and camp counselors rated boys on social withdrawal in the camp setting. At age 20, the boys were invited to participate in an fMRI assessment of their neural response to reward and completed a structured clinical interview.

Originally, 310 boys and their families were recruited to participate in the longitudinal project. Attrition tended to be modest at each wave, with 86% having teacher-reported withdrawn behavior data from ages 6 to 10. Although all 310 boys were invited to participate in a summer camp study (SCS), only 145 elected to participate due to the time commitment involved in the SCS. Of the 310 boys, 186 boys participated in fMRI scan at age 20, with 166 boys having usable fMRI data ($n = 12$ removed due to difficulty with the task; $n = 6$ due to insufficient coverage; $n = 2$ due to being on drugs or experiencing psychosis during the scan). There were no significant differences in mother's education level of family income for youth participating in the camp or differences in peer nominations of social withdrawal for participants with fMRI data compared with those without these data. Altogether, the number of participants with usable scan data, childhood social withdrawal data, fearfulness and sociability data and clinical diagnosis data was 129.

Fearfulness and sociability

At age 5.5, parents reported on boys' fearfulness and sociability using the EASI (EASI, Buss and Plomin, 1975). The fear emotionality and sociability subscales were used for the sample. A sample item from the fear emotionality subscale is 'he tends to be nervous in new situations' and a sample item from sociability scale is 'he makes friends very quickly'. Each subscale originally had 5 items; however, reliability estimates were low for the full 5-item subscales (0.50 for fear emotionality and 0.56 for sociability) and thus one item was removed from each subscale to increase reliability. The reverse-scored item 'he tends to be shy' from the sociability subscale and the reverse-scored item 'he has fewer fears than most children his age' from the fearfulness subscale were removed. Reliability for the 4-item fearfulness and sociability subscales were 0.71 and 0.64, respectively. Results were substantively similar when using the 5-item fearfulness and sociability subscales and the shortened subscales.

Social withdrawal

From ages 6 to 10, boys' teachers reported on boys' withdrawn behavior in the classroom using the Teacher Report Form (TRF; Achenbach, 1991). Internal consistency ranged from 0.80–0.86 across the 5 time-points. Sample items include 'withdrawn, doesn't get involved with others' and 'would rather be alone than with others'. Teacher-reported

withdrawn behavior was modestly to moderately correlated across ages (from age 6 through age 10; $rs = 0.23–0.50$, $Ps < 0.02$).

At age 9/10, boys attended one of three sessions of summer camp. Each group ('huddle') of boys within a session was composed of 10–12 boys and lasted for 10 days across a 2-week period. Groups were led by undergraduate-level counselors and were heterogeneous with respect to child age. Boys were placed in camp groups with other boys whom they had not previously met (Trentacosta and Shaw, 2009).

At the end of both weeks of a session, boys were told to nominate as many peers as they would like on four items associated with social withdrawal. These items included 'very shy' and 'usually ignored' and peer nominations for both weeks were strongly correlated with one another ($r = 0.75$, $P < 0.01$). At the end of the 2-week session, camp counselors reported on boys' withdrawn behavior using a 32-item behavioral ratings measure based on the Playground Observer Impressions (Reid et al., 1991) on each child. We used the four item shy/withdrawn subscale of this measure ($\alpha = 0.79$). Sample items include 'did the child seem detached and distant?' and 'is child ignored by peers?' Counselor ratings were correlated (two counselors per boy, $r = 0.57$, $P < 0.01$). This method of peer-rated and counselor-rated social withdrawal previously predicted later depressive symptoms (Morgan et al., 2013), providing evidence of its predictive validity.

A composite social withdrawal score was created by centering and then averaging boys' teacher-reported withdrawn behavior across age 6 to 10, peer nominations of social withdrawal at camp at 9/10 and camp counselor ratings of withdrawn behavior at camp at 9/10 ($rs = 0.27–0.35$, $Ps < 0.01$ for three scores). Boys who had scores of social withdrawal from one or more reporter (but not necessarily all three forms of reporters) received a composite social withdrawal score based on the average of available data (59% had more than one form of data). There were no significant differences in family income, socio-economic status or maternal education level for boys with multiple forms of social withdrawal data relative to those with only one form ($Fs = 0.3–2.03$, ns).

Boys' clinical history

At age 20, boys reported on their lifetime history of Axis I clinical disorders using the SCID (Spitzer et al., 1990) with a clinically trained staff person trained to reliability with a licensed clinical psychologist. Of the 129 boys, 15 boys had a history of Major Depressive Disorder (MDD) or Dysthymia (six were currently depressed) and 10 met criteria for Social Phobia. Three of these boys met criteria for both Social Phobia and MDD and were retained in t-test analyses for Hypothesis 3 which evaluated group differences in depression vs healthy and social phobia vs healthy. Boys with MDD and comorbid psychiatric illness ($n = 3$ with Substance Dependence) were included in the analyses (depression group) as were boys with Social Phobia and comorbid psychiatric illnesses ($n = 2$ with other Anxiety Disorders, $n = 1$ with Antisocial Personality Disorder) (social phobia group).

Ninety-seven boys had no lifetime history of a clinical disorder and comprised our healthy comparison group. Twelve boys met criteria for another psychiatric illness other than MDD or Social Phobia (Substance Dependence, Antisocial Personality Disorder, Generalized Anxiety Disorder, Specific Phobia) and were not included in these t-test analyses.

Boys' symptomatology

At age 20, boys reported on their current affective symptoms using the Beck Depression Inventory (BDI; Beck et al., 1988a) and the Beck Anxiety Inventory (BAI; Beck et al., 1988b). The measures had strong reliability ($\alpha = 0.86$ & 0.93).

Neural response to reward

Boys completed fMRI with a monetary reward paradigm at age 20. The fMRI paradigm was an 8-min slow event-related card-guessing game that evaluates neural response to the anticipation and receipt of monetary reward (Nusslock et al., 2012). Participants received win, loss or no-change feedback for each trial. Participants were told that their performance would determine a monetary reward after the scan, with $1 for each win trial and 50 cents deducted for each loss trial. Trials were presented in pseudorandom order with predetermined outcomes. Earnings totaled $6. Trials were presented in a single run, with 24 trials total and a balanced number of trial types within runs (i.e. 12 possible-win vs no-change and 12 possible-loss trials). During each trial, participants guessed via button press whether the value of a visually presented card was high or low (4 s), learned the trial type (possible-win or possible-loss) and anticipated feedback (6 s) and received feedback (1 s plus 9 s inter-trial interval). Participants were unaware of fixed outcome probabilities (i.e. that all participants received the same trials and outcome). During debriefing, participants stated that they understood the task and thought that the outcomes were due to chance.

fMRI acquisition, preprocessing

Each participant was scanned using a Siemens 3T TIM Trio scanner. BOLD functional images were acquired with a gradient echo planar imaging (EPI) sequence and covered 39 axial slices (3.1 mm thick) beginning at the cerebral vertex and encompassing the entire cerebrum and the majority of the cerebellum (TR/TE = 2000/25 ms, FOV = 20 cm, matrix = 64 × 64). All scanning parameters were selected to optimize the quality of the BOLD signal while maintaining a sufficient number of slices to acquire whole-brain data. Before the collection of fMRI data for each participant, we acquired a reference EPI scan that we visually inspected for artifacts (e.g. ghosting) and for good signal across the entire volume of acquisition. The fMRI data from all included participants were cleared of such problems.

Preprocessing and whole-brain image analyses were completed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). For each scan, structural images for each participant were segmented to focus on gray matter, and functional images were realigned to correct for head motion, coregistered to the segmented structural data, spatially normalized into standard stereotaxic space (Montreal Neurological Institute template) using a 12-parameter affine model and smoothed with a 6-mm full-width at half-maximum Gaussian filter. Preprocessed data were analyzed using first-level random effects models that account for scan-to-scan variability and second-level random effects models that account for participant-to-participant variability to determine task-specific regional responses. Participants' first-level results were inspected individually for adequate coverage of the ventral striatum (> 80% of voxels with good signal; $n = 6$ were excluded due to < 80% of coverage). All remaining participants had movement < 2 mm in each plane.

Data analytic strategy

Before conducting level 2 analyses, we constructed a combined mPFC/striatum mask using the WFU PickAtlas Tool (v1.04). The striatal ROI within the mask was defined as a 3642-voxel size 20-mm radius sphere, centered on the ventral striatum using Talairach coordinates $x = 0$, $y = 0$ and $z = 0$ and encompassing dorsal and ventral striatum (Forbes et al., 2009). The mPFC ROI within the mask was centered around coordinates $x = 0$, $y = 42$ and $z = 18$, and defined as a 5393-voxel size 25 mm-radius sphere including medial Brodmann Area (BA) 9, medial BA 10 and BA32 (Forbes et al., 2010). Next, we reduced our combined ROI mask to a sample-specific ROI mask by conducting within-T analyses in SPM8 (in which activation in reward-related
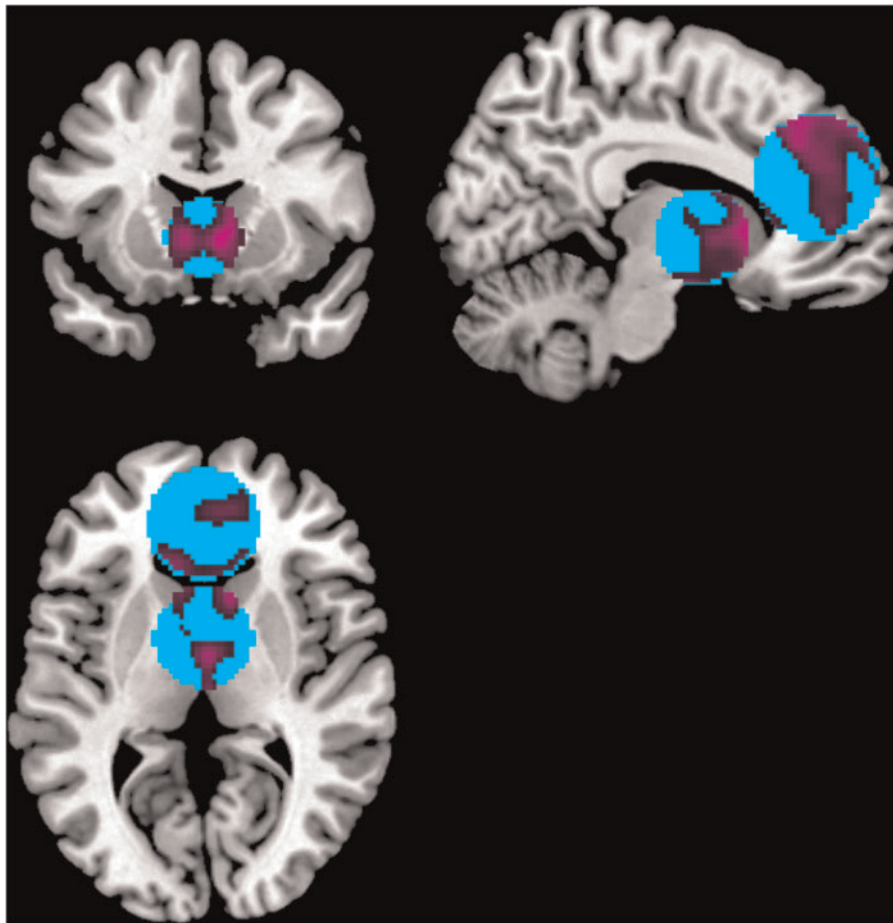
Fig. 1 Anatomical masks (turquoise) with sample-specific functional masks (purple) overlaid.

regions during reward anticipation *vs* baseline was our outcome variable) and using our combined ROI mask as a mask for these analyses. Simulations in AFNI using the AlphaSim program determined that the per-voxel threshold of $P = 0.05$ required for significant clusters to create these combined masks was 243 voxels.

We then saved our significant cluster for use as a sample-specific combined striatum/mPFC mask which was used for our remaining level 2 analyses (see Figure 1). Simulations in AFNI using the AlphaSim program determined that the per-voxel threshold of $P = .05$ for this mask was 130 voxels.

For our analyses of interest (level 2 analyses), we conducted a multiple regression model in SPM8 in which (i) social withdrawal during childhood, (ii) fearfulness or sociability and (iii) the two 2-way multiplicative interactions between social withdrawal and each of these factors were entered as predictors of reward anticipation. We focused on reward anticipation given that VS function is more closely linked to anticipatory positive affect (Haber and Knutson, 2010). Significant multiplicative interactions were explored using simple slope analyses (Preacher *et al.*, 2006). We created values of high and low fearfulness by subtracting and adding one standard deviation from our centered fearfulness score. We then re-computed our regression models using the high or low fearfulness score to explore the effect of social withdrawal on reward response for high or low fearfulness.

Next, we explored how reward-related VS or mPFC regions associated with social withdrawal were associated with lifetime history of affective disorders. *T*-tests were conducted in SPM8 with Depression (MDD, Dysthymia) *vs* healthy or Social Phobia *vs* healthy entered as

the predictor variable of interest and reward anticipation > baseline as the outcome variable. Using conjunction analysis (Nichols *et al.*, 2005), we used the functional mask from our significant interaction findings on reward function to determine whether diagnosis of depression or social phobia was related to alterations in reward function in clusters associated with the combination of social withdrawal and fearfulness or sociability. Conjunction analysis is useful, as it is valid even when making non-independent comparisons (Nichols *et al.*, 2005).

Whole brain analyses were used to confirm that our ROI remained significant in unconstrained results. All tests were set to a threshold of $P < 0.05$ and corrected for multiple comparisons using simulations in the AFNI AlphaSim program (130 voxels required for sample-specific mask; 30 voxels for social withdrawal x fearfulness mask; 580 voxels for whole brain findings).

RESULTS

Table 1 lists the means, standard deviations and interrcorrelations for fearfulness, sociability and social withdrawal for all boys in the sample and for both diagnostic groups. There were no significant differences in fearfulness, sociability or social withdrawal for boys with social phobia or depression relative to healthy boys (Fs = 0.02–0.29, *ns*).

Hypothesis 1

Greater social withdrawal was associated with greater activation in the striatum when anticipating reward [caudate head, 205 voxels, 2, 14, 1, df = 123, $t = 4.35$]. Greater social withdrawal was associated with greater activation in the dmPFC when anticipating reward [medial BA 9, 142 voxels, 10, 38, 22, df = 123, $t = 3.15$] (Figure 2).

Table 1 Means, standard deviations and intercorrelations of fearfulness, sociability and social withdrawal

Variable	All boys M (s.d.)	DEP M (s.d.)	SP M (s.d.)	Range	1	2	3
1. Fearfulness	7.19 (2.64)	7.53 (2.20)	7.30 (2.71)	4.00–16.00			
2. Sociability	15.29 (3.09)	14.80 (3.19)	14.00 (4.22)	7.00–20.00	−0.09		
3. Social withdrawal	−0.06 (0.77)	−0.15 (0.93)	0.06 (1.00)	−1.17–2.55	−0.09	−0.22*	

Note. M = Mean; s.d. = Standard Deviation; DEP = Major Depressive Disorder or Dysthymia; SP = Social Phobia.
*$P < 0.05$.

Sociability and fearfulness were not directly associated with reward anticipation.

Hypothesis 2

The interactive effect of social withdrawal and fearfulness predicted activation in the striatum when anticipating reward [caudate head, 192 voxels, −2, 2, 0, df = 123, t = 3.53]. Simple slopes post hoc analyses in SPM8 revealed that social withdrawal was associated with greater striatal response (but not mPFC response) when anticipating reward only for boys with high fearfulness [caudate head, 165 voxels, 0, 16, 1, df = 123, t = 3.41] after constraining for the significant interaction clusters (Figure 3). No significant interaction was found between social withdrawal and sociability in predicting reward anticipation.

Hypothesis 3

Based on our findings for a significant interaction of social withdrawal and fearfulness, we focused our next set of analyses on these findings and did not consider the combination of social withdrawal and low sociability, which was not associated with neural response to reward. Using the functional mask from our significant social withdrawal x fearfulness interaction on reward anticipation (192 voxels), we evaluated how reward-related activation associated with the combination of higher levels of social withdrawal and fearfulness was associated with lifetime diagnosis of depression and social phobia using t-tests conducted in SPM8 (Table 2).[1]

As predicted, boys with a history of depression showed lower levels of striatal activation in clusters associated with the combination of social withdrawal and fearfulness when anticipating reward relative to emotionally healthy boys [caudate head, 165 voxels, 6, 12, −1, df = 110, t = 5.99].[2]

Also as predicted, we found that boys with a history of social phobia showed higher levels of striatal activation in clusters associated with the combination of social withdrawal and fearfulness when anticipating reward relative to emotionally healthy boys [caudate head, 172 voxels, 4, 14, −1, df = 105, t = 3.35].[3]

Analyses in which we used BAI and BDI did not yield significant clusters after correcting for multiple comparisons.

Whole brain analyses confirmed that our ROIs were significant regions of interest using an AlphaSim cluster-corrected level of P = .05, even when unconstrained.

DISCUSSION

We found evidence that social withdrawal during childhood (6–10 years old) was associated with alterations in reward-related

brain function at age 20 and that this effect was moderated by child fearfulness. Social withdrawal was related to greater activation in the striatum and mPFC when anticipating rewards at age 20. Interactive effects revealed that the striatal association during reward anticipation was only significant for children with high levels of fearfulness. These findings suggest that socially withdrawn children may be more sensitive to reward feedback and place greater salience and value on rewards if they are prone to high levels of hyper-vigilance and social reticence in novel situations.

In addition to mirroring previous findings that adolescents with a trait levels of social reticence (i.e. behavioral inhibition) show greater sensitivity to reward (Guyer et al., 2006b), our findings add greater specificity to our understanding of how these social characteristics influence reward processing. That is, as boys with low levels of sociability (i.e. withdrawing behaviorally due to preferred solitude) did not show alterations in reward response, it is fearfulness that appears to be driving the relation between social withdrawal and neural response to reward.

Social withdrawal may limit boys' experience with rewarding events that likely shape adaptive brain function in reward-related regions. One possibility is that social interactions influence sensitivity within reward and threat circuitry, as other research has shown that time with friends is associated with reduced sensitivity to rejection in the subgenual ACC, a region of the prefrontal cortex associated with negative affect (Masten et al., 2012). Withdrawing in social contexts may heighten the value of rewards (i.e. pursuing reward feeling more important for these fearful, withdrawn boys) and boys' concern with self-performance relative to enjoying the pursuit of rewarding experiences. We found a significant association between heightened caudate and dmPFC activation and social withdrawal in our study. Given that the dmPFC has been implicated in self-related processing (Denny et al., 2012), withdrawn children may engage in greater self-referential processing when anticipating rewards, judging their ability to win rewards in relation to others. Altogether, our findings contribute to our understanding of how social experiences can influence reward response.

Furthermore, we found that neural response to reward in regions associated with the combination of social withdrawal and fearfulness predicted two forms of psychopathology. Function in this striatal cluster predicted not only history of social phobia, but also history of depression. Indeed, our findings mirror previous research that has found blunted striatal activation in depressed adolescents and adults (Zhang et al., 2013) and heightened striatal activation in anxious adolescents (Guyer et al., 2012), and also mirrors research that has demonstrated increased risk for both social anxiety and depression in socially withdrawn, reticent children (Rubin et al., 2009; Silk et al., 2012). Thus, disruption to function in neural reward circuitry could be a mechanism for both forms of psychopathology. Based on our findings, it is possible that fearful, withdrawn boys who are less motivated by rewards may be vulnerable to depression whereas fearful, withdrawn boys who are sensitive to the value and importance of rewards may be at greater risk for developing social phobia. It should be noted that

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[1] Results were substantively similar when we removed boys with clinical history of depression or social phobia from the social withdrawal x fearfulness analyses [caudate head, 62 voxels, −2, 0, 0, df = 101, t = 2.98] and used those results as a mask for our depression and social phobia diagnoses models [depression: caudate head, 55 voxels, −4, 0, 0, df = 110, t = 3.58; social phobia: includes caudate head, 61 voxels, 4, −6, 4, df = 105, t = 3.18], although findings were only significant at uncorrected levels.

[2] Results were substantively similar when removing the three boys with history of substance dependence [caudate head, 165 voxels, 6, 12, −1, df = 107, t = 5.96 for reward anticipation].

[3] Results were substantively similar when removing the participant who also met criteria for Antisocial Personality Disorder [caudate head, 171 voxels, 4, 14, −1, df = 104, t = 3.64 for reward anticipation].
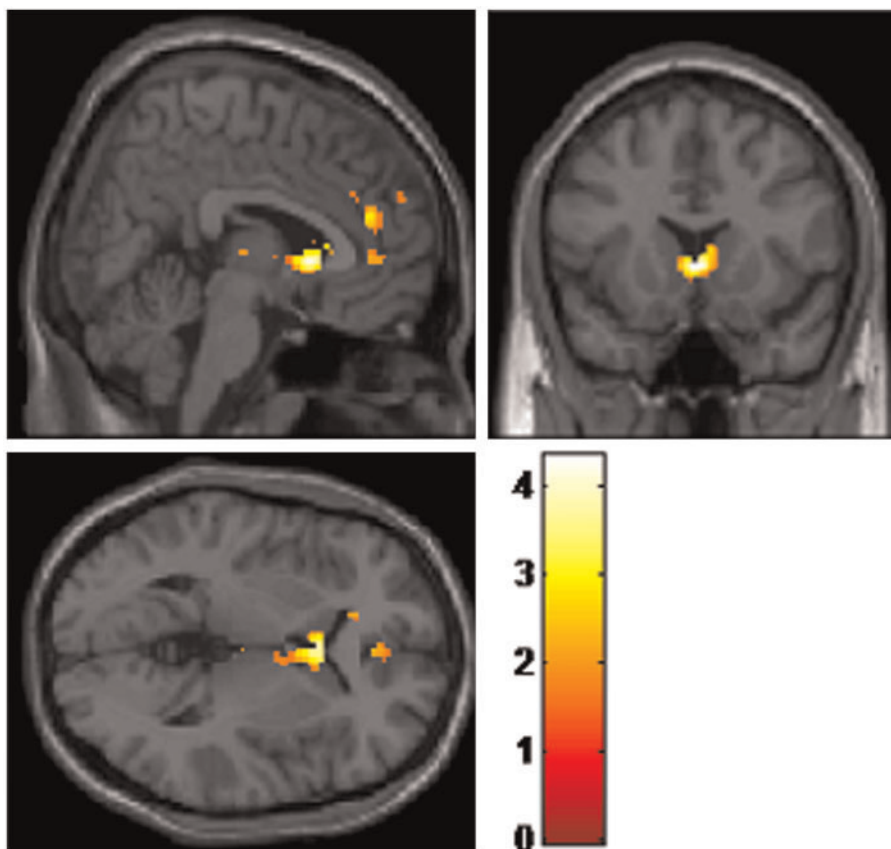
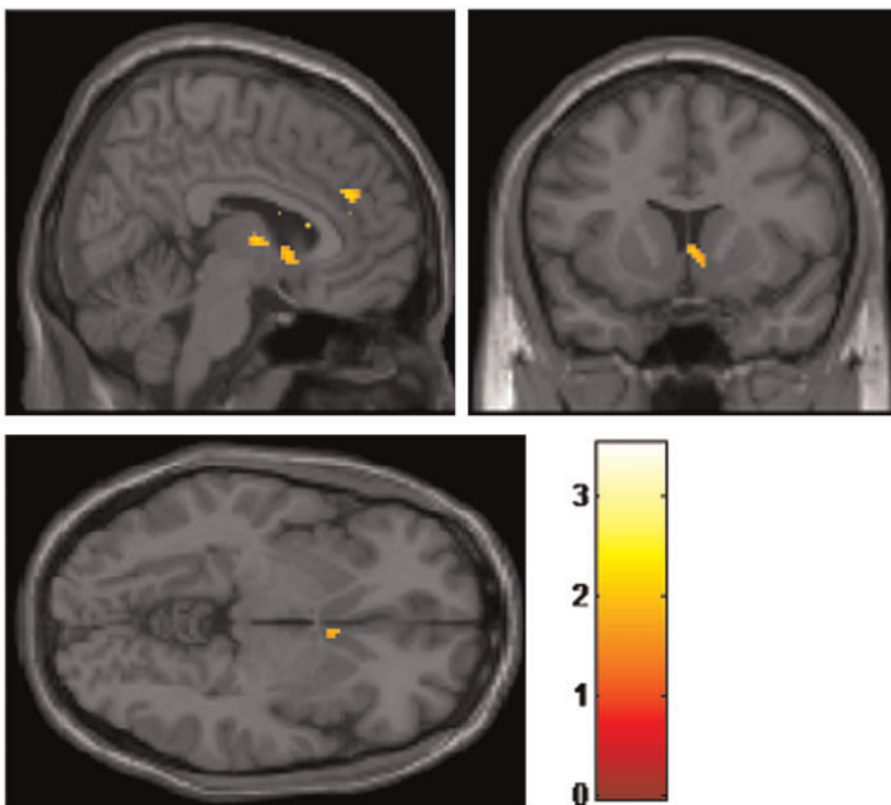**Fig. 2** Main effect of childhood social withdrawal on age 20 reward anticipation.

Fig. 3 Interactive effect of childhood social withdrawal and fearfulness on striatal activation during reward anticipation.

Table 2 Child fearfulness, sociability and social withdrawal on reward response

Condition	Region	x	y	z	t	Cluster size
Reward anticipation	Model 1					
	Child social withdrawal					
	Caudate head (+)	2	14	1	4.35	205
	Medial BA 9 (+)	10	38	22	3.15	142
	Fearfulness					
	Sociability					
	Child social withdrawal X fearfulness					
	Caudate head (+)	−2	2	0	2.47	192
	Simple slopes social withdrawal (High Fearful)					
	Caudate head (+)	0	16	1	3.41	165
	Child social withdrawal X sociability					
Reward anticipation	Diagnosis model 1					
	Depression					
	Caudate head (−)	6	12	0	5.99	165
	Social phobia					
	Caudate head (−)	4	14	0	3.35	172

Talairach coordinates. Findings are significant at $P < 0.05$. Multiple comparisons are controlled for using AlphaSim.

altered reward function did not predict severity level of depression and anxiety, perhaps suggesting that disrupted striatal function associated with social withdrawal and fearfulness may distinguish clinical disorder from non-disorder but may be less be predictive of subthreshold symptoms. Furthermore, given the chronology of the psychiatric history data and neural function data, it could also be said that prior psychopathology contributed to altered reward functioning in our sample.

The combination of low sociability and greater social withdrawal was not associated with an altered reward response to monetary rewards. Boys with these characteristics may spend more time alone due to preferred solitude and may find pleasure in non-social tasks. This combination could reflect an experience of solitary pursuits as rewarding, with function in reward circuitry unaltered from its typical response. Whereas social fearfulness is likely experienced as awkward and uncomfortable by the boys, preferred solitude may be experienced as more benign and even pleasant.

Our multi-method longitudinal study has many strengths. The use of a naturalistic camp setting in which novel peers rated boys on their socially withdrawn behavior (and in which camp counselors corroborated these ratings) increased the ecological validity of our study. We used repeated measurement of teacher ratings of socially withdrawn behavior in the classroom (age 6–10) to create a more comprehensive and stable measure of childhood social withdrawal. The use of a longitudinal design demonstrates that the association between social withdrawal and reward response may begin early in development. This finding has important implications for intervention, as fearful, withdrawn boys may benefit from approaches that target integration of withdrawn boys into the peer environment and exposure to feared social cues prior to the vulnerable period of adolescence. However, as we did not measure reward response prior to age 20, we are unable to determine whether social withdrawal precedes altered reward response. It is possible that altered reward response may lead to withdrawing in social situations in an effort to modulate the intense feelings that accompany pursuit of reward. These associations may emerge early when trait-like differences in fearfulness emerge and stabilize. Due to the design of our study, we were unable to test this potential effect.

We evaluated our research questions using a monetary reward task with a sample of low-income boys from large urban community.

Future research should evaluate these research questions with girls, too, and with boys and girls from different socioeconomic backgrounds and communities (e.g. rural, suburban). The use of a personally relevant social reward paradigm would have allowed us to evaluate how socially withdrawn boys who are high on fearfulness *and* low on sociability respond to social rewards.

We explored whether altered reward function associated with social withdrawal and fearfulness predicted history of affective disorders at age 20. However, the base rate of these disorders was relatively low in this sample ($n = 15$ for Depression; $n = 10$ for Social Phobia), and our sample had high rates of comorbid disorders. Also, our evaluation of reward function associated with childhood social withdrawal and fearfulness on continuous measures of anxiety and depression produced non-significant results. Nevertheless, we found significant effects in our hypothesized directions, even when we adjusted for the presence of other disorders, and we believe that our findings provide valuable preliminary evidence of these effects. Case-control studies with larger sample sizes are needed to corroborate these findings.

Overall, our findings are important and compelling. To our knowledge, no one has evaluated how real-world childhood social experiences may influence reward-related brain function during late adolescence. Evaluation of this research question is important, as reward-related processes have been implicated in the pathophysiology of various clinical disorders (Guyer *et al.*, 2012; Zhang *et al.*, 2013), and identification of causal or associated processes is important for preventive intervention development. In this case, interventions targeting fearful, withdrawn children may aid their development of more adaptive reward-related self-regulation skills, potentially reducing risk for psychopathology during the vulnerable period of adolescence.

Conflict of Interest
None declared.

REFERENCES

Achenbach, T.M. (1991). *Manual for the Teacher's Report Form and 1991 Profiles*. Department of Psychiatry, University of Vermont.

Bar-Haim, Y., Fox, N.A., Benson, B., et al. (2009). Neural correlates of reward processing in adolescents with a history of inhibited temperament. *Psychological Science*, 20, 1009–18.

Beck, A.T., Steer, R.A., Garbin, M.G. (1988a). Psychometric properties of the Beck Depression Inventory. Twenty-five years of evaluation. *Clinical Psychology Review*, 8, 77–100.

Beck, A.T., Epstein, N., Brown, G., Steer, R.A. (1988b). An inventory for measuring clinical anxiety: psychometric properties. *Journal of Consulting and Clinical Psychology*, 56, 893–7.

Buss, A.H., Plomin, R. (1975). *A Temperament Theory of Personality Development*. New York: Wiley.

Chronis-Tuscano, A., Degnan, K.A., Pine, D.S., et al. (2009). Stable early maternal report of behavioral inhibition predicts lifetime social anxiety disroder in adolescence. *Journal of the American Academy of Child and Adolescent Psychiatry*, 48, 928–35.

Coplan, R.J., Armer, M. (2007). A "multitude" of solitude: a closer look at social withdrawal and nonsocial play in early childhood. *Child Development Perspectives*, 1, 26–32.

Coplan, R.J., Closson, L.M., Arbeau, K.A. (2007). Gender differences in the behavioral associates of loneliness and social dissatisfaction in kindergarten. *Journal of Child Psychology and Psychiatry*, 48, 988–95.

Costello, E.J., Pine, D.S., Hammen, C., et al. (2002). Development and natural history of mood disorders. *Biological Psychiatry*, 52, 529–42.

Davey, C.G., Yucel, M., Allen, N.B. (2008). The emergence of depression in adolescence: development of prefrontal cortex and the representation of reward. *Neuroscience Biobehavial Review*, 32, 1–19.

Denny, B.T., Kober, H., Wager, T.D., Ochsner, K.N. (2012). A meta-analysis of functional neuroimaging studies of self- and other judgments reveals a spatial gradient for mentalizing in medial prefrontal cortex. *Journal of Cognitive Neuroscience*, 24, 1742–52.

Forbes, E.E., Hariri, A.R., Martin, S.L., et al. (2009). Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. *American Journal of Psychiatry*, 166, 64–73.

Forbes, E.E., Ryan, N.D., Phillips, M.L., et al. (2010). Healthy adolescents' neural response to reward: Associations with puberty, positive affect, and depressive symptoms. *Journal of the American Association for Child and Adolescent Psychiatry*, 49, 162–72.

Guyer, A.E., Kaufman, J., Hodgon, H.B., et al. (2006a). Behavioral alterations in reward system function: The role of childhood maltreatment and psychopathology. *Journal of the American Academy of Child and Adolescent Psychiatry*, 45, 1059–67.

Guyer, A.E., Nelson, E.E., Perez-Edgar, K., et al. (2006b). Striatal functional alteration in adolescents characterized by early childhood behavioral inhibition. *Journal of Neuroscience*, 26, 6399–405.

Guyer, A.E., Choate, V.R., Detloff, A., et al. (2012). Striatal functional alteration during incentive anticipation in pediatric anxiety disorders. *American Journal of Psychiatry*, 169, 205–12.

Haber, S.N., Knutson, B. (2010). The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology*, 35, 4–26.

Healey, K.L., Morgan, J.K., Musselman, S.C., Olino, T.M., Forbes, E.E. (2014). Social anhedonia and medial prefrontal response to mutual liking in late adolescents. *Brain and Cognition*, 89, 39–50.

Izuma, K., Saito, D.N., Sadato, N. (2008). Processing of social and monetary rewards in the human striatum. *Neuron*, 58, 284–94.

Kagan, J., Reznick, J.S., Snidman, N. (1987). The physiology and psychology of behavioral inhibition in children. *Child Development*, 58, 1459–73.

Koob, G.F., Le Moal, M. (2008). Neurobiological mechanisms for opponent motivational processes in addiction. *Philosophical Transactions of the Royal Society*, 363, 3113–23.

Masten, C.L., Telzer, E.H., Fuligni, A.J., Lieberman, M.D., Eisenberger, N.I. (2012). Time spent with friends in adolescence relates to less neural sensitivity to later peer rejection. *Social Cognitive and Affective Neuroscience*, 7, 106–14.

Matthews, K., Robbins, T.W. (2003). Early experience as a determinant of adult behavioral responses to reward: The effects of repeated maternal separation. *Neuroscience and Biobehavioral Reviews*, 27, 45–55.

Morgan, J.K., Shaw, D.S., Forbes, E.E. (2013). Physiological and behavioral withdrawal in social contexts as predictors of adolescent depressive symptoms. *Journal of Youth and Adolescence*, 42, 1117–27.

Nichols, T., Brett, M., Andersson, J., Wager, T., Poline, J. (2005). Valid conjunction inference with minimum statistic. *Neuroimage*, 25, 653–80.

Nusslock, R., Almeida, J.R.C., Forbes, E.E., et al. (2012). Waiting to win: elevated striatal and orbitofrontal cortical activity during reward anticipation in euthymic bipolar disorder adults. *Bipolar Disorders*, 14, 249–60.

Preacher, K.J., Curran, P.J., Bauer, D.J. (2006). Computational tools for probing interactions in multiple linear regression, multilevel modeling, and latent curve analysis. *Journal of Educational and Behavioral Statistics*, 31, 437–48.

Price, J.L., Drevets, W.C. (2010). Neurocircuitry of mood disorders. *Neuropsychopharmacology*, 35, 192–216.

Reid, J.B., Fetrow, R.A., Mayne, T. (1991). *LIFT Playground Observer Impressions* Unpublished measure, Oregon Social Learning Center.

Rubin, K.H., Coplan, R.J., Bowker, J.C. (2009). Social withdrawal in childhood. *Annual Reviews of Psychology*, 60, 141–71.

Shaw, D.S., Hyde, L.W., Brennan, L.M. (2012). Early predictors of boys' antisocial trajectories. *Development and Psychopathology*, 24, 871–88.

Silk, J.S., Davis, S., McMakin, D.L., Dahl, R.E., Forbes, E.E. (2012). Why do anxious children become depressed teenagers? The role of social evaluative threat and reward processing. *Psychological Medicine*, 42, 2095–107.

Spitzer, R.L., Williams, J.B.W., Gibbon, M., First, M.B. (1990). *Structured Clinical Interview for DSM-III-R, Patient Edition/Non-patient Edition (SCID-P/SCID-NP)*. Wahsington, DC: American Psychiatric Press.

Trentacosta, C.J., Shaw, D.S. (2009). Emotional self-regulation, peer rejection, and antisocial behavior: Developmental associations from early childhood to early adolescence. *Journal of Applied Developmental Psychology*, 30, 356–65.

Zhang, W.N., Chang, S.H., Guo, L.Y., Zhang, K.L., Wang, J. (2013). The neural correlates of reward-related processing in major depressive disorder: a meta-analysis of functional magnetic resonance imaging studies. *Journal of Affective Disorders*, 151, 531–9.